Toxicological Profile for Vinyl Acetate

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U.S. Department of Health and Human Services
Agency for Toxic Substances and Disease Registry

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DISCLAIMER

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FOREWORD

This toxicological profile is prepared in accordance with guidelines developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

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

The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a relevance to public health discussion which would allow a public health professional to make a real-time determination of whether the presence of a particular substance in the environment poses a potential threat to human health. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to the protection of public health are identified by ATSDR.

Each profile includes the following:

(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a toxic substance to ascertain the levels of significant human exposure for the substance due to associated acute-, intermediate-, and chronic-duration exposures;

(B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health due to acute-, intermediate-, and chronic-duration exposures; and

(C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

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

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staff of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.

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VERSION HISTORY

Date	Description
January 2025	Final toxicological profile released
August 2023	Draft for public comment toxicological profile released
July 1992	Final toxicological profile released

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These experts collectively have knowledge of toxicology, chemistry, and/or health effects. All reviewers were selected in conformity with Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

ATSDR scientists review peer reviewers' comments and determine whether changes will be made to the profile based on comments. The peer reviewers' comments and responses to these comments are part of the administrative record for this compound.

The listing of peer reviewers should not be understood to imply their approval of the profile's final content. The responsibility for the content of this profile lies with ATSDR.

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CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

Vinyl acetate is a man-made compound that is used in the production of polymers and copolymers, including polyvinyl acetate, polyvinyl alcohol, polyvinyl acetals, ethylene-vinyl acetate (EVA) copolymer, and polyvinyl chloride-acetate copolymer. It is used in adhesives, paint and powder coatings, plastics and resins, rubber foam, packaging, sporting equipment (e.g., ski boots, bicycle seats), auto-related films, and intermediates in construction and building materials. Vinyl acetate also is approved for use as a food additive (masticatory substance, solvent/vehicle) and as a component in polymerized food packaging (e.g., EVA copolymers).

Vinyl acetate has been detected at low levels in ambient air and water, with the most frequent detections in outdoor air. It has also been detected at low levels in air and soil near hazardous waste sites. Volatilization to the atmosphere is an important transport process if it is released to surface water and soils, due to the high vapor pressure of vinyl acetate. Based on the low soil adsorption coefficient and high water solubility, vinyl acetate is expected to be highly mobile in soils and is likely to partition to groundwater when released to subsurface soils. The low octanol/water partition coefficient for vinyl acetate suggests that it is unlikely to bioconcentrate/biomagnify in terrestrial or aquatic organisms/food chains. This apparent lack of vinyl acetate bioconcentration indicates that 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 an atmospheric lifetime on the order of hours to days. In soil, surface water, and groundwater, the compound undergoes hydrolysis and biotransformation, with half-lives on the order of hours to days. The main products of these transformation processes are acetic acid, acetaldehyde, and acetate.

General population exposure to vinyl acetate is expected to be low. Potential sources of exposure include inhalation of contaminated ambient air and cigarette smoke, dermal contact with products containing the compound (e.g., glues and paints), ingestion of food items containing the compound, and dermal and inhalation exposure during domestic water use (e.g., showering or washing activities) if the water contains vinyl acetate. Vapor intrusion of vinyl acetate into structures from contaminated soil and groundwater may result in indoor air levels of vinyl acetate in buildings and residences. Since vinyl acetate has been detected at hazardous waste sites, populations living near contaminated sites may have increased exposure via ambient air, groundwater contamination, and/or vapor intrusion, compared to the

general population. Occupational exposure to vinyl acetate occurs via inhalation of contaminated workplace air. Workers may also be exposed by dermal contact with vinyl acetate vapor or liquids and products containing the compound.

1.2 SUMMARY OF HEALTH EFFECTS

Information on the noncancer toxicity of vinyl acetate comes primarily from studies in laboratory animals; however, a limited number of human controlled exposure and occupational studies contribute to the identification of primary toxicity targets. The majority of animal studies evaluate inhalation or oral exposure, with only a few evaluating dermal exposure.

As illustrated in Figures 1-1 and 1-2, sensitive noncarcinogenic effects in laboratory animals following vinyl acetate exposure include respiratory effects (inhalation) and developmental effects (inhalation, oral). Decreased body weight effects were also noted in some drinking water studies; however, assessment of compound-related effects on body weight is difficult due to concomitant decreases in water and/or food intake. No additional nonneoplastic effects were noted at concentrations or doses below high levels associated with increased mortality. Therefore, the systematic review was limited to respiratory and developmental effects, resulting in the following hazard identification conclusions:

- Respiratory system effects are a presumed health effect for humans following inhalation exposure.
- The data are inadequate to conclude whether developmental effects will occur in humans.

Respiratory Effects. The primary target of vinyl acetate toxicity following inhalation exposure in humans and animals is the respiratory system, presumably due to chronic irritation at the portal of entry. Limited human data report irritation of the nose and throat following controlled and occupational exposure in small groups. Some individuals reported mild irritation after acute exposure to concentrations ranging from 4 to 34 ppm, with exposures of 72 ppm associated with persistent irritation (Deese and Joyner 1969; Union Carbide 1973). Limited data suggest that repeated occupational exposure to vinyl acetate is generally without adverse respiratory effect at levels <10 ppm (Deese and Joyner 1969). However, subjective respiratory complaints and mild reductions in pulmonary function were reported in one study at an average concentration of 3.61 ppm (range of 0.02–11.71 ppm) (Khoshakhlagh et al. 2023). In laboratory rats and mice, damage to the respiratory system is consistently reported following inhalation exposure at acute- and intermediate-duration exposures ≥598.5 ppm (Bogdanffy et al. 1997; Hazleton

Figure 1-1. Health Effects Found in Animals Following Inhalation Exposure to Vinyl Acetate

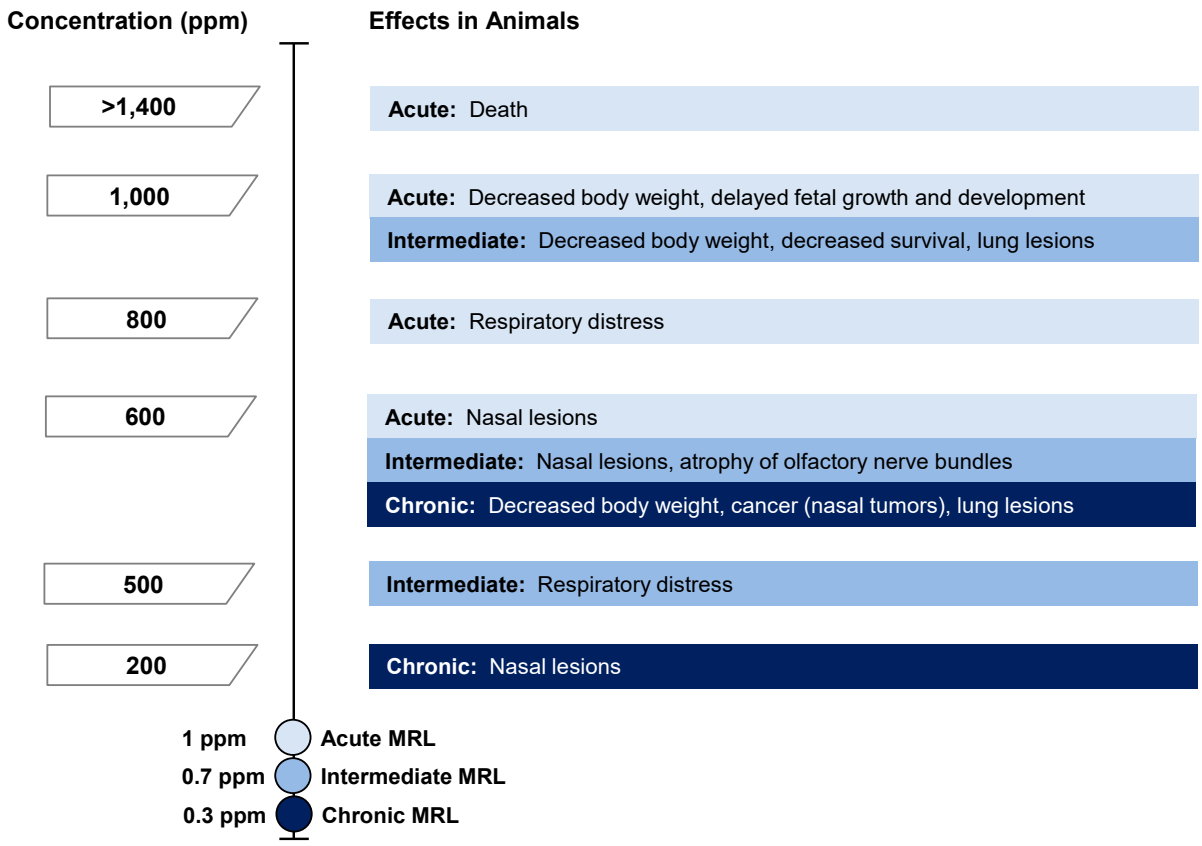
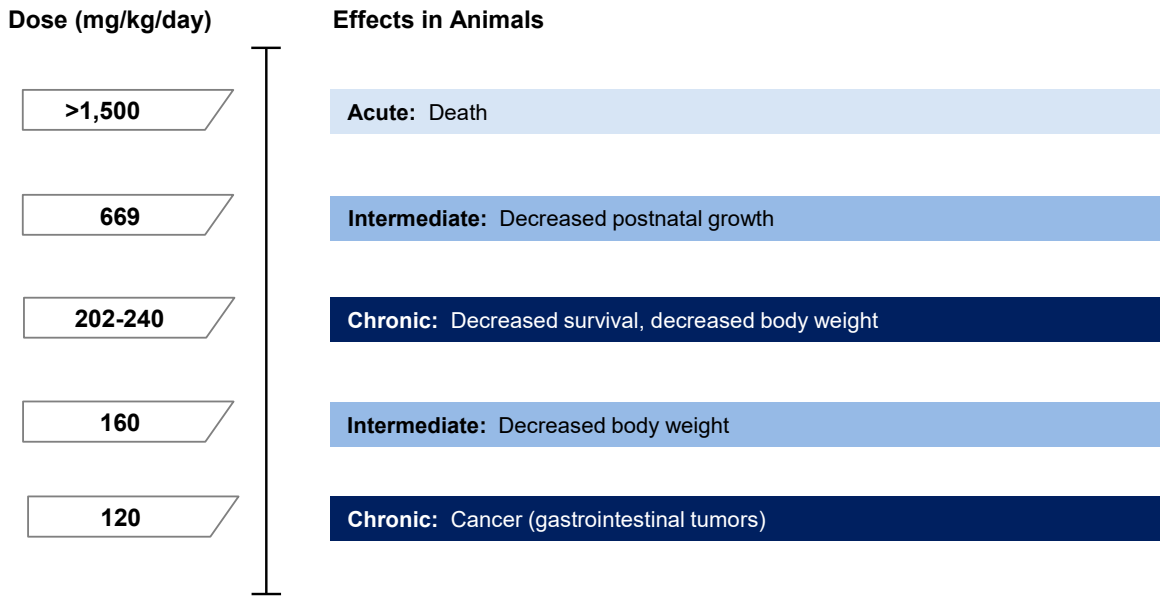


Figure 1-2. Health Effects Found in Animals Following Oral Exposure to Vinyl Acetate



1980b, 1980c; Krieger et al. 2020) and chronic-duration exposures ≥200.5 ppm (Bogdanffy et al. 1994a; Hazleton 1988). While lesions were found throughout the respiratory tract, findings indicated that the extrathoracic region is more susceptible to the irritant effects of inhaled vinyl acetate than the lower respiratory tract. The olfactory epithelium of the nasal cavity in rats appears to be particularly susceptible to vinyl acetate toxicity, with degenerative, necrotic, and/or hyperplastic lesions following exposure for acute-, intermediate-, or chronic-duration exposure (Bogdanffy et al. 1994a, 1997; Krieger et al. 2020). These effects are attributed to intracellular acidification resulting from metabolism of vinyl acetate to acetic acid (Bogdanffy 2002).

Developmental Effects. No studies were located regarding developmental effects in humans following exposure to vinyl acetate. No exposure-related embryolethality or teratogenicity were observed in rat offspring following maternal exposure to inhalation concentrations up to 1,005 ppm (Hazleton 1980d; Hurtt et al. 1995) or drinking water concentrations up to 477 mg/kg/day during gestation (Hurtt et al. 1995) or drinking water concentrations up to 697 mg/kg/day in a 2-generation study (Mebus et al. 1995). In the inhalation study, fetal effects at 1,005 ppm included decreased weight and length as well as delayed ossification; these effects may have been secondary to decreased maternal weight. No changes in fetal growth or development were observed following oral exposure during gestation. However, F1 pup weight at weaning was decreased in the 2-generation drinking-water study. As with the inhalation study, this may be secondary to decreased F0 maternal water intake (which may impair milk production) as well as decreased F0 maternal body weight gain during lactation (Mebus et al. 1995). F2 pup weights were not decreased, despite decreases in F1 maternal water intake and body weights.

Cancer. No adequate studies evaluating carcinogenic potential of vinyl acetate in humans have been found. Studies in animals indicate that vinyl acetate causes route-specific tumors at the portal of entry, with exposure-related neoplastic lesions in the upper respiratory system in rats following chronic-duration inhalation exposure (Bogdanffy et al. 1994a; Hazleton 1988) and in the oral cavity and upper gastrointestinal tract of rats and mice following chronic-duration drinking-water exposure (Belpoggi et al. 2002; Maltoni et al. 1997; Minardi et al. 2002). Observed portal-of-entry effects are attributed to rapid hydrolysis of vinyl acetate following contact with mucosal surfaces (Albertini 2013; Bogdanffy 2002; Bogdanffy and Valentine 2003; Bogdanffy et al. 1999, 2001, 2004; Slikker et al. 2004). Hydrolysis products include acetaldehyde, a known genotoxicant, and acetic acid, which lowers cellular pH, resulting in cellular damage and subsequent proliferation. Evidence for neoplastic effects at sites distant from the site of administration is limited but includes uterine carcinoma in rats following exposure to vinyl acetate in drinking water for 104 weeks following *in utero* exposure (Belpoggi et al. 2002).

The International Agency for Research on Cancer (IARC) has determined that vinyl acetate is possibly carcinogenic to humans (Group 2B) based on inadequate evidence in humans and limited evidence in experimental animals (IARC 1995). The U.S. Environmental Protection Agency (EPA) (IRIS 1990) and the Department of Health and Human Services (HHS) (NTP 2021) have not evaluated the potential for vinyl acetate to cause cancer in humans.

1.3 MINIMAL RISK LEVELS (MRLs)

The inhalation database was considered adequate for deriving acute-, intermediate-, and chronic-duration MRLs. As presented in Figure 1-3, the available inhalation data for vinyl acetate suggest that the respiratory system is the most sensitive target of toxicity in laboratory animals following inhalation exposure. Additional effects noted at higher exposure levels included neurological, developmental, body weight, and cancer effects. No other effects were noted below high concentrations associated with increased mortality.

The oral database was considered inadequate for deriving acute-, intermediate-, or chronic-duration MRLs. No exposure-related effects were observed in acute-duration oral exposure studies in animals below the lowest identified median lethal dose (Figure 1-4). Following intermediate- and chronic-duration oral exposure, decreased body weights were observed in drinking water studies; however, some of the observed body weight decreases may be attributable to observed decreases in drinking water intake (due to unpalatability of test substance) and/or decreased food consumption. Decreased body weights were also observed in F1 rats at weaning from a 2-generation study. Similar to adult findings, F1 body weight effects are of unclear biological relevance because they may be secondary to decreased maternal water intake (which may impair milk production) rather than direct toxic action of vinyl acetate. No additional non-neoplastic targets were identified following intermediate- or chronic-duration oral exposure (Figure 1-4).

The MRL values are summarized in Table 1-1 and discussed in greater detail in Appendix A.

Figure 1-3. Summary of Sensitive Targets of Vinyl Acetate – Inhalation

Available data indicate that the respiratory system is the most sensitive target of vinyl acetate inhalation exposure.

Numbers in circles are the lowest LOAELs for all health effects in animals.
No reliable dose response data were available for humans

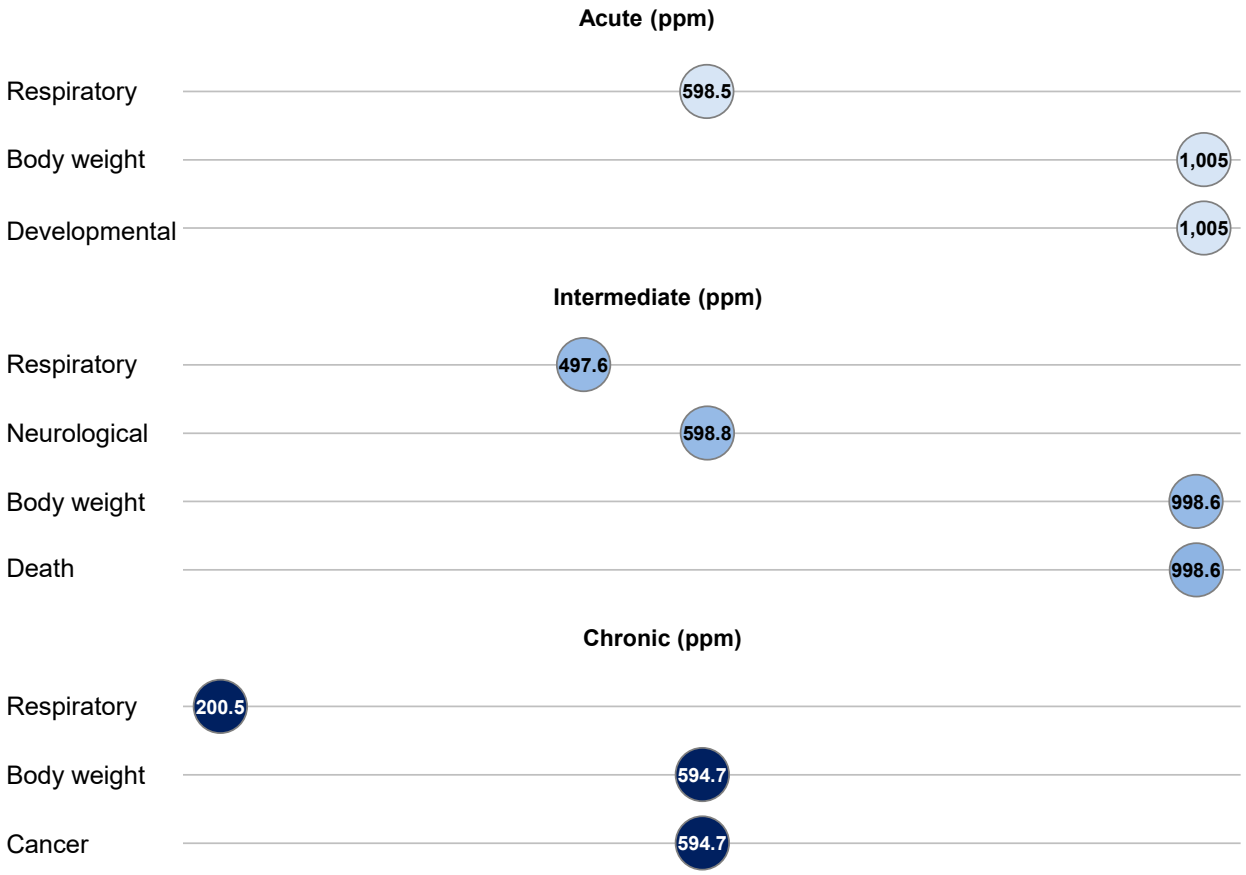


Figure 1-4. Summary of Sensitive Targets of Vinyl Acetate – Oral

Available data indicate that the body weight effects, the developing organism, and cancer are the most sensitive targets of vinyl acetate oral exposure.

Numbers in circles are the lowest LOAELs for all health effects in animals; no human data were identified.

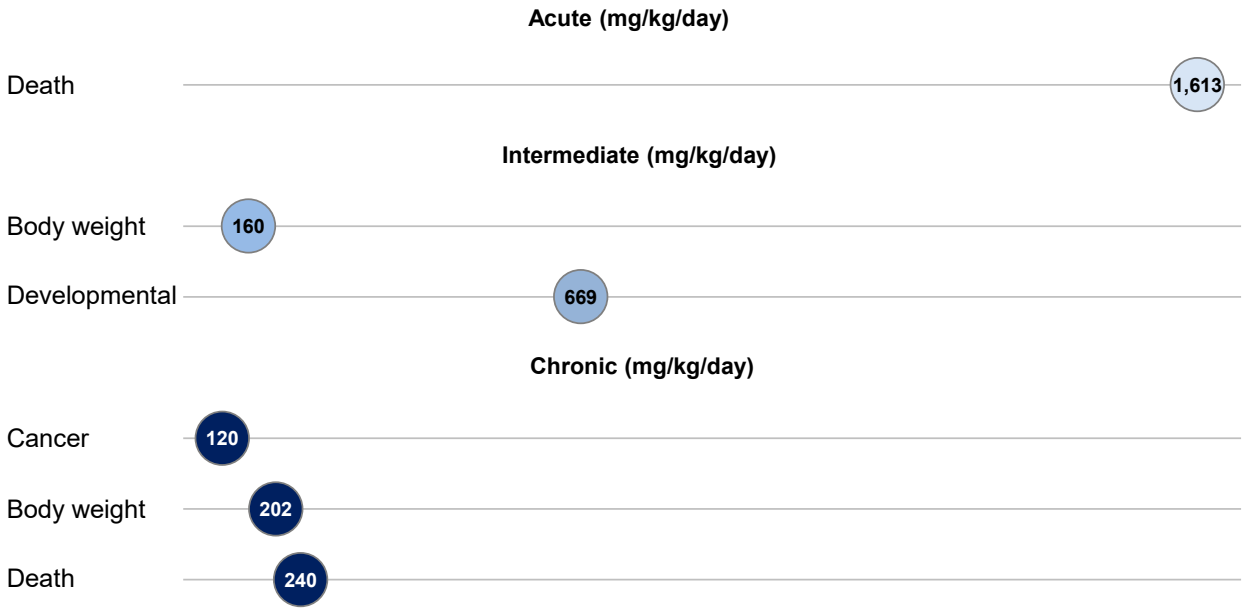


Table 1-1. Minimal Risk Levels (MRLs) for Vinyl Acetate[a]

Exposure route	Exposure duration	MRL	Critical effect	POD type	POD value[b]	Uncertainty/ modifying factor	Reference
Inhalation	Acute	**1 ppm** (3.5 mg/m^3)	Nasal lesions	$NOAEL_{HEC}$	29.1 ppm	UF: 30	Bogdanffy et al. 1997
	Intermediate	**0.7 ppm** (2.5 mg/m^3)	Nasal lesions	$NOAEL_{HEC}$	21.6 ppm	UF: 30	Bogdanffy et al. 1997
	Chronic	**0.3 ppm** (1.1 mg/m^3)	Nasal lesions	$NOAEL_{HEC}$	8.52 ppm	UF: 30	Bogdanffy et al. 1994a; Hazleton 1988
Oral	Acute	None	–	–	–	–	–
	Intermediate	None	–	–	–	–	–
	Chronic	None	–	–	–	–	–

[a]See Appendix A for additional information.
[b]HEC values were calculated using a PBPK model (Bogdanffy et al. 1999; Hinderliter et al. 2005) with model parameters from Bogdanffy et al. (1999) and Plowchalk et al. (1997) with the exception of body weights, which were based on TWA body weights calculated for the principal study. Parameters in this model account for adjustments to a continuous (24 hours/day) exposure scenario. See Appendix A for additional details and calculations.

HEC = human equivalent concentration; NOAEL = no-observed-adverse-effect level; PBPK = physiologically based pharmacokinetic; POD = point of departure; TWA = time-weighted average; UF = uncertainty factor

CHAPTER 2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of vinyl acetate. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

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

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized by health effect. These data are discussed in terms of route of exposure (inhalation, oral, and dermal) and three exposure periods: acute (≤14 days), intermediate (15–364 days), and chronic (≥365 days).

As discussed in Appendix B, a literature search was conducted to identify relevant studies examining health effect endpoints. Figure 2-1 provides an overview of the database of studies in humans or experimental animals included in this chapter of the profile. These studies evaluate the potential health effects associated with inhalation, oral, or dermal exposure to vinyl acetate, but may not be inclusive of the entire body of literature. A systematic review of the scientific evidence of the health effects associated with exposure to vinyl acetate was also conducted; the results of this review are presented in Appendix C.

Animal inhalation studies are presented in Table 2-1 and Figure 2-2, animal oral studies are presented in Table 2-2 and Figure 2-3, and human and animal dermal studies are presented in Table 2-3.

Levels of significant exposure (LSEs) for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. Effects have been classified into "less serious LOAELs" or "serious LOAELs (SLOAELs)." "Serious" effects (SLOAELs) are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether

an endpoint should be classified as a NOAEL, “less serious” LOAEL, or “serious” LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these endpoints. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between “less serious” and “serious” effects. The distinction between “less serious” effects and “serious” effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health. Levels of exposure associated with cancer (Cancer Effect Levels, CELs) of vinyl acetate are indicated in Tables 2-1 and 2-2 and Figures 2-2 and 2-3.

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

The health effects of vinyl acetate have been evaluated in 9 human studies and 48 animal studies. As illustrated in Figure 2-1, most of the health effects data come from inhalation and oral exposure studies in animals. For the purposes of Figure 2-1, all human and animal inhalation studies were classified as such; however, it is acknowledged that dermal and ocular effects associated with inhalation studies are likely attributable to direct contact with vinyl acetate vapors. Therefore, ocular and dermal effects from inhalation studies are counted as dermal exposure in Figure 2-1 and are listed in the dermal LSE table. For animal data, inhalation and oral studies are available for all health effect and exposure duration categories. The dermal animal database is limited to six acute studies and one intermediate-duration study, evaluating limited endpoints. The most examined endpoints in animal studies were death, body weight, respiratory, and gastrointestinal effects. The available human studies were predominantly focused on evaluation of respiratory, dermal, and ocular effects.

A systematic review was conducted on potential toxicity targets of vinyl acetate exposure, which included respiratory effects for inhalation exposure and developmental effects following inhalation or oral exposure (see Appendix C for details). Decreased body weight effects were also noted in some drinking water studies; however, assessment of compound-related effects on body weight is difficult due to

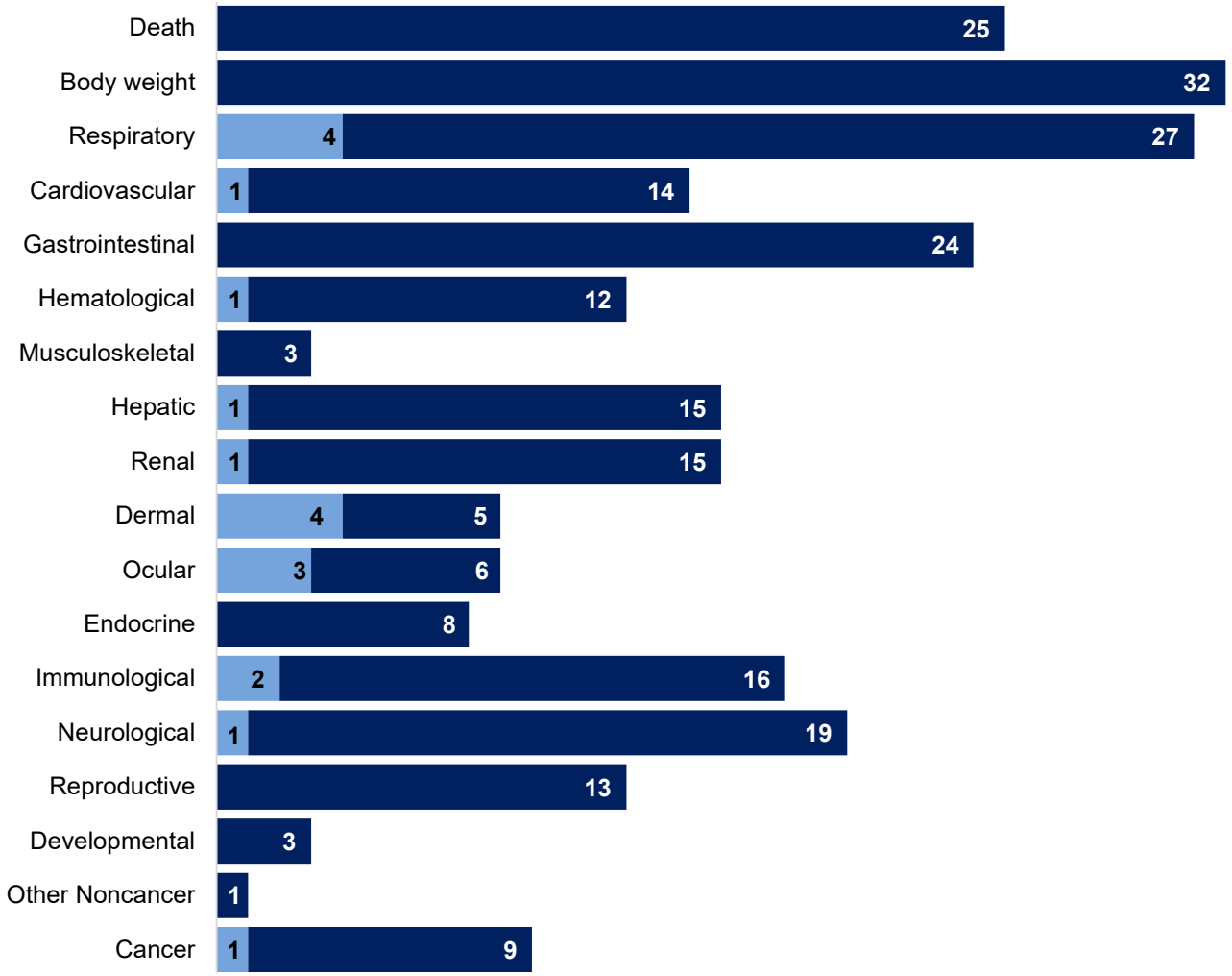
concomitant decreases in water and/or food intake. Based upon systematic review, the results of the animal studies, along with limited human data, support the following hazard identification conclusions:

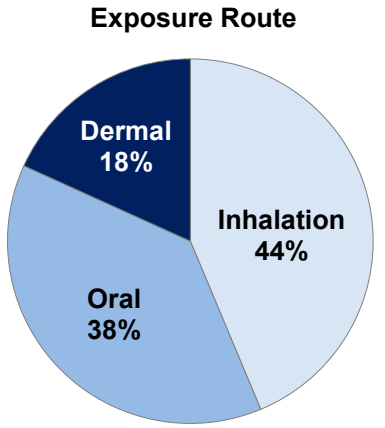
- **Respiratory Effects.** Respiratory effects are a presumed health effect for humans exposed to vinyl acetate based on inadequate evidence of respiratory effects in humans and a high level of evidence of upper and lower respiratory tract damage in laboratory animals following acute-, intermediate-, and chronic-duration inhalation exposure. The nasal cavity appears to be the most sensitive target tissue in rats and mice following inhalation exposure, particularly the olfactory nasal epithelium. Lower respiratory tract lesions were also consistently observed at higher concentrations. In acute-duration lethality studies, all deaths were attributed to lung damage, and deaths were preceded by labored breathing and/or respiratory distress.

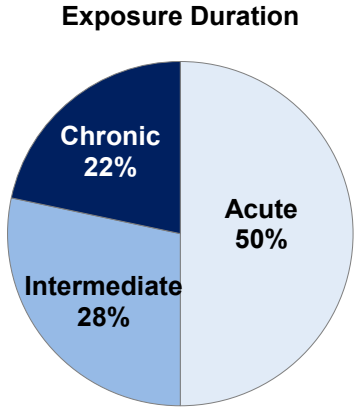
- **Developmental Effects.** Available data are inadequate to determine if developmental effects will occur in humans following exposure to vinyl acetate based on no human data and a low level of evidence in laboratory animals following oral exposure. There is some evidence for impaired growth and development in rats following developmental exposure to vinyl acetate via inhalation or oral exposure. Decreased fetal growth and delayed ossification were observed in rat fetuses following maternal inhalation exposure during gestation at concentrations associated with decreased maternal weight. Decreased F1 weanling weights were also observed in rats in a 2-generation drinking-water study. However, these effects may have been secondary to decreased maternal water intake and body weight gain during lactation (which could impair milk production). No effects were noted in F2 pup weights in the 2-generation study, despite F1 dam body weight effects. In an oral gestation-only study, neither maternal nor fetal effects were noted.

Figure 2-1. Overview of the Number of Studies Examining Vinyl Acetate Health Effects*

Most studies examined the potential death, body weight, respiratory, and gastrointestinal effects of vinyl acetate
Fewer studies evaluated health effects in humans than animals (counts represent studies examining endpoint)







*Includes studies discussed in Chapter 2. A total of 57 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

Table 2-1. Levels of Significant Exposure to Vinyl Acetate – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE									
Bogdanffy et al. 1997									
1	Rat (Sprague-Dawley) 5 M	6 hours (WB)	0, 50.8, 199.6, 598.5, 1,007.3	HP	Resp	199.6	598.5		Minimal-to-moderate degeneration/ necrosis of the olfactory epithelium, cell proliferation in nasal epithelium
Bogdanffy et al. 1997									
2	Rat (Sprague-Dawley) 5 M	5 days 6 hours/day (WB)	0, 50.8, 199.6, 598.5, 1,007.3	BW, HP	Bd wt	598.5	1,007.3		14% decrease in body weight
					Resp	199.6[b]	598.5		Mild-to-severe olfactory epithelium regenerative hyperplasia
Carpenter et al. 1949									
3	Rat (Sherman) 6 NS	4 hours (WB)	4,000	LE	Death			4,000	Exposure level categorized as killing 2/6, 3/6, or 4/6 rats (exact mortality not reported)
Hurtt et al. 1995; Hazleton 1980d									
4	Rat (Sprague-Dawley) 22–24 F	10 days GDs 6–15 6 hours/day (WB)	0, 51.8, 197.5, 1,005	CS, BW, FI, WI, GN, HP, FX	Bd wt	197.5	1,005		9–12% decrease in maternal body weight on GDs 10–20
					Repro	1,005			
					Develop	197.5		1,005	28% decrease in fetal weight; 12% decrease in crown-to-rump-length, delayed ossification
Krieger et al. 2020									
5	Rat (Sprague-Dawley) 21 M	6 hours (WB)	0, 50.4, 201.6, 604.8, 1,009.7	LE, CS, BW, HP	Bd wt	1009.7			
					Resp	201.6	604.8		Slight-to-marked degeneration/necrosis of nasal tissue (primarily proximal olfactory epithelium)

Table 2-1. Levels of Significant Exposure to Vinyl Acetate – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Krieger et al. 2020									
6	Rat (Sprague-Dawley) 21 M	5 days 6 hours/day (WB)	0, 50.4, 201.6, 604.8, 1,009.7	LE, CS, BW, HP	Bd wt	604.8	1,009.7		12% decrease in body weight with 51% decrease in food consumption; 5% body weight loss (compared to 12% body weight gain in controls)
					Resp	201.6	604.8		Slight-to-moderate atrophy and necrosis of nasal tissue
Union Carbide 1973									
7	Rat (NS) 6 M, 6 F	4 hours (WB)	1,640, 3,280, 6,560	LE, CS, GN	Death			3,680	LC_{50}
					Resp	1,640		3,280	Respiratory distress (gasping) prior to death; lung congestion and hemorrhage in rats that died
Union Carbide 1973									
8	Mouse (NS) 6 NS	4 hours (WB)	410, 820, 1,640, 3,280, 6,560	LE, CS, GN	Death			1,460	LC_{50}
					Resp	410		820	Labored breathing; respiratory distress (gasping) prior to death; excess pleural fluid and lung hemorrhage in mice that died
Union Carbide 1973									
9	Rabbit (NS) 4 M	4 hours (WB)	1,640, 3,280, 6,560	LE, CS, GN	Death			2,760	LC_{50}
					Resp	1,640		3,280	Labored breathing, nasal irritation; excess pleural fluid and lung hemorrhage in rabbits that died
Union Carbide 1973									
10	Guinea pig (NS) 6 M	4 hours (WB)	1,640, 3,280, 6,560, 13,120	LE, CS, GN	Death			5,210	LC_{50}
					Resp	1,640		3,280	Labored breathing; respiratory distress (gasping) prior to death; lung congestion, hemorrhage, and emphysemic changes in animals that died

Table 2-1. Levels of Significant Exposure to Vinyl Acetate – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
INTERMEDIATE EXPOSURE									
Bogdanffy et al. 1997									
11	Rat (Sprague-Dawley) 5 M	4 weeks 5 days/week 6 hours/day (WB)	0, 50.8, 199.6, 598.5, 1,007.3	BW, HP	Bd wt	598.5	1,007.3		>10% decrease in body weight
					Resp	199.6[c]	598.5		Mild-to-severe olfactory epithelium hyperplasia
					Neuro	199.6	598.5		Degeneration and atrophy of nerve bundles in olfactory epithelium
Gage 1970									
12	Rat (Wistar) 4 M, 4 F	15 days 6 hours/day (WB)	0, 100, 250, 630, 2,000	CS, BW, HE, HP	Resp	630		2,000	Respiratory difficulty, excess macrophages in the lungs
					Hemato	2,000			
					Hepatic	2,000			
					Renal	2,000			
					Endocr	2,000			
					Immuno	2,000			
Hazleton 1979c									
13	Rat (Sprague-Dawley) 5 M, 5 F	4 weeks 5 days/week 6 hours/day (WB)	0, 51.3/1,488.5, 150.5, 497.6, 1,000.2	LE, CS, BW, HE, OW, GN	Bd wt	1,000.2			
					Resp	150.5		497.6	Respiratory distress
					Cardio	1,000.2			
					Gastro	1,000.2			
					Hemato	1,000.2			
					Hepatic	1,000.2			
					Renal	1,000.2			
					Immuno	1,000.2			
					Neuro	1,000.2			

[Note: On day 10, the low exposure level was increased from 51.3 to 1,488.5 ppm; TWA concentration of 1,129.2 ppm]

Table 2-1. Levels of Significant Exposure to Vinyl Acetate – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Hazleton 1980c									
14	Rat (Sprague-Dawley) 10 M, 10 F	3 months 5 days/week 6 hours/day (WB)	0, 51.1, 199.9, 998.9	LE, CS, BW, HE, UR, OW, OP, GN, HP	Bd wt	199.9		998.9	Decreased body weight (19% in males, 22% in females); decreased body weight gain (28% in males, 44% in females)
					Resp	199.9		998.9	Intermittent respiratory distress, focal histiocytic alveolitis
					Cardio	998.9			
					Gastro	998.9			
					Hemato	998.9			
					Hepatic	998.9			
					Renal	998.9			
					Ocular	998.9			
					Immuno	998.9			
					Neuro	998.9			
					Repro	998.9			
Krieger et al. 2020									
15	Rat (Sprague-Dawley) 21 M	4 weeks 5 days/week 6 hours/day (WB)	0, 50.4, 201.6, 604.8, 1,009.7	LE, CS, BW, HP	Bd wt	604.8	1,009.7		16% decrease in body weight and 52% decrease in body weight gain with 25% decrease in food consumption
					Resp	201.6	604.8		Slight-to-marked atrophy of the olfactory epithelium; slight respiratory metaplasia of nasal tissue

Table 2-1. Levels of Significant Exposure to Vinyl Acetate – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Krieger et al. 2020									
16	Rat (Sprague-Dawley) 21 M	13 weeks 5 days/week 6 hours/day (WB)	0, 50.4, 201.6, 604.8, 1,009.7	LE, CS, BW, HP	Bd wt	201.6	604.8		15% decrease in body weight and 29% decrease in body weight gain with 14% decrease in food consumption
					Resp	201.6	604.8		Slight-to-marked atrophy and necrosis/degeneration of the olfactory epithelium; slight respiratory metaplasia of nasal tissue
Hazleton 1979b									
17	Mouse (CD-1) 5 M, 5 F	4 weeks 5 day/week 6 hours/day (WB)	0, 51.3/1488.7, 150.5, 497.6, 1,000.2	LE, CS, BW, HE, OW, GN	Bd wt	497.6 M 1,000.2 F	1,000.2 M		16% decrease in body weight
					Resp	150.5		497.6	Intermittent respiratory distress
					Cardio	1,000.2			
					Gastro	1,000.2			
					Hemato	1,000.2			
					Hepatic	1,000.2			
					Renal	1,000.2			
					Immuno	1,000.2			
					Neuro	1,000.2			

[Note: On day 8, the low exposure level was increased from 51.3 to 1,497.6 ppm, for a TWA concentration of 1,136.0 ppm]

Table 2-1. Levels of Significant Exposure to Vinyl Acetate – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Hazleton 1980b									
18	Mouse (CD-1) 10 M, 10 F	3 months 5 days/week 6 hours/day (WB)	0, 51.1, 199.8, 998.6	LE, CS, BW, BC, HE, OW, GN, HP	Death			998.6	9/20 died during orbital sinus blood sampling procedure (increased susceptibility to anesthesia)
					Bd wt	199.8		998.6	Decreased body weight (24% in males, 20% in females); decreased body weight gain (60% in males, 50% in females)
					Resp	199.8		998.6	Intermittent respiratory distress, increased absolute (10–20%) and relative (48–55%) lung weight, focal and diffuse rhinitis, mild multifocal bronchitis, hyperplasia, and metaplasia of the upper respiratory tract
					Cardio	998.6			
					Gastro	998.6			
					Hemato	998.6			
					Hepatic	998.6			
					Renal	998.6			
					Immuno	998.6			
					Neuro	998.6			
					Repro	998.6			

Table 2-1. Levels of Significant Exposure to Vinyl Acetate – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
CHRONIC EXPOSURE									
Bogdanffy et al. 1994a; Hazleton 1988									
19	Rat (Sprague-Dawley) 60 M, 60 F	104 weeks 5 days/week 6 hours/day (WB)	0, 49.4, 200.5, 594.7	LE, CS, BW, BC, HE, UR, OW, GN, HP	Bd wt	200.5 F 594.7 M	594.7 F		14% decrease in terminal body weight
					Resp	49.4[d]	200.5	594.7	LOAEL: Slight-to-moderate nonneoplastic lesions in the olfactory epithelium Serious LOAEL: Moderate-to-severe nasal and lung lesions
					Cardio	594.7			
					Gastro	594.7			
					Hemato	594.7			
					Musc/skel	594.7			
					Hepatic	594.7			
					Renal	594.7			
					Dermal	594.7			
					Ocular	594.7			
					Endocr	594.7			
					Immuno	594.7			
					Neuro	594.7			
					Repro	594.7			
					Cancer			594.7 M	CEL: Nasal cavity tumors (inverted papilloma, squamous cell carcinoma, carcinoma in situ)
Bogdanffy et al. 1994a; Hazleton 1988									
20	Mouse (Crl:CD-1(ICR)BR) 60 M, 60 F	104 weeks 5 days/week 6 hours/day (WB)	0, 49.4, 200.5, 594.7	LE, CS, BW, BC, HE, OW, GN, HP	Bd wt	200.5	594.7		11–15% decrease in terminal body weight
					Resp	49.4	200.5		Nonneoplastic nasal lesions at ≥200.5 ppm; lung lesions and epithelial hyperplasia of the trachea and bronchi at 594.7 ppm

Table 2-1. Levels of Significant Exposure to Vinyl Acetate – Inhalation (ppm)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Cardio	594.7			
					Gastro	594.7			
					Hemato	594.7			
					Musc/skel	594.7			
					Hepatic	594.7			
					Renal	594.7			
					Dermal	594.7			
					Ocular	594.7			
					Endocr	594.7			
					Immuno	594.7			
					Neuro	594.7			
					Repro	594.7			

Shaded rows indicate the MRL principal studies.

[a]The number corresponds to entries in Figure 2-2; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-2. Where such differences exist, only the levels of effect for the most sensitive sex are presented.
[b]Used to derive an acute-duration MRL of 1 ppm; a human equivalent concentration of 29.1 ppm for continuous exposure was calculated using a PBPK model developed by Bogdanffy et al. (1999) and Hinderliter et al. (2005) and divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustment and 10 for human variability); see Appendix A for more detailed information regarding the MRL.
[c]Used to derive an intermediate-duration MRL of 0.7 ppm; a human equivalent concentration of 21.6 ppm for continuous exposure was calculated using a PBPK model developed by Bogdanffy et al. (1999) and Hinderliter et al. (2005) and divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustment and 10 for human variability); see Appendix A for more detailed information regarding the MRL.
[d]Used to derive a chronic-duration MRL of 0.3 ppm; a human equivalent concentration of 8.52 ppm for continuous exposure was calculated using a PBPK model developed by Bogdanffy et al. (1999) and Hinderliter et al. (2005) and divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustment and 10 for human variability); see Appendix A for more detailed information regarding the MRL.

BC = blood chemistry; Bd wt or BW = body weight; Cardio = cardiovascular; CEL = cancer effect level; CS = clinical signs; Develop = developmental; Endocr = endocrine; F = female(s); FI = food intake; Gastro = gastrointestinal; GD = gestation day; GN = gross necropsy; HE = hematology; Hemato = hematological; HP = histopathology; Immuno = immunological; LC_{50} = concentration producing 50% death; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); MRL = Minimal Risk Level; Musc/skel = muscular/skeletal; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; OP = ophthalmology; OW = organ weight; PBPK = physiologically based pharmacokinetic; Repro = reproductive; Resp = respiratory; TWA = time-weighted average; UR = urinalysis; (WB) = whole body; WI = water intake

Figure 2-2. Levels of Significant Exposure to Vinyl Acetate – Inhalation Acute (≤14 days)

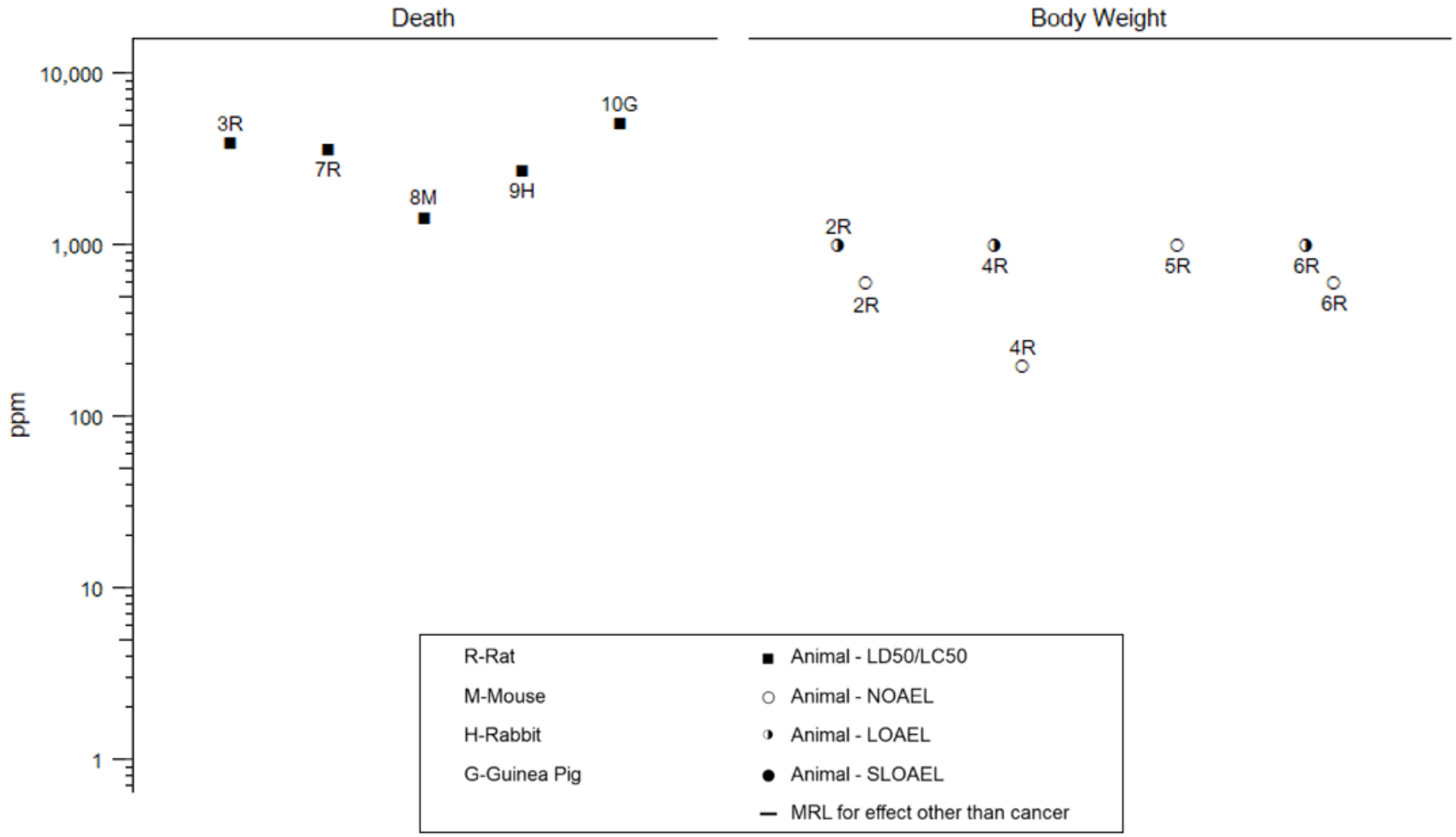


Figure 2-2. Levels of Significant Exposure to Vinyl Acetate – Inhalation Acute (≤14 days)

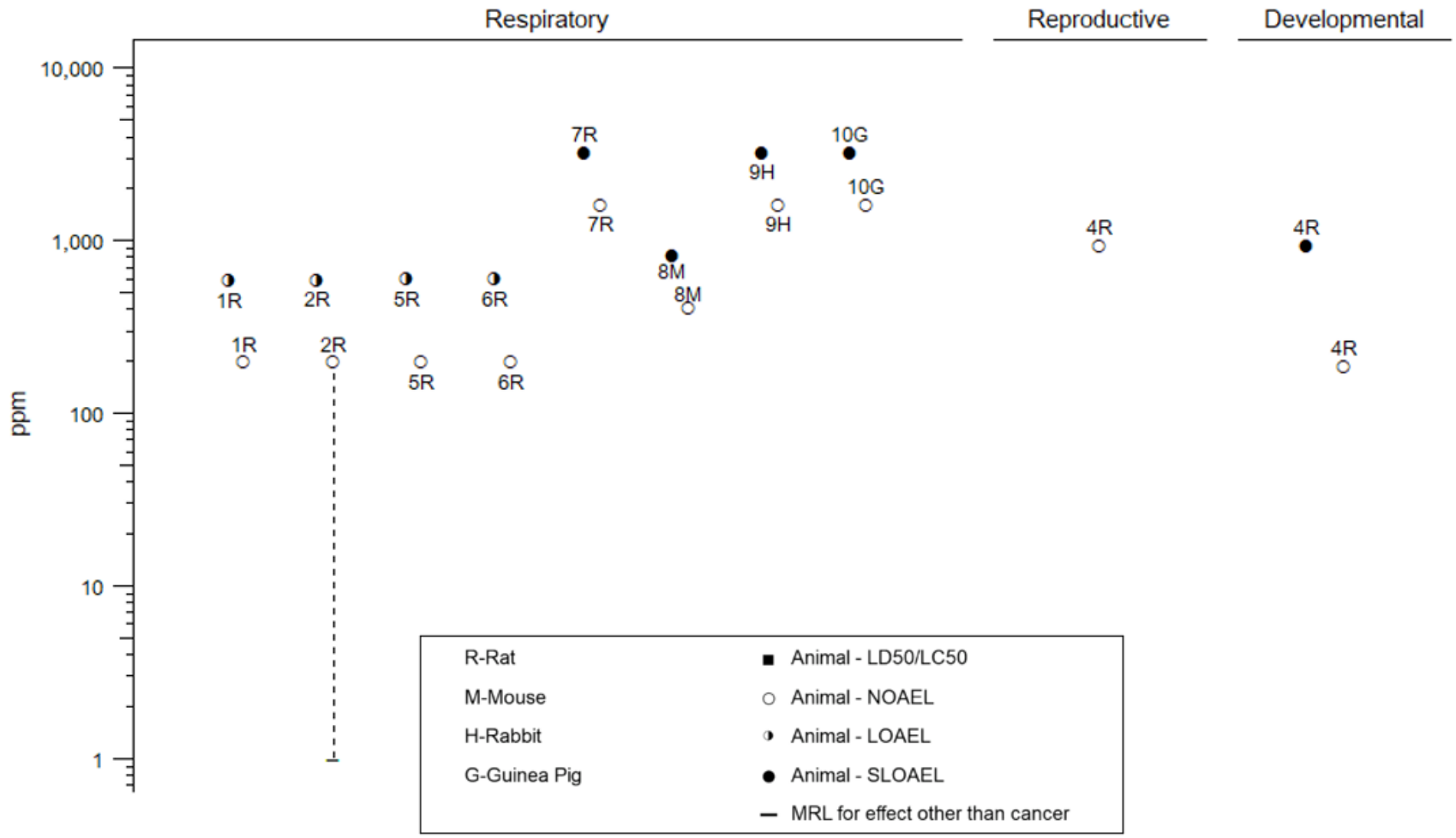


Figure 2-2. Levels of Significant Exposure to Vinyl Acetate – Inhalation Intermediate (15–364 days)

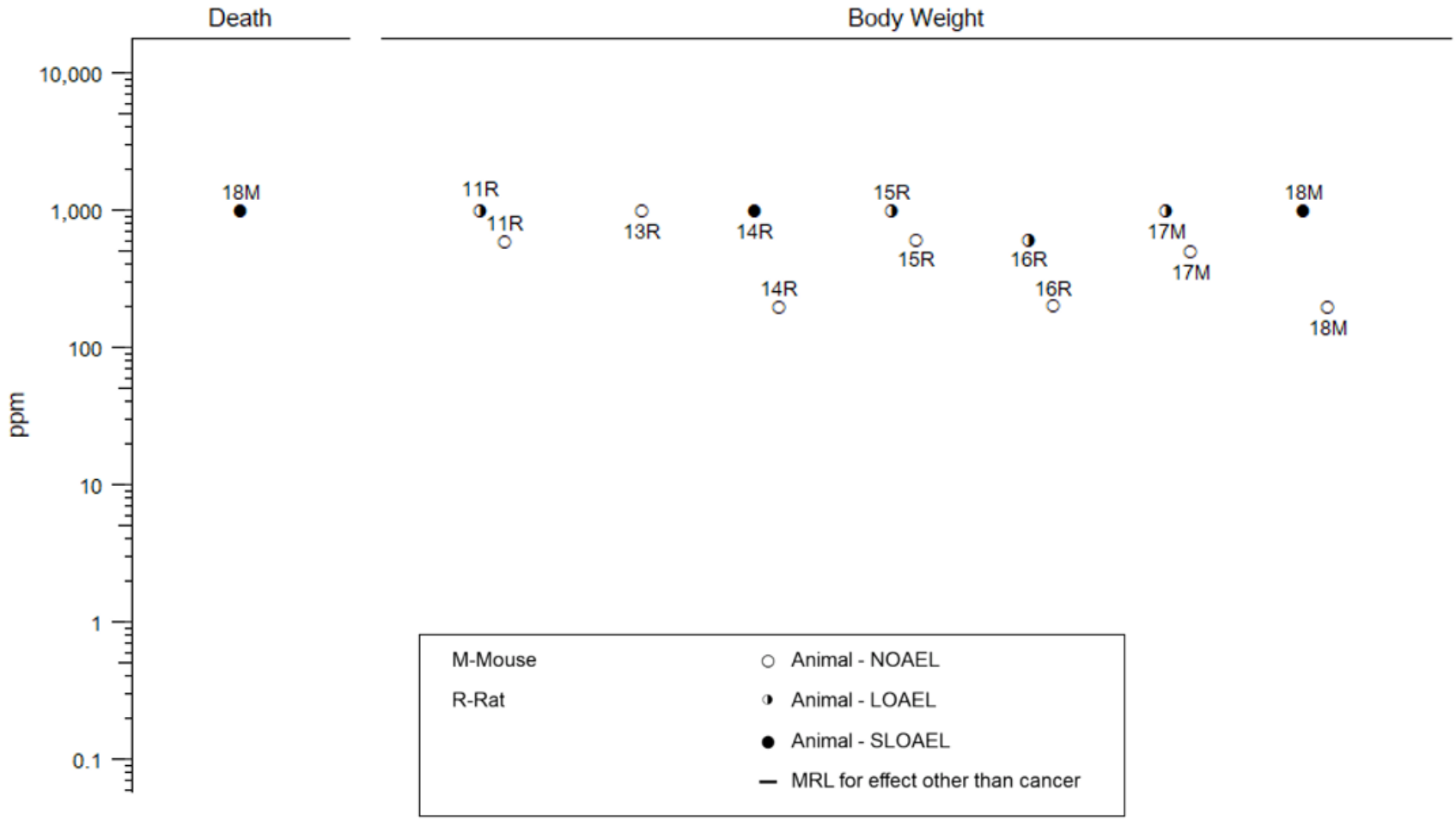


Figure 2-2. Levels of Significant Exposure to Vinyl Acetate – Inhalation Intermediate (15–364 days)

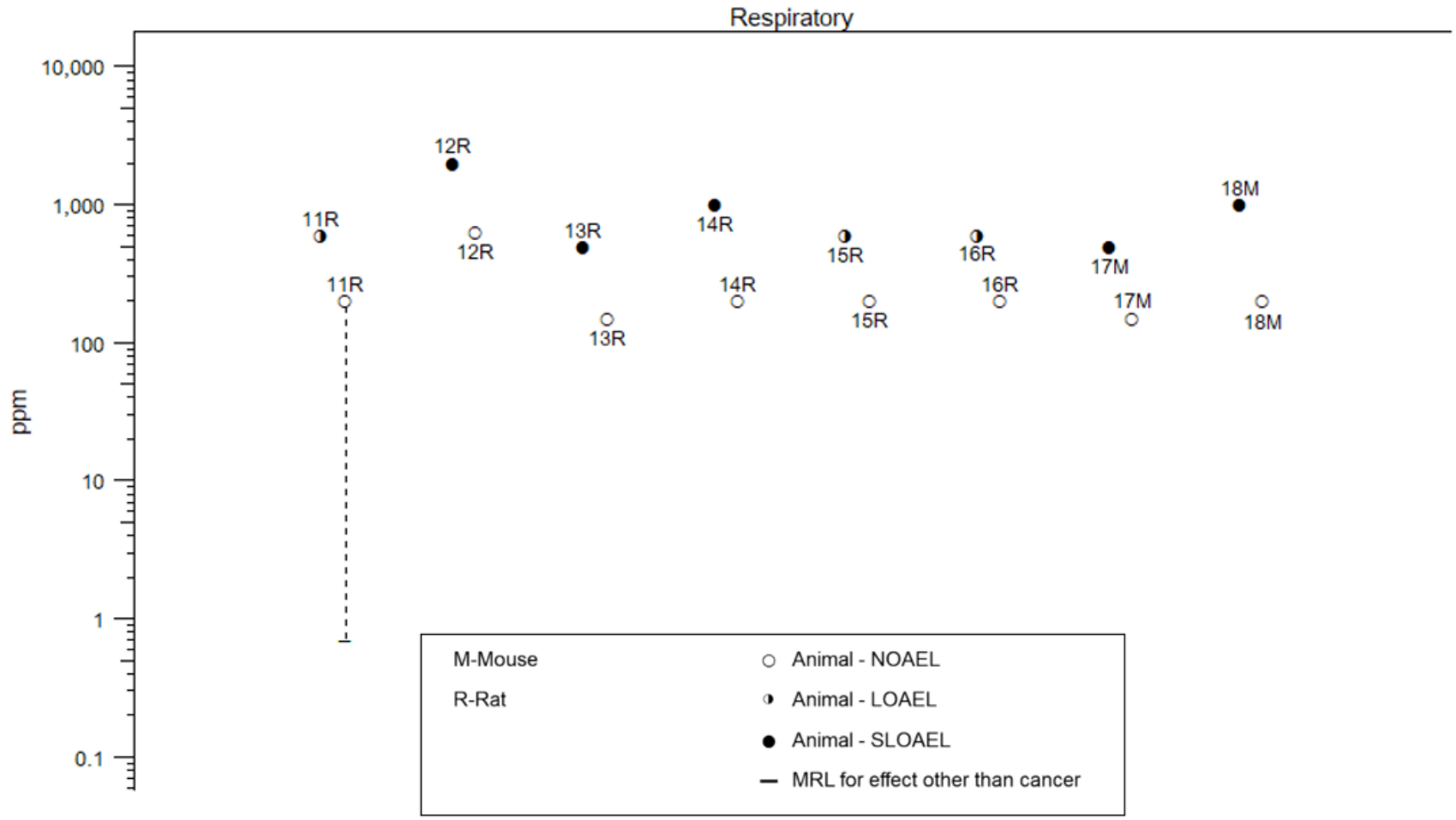


Figure 2-2. Levels of Significant Exposure to Vinyl Acetate – Inhalation Intermediate (15–364 days)

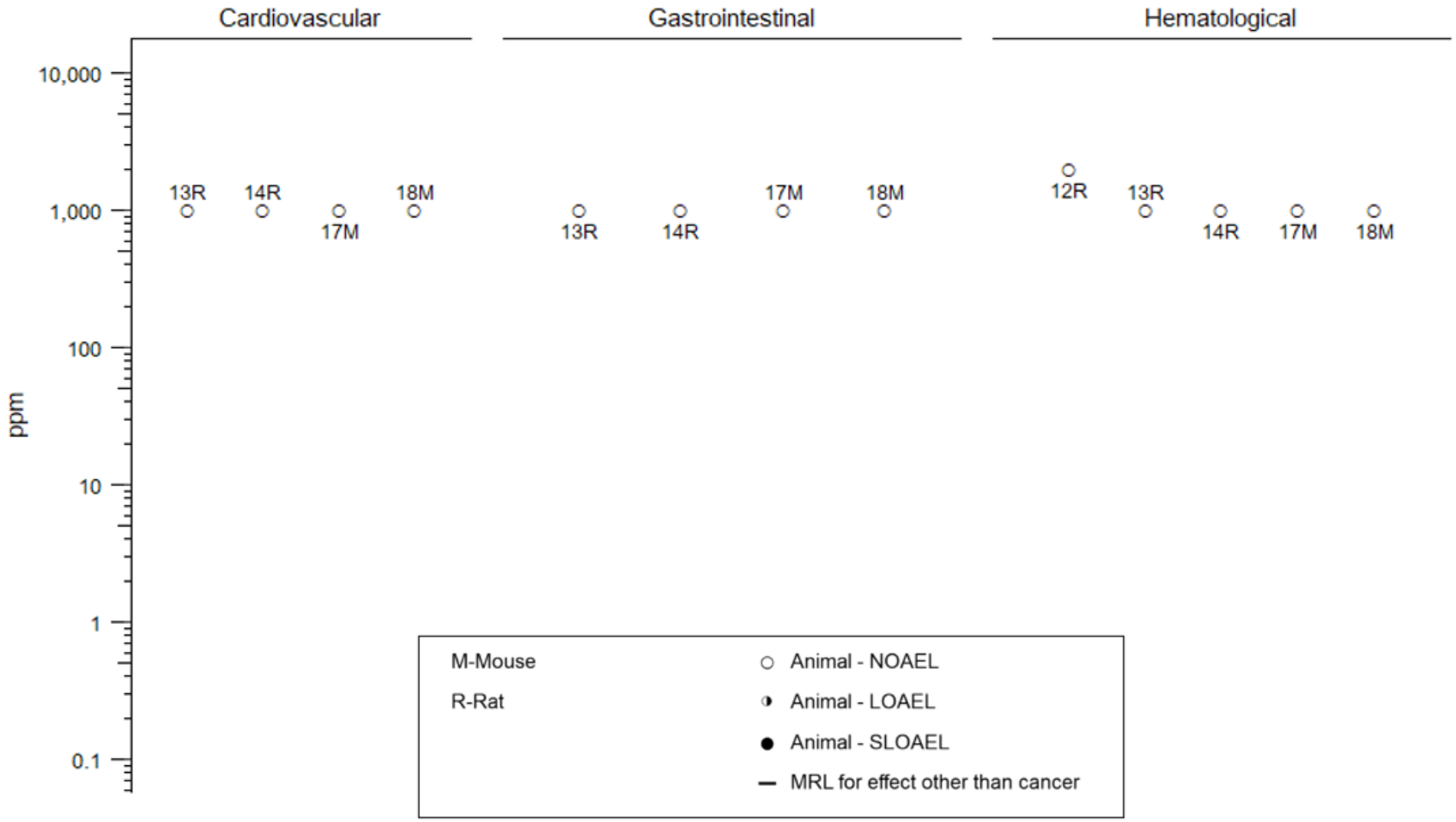


Figure 2-2. Levels of Significant Exposure to Vinyl Acetate – Inhalation Intermediate (15-364 days)

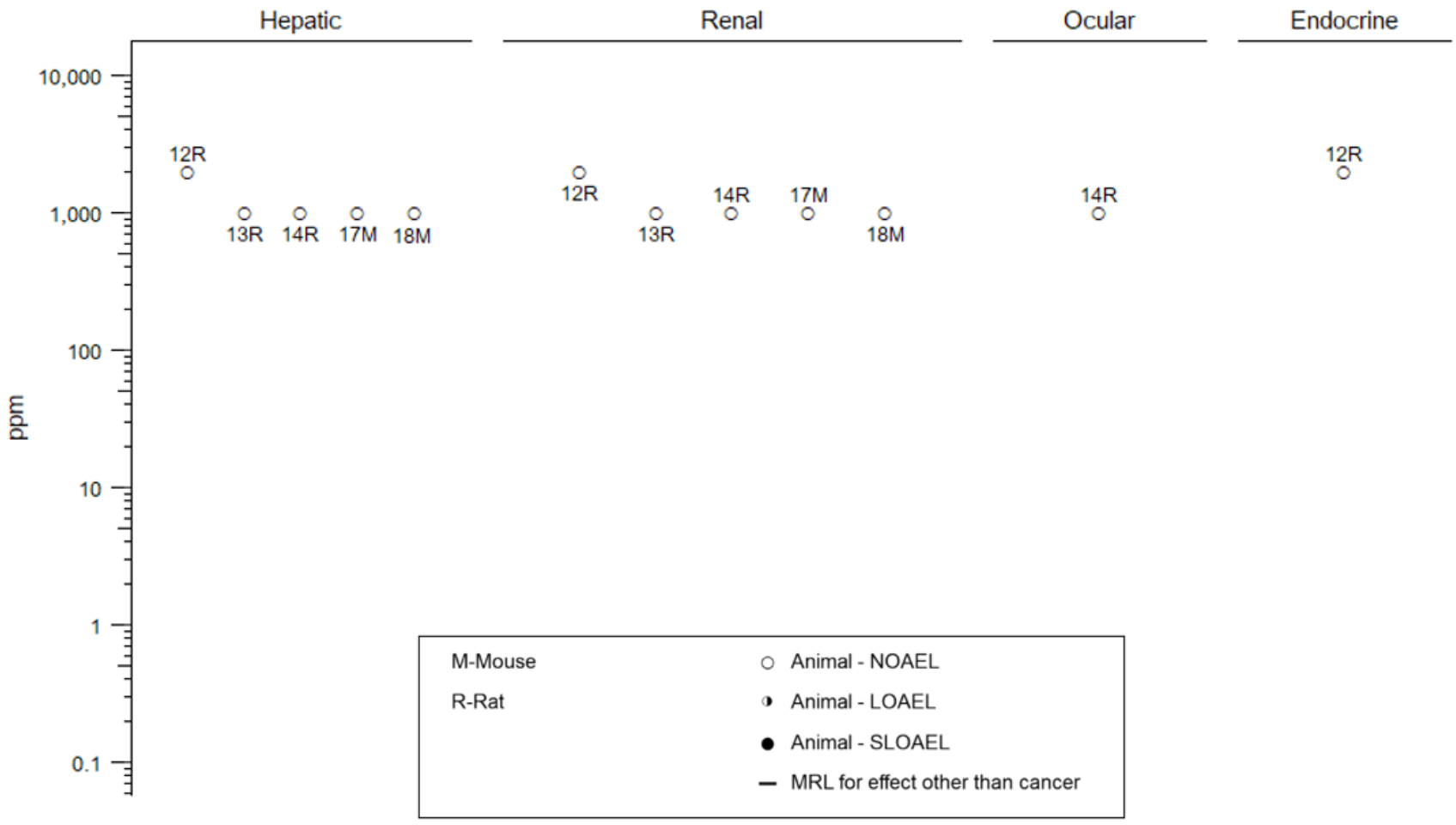


Figure 2-2. Levels of Significant Exposure to Vinyl Acetate – Inhalation Intermediate (15-364 days)

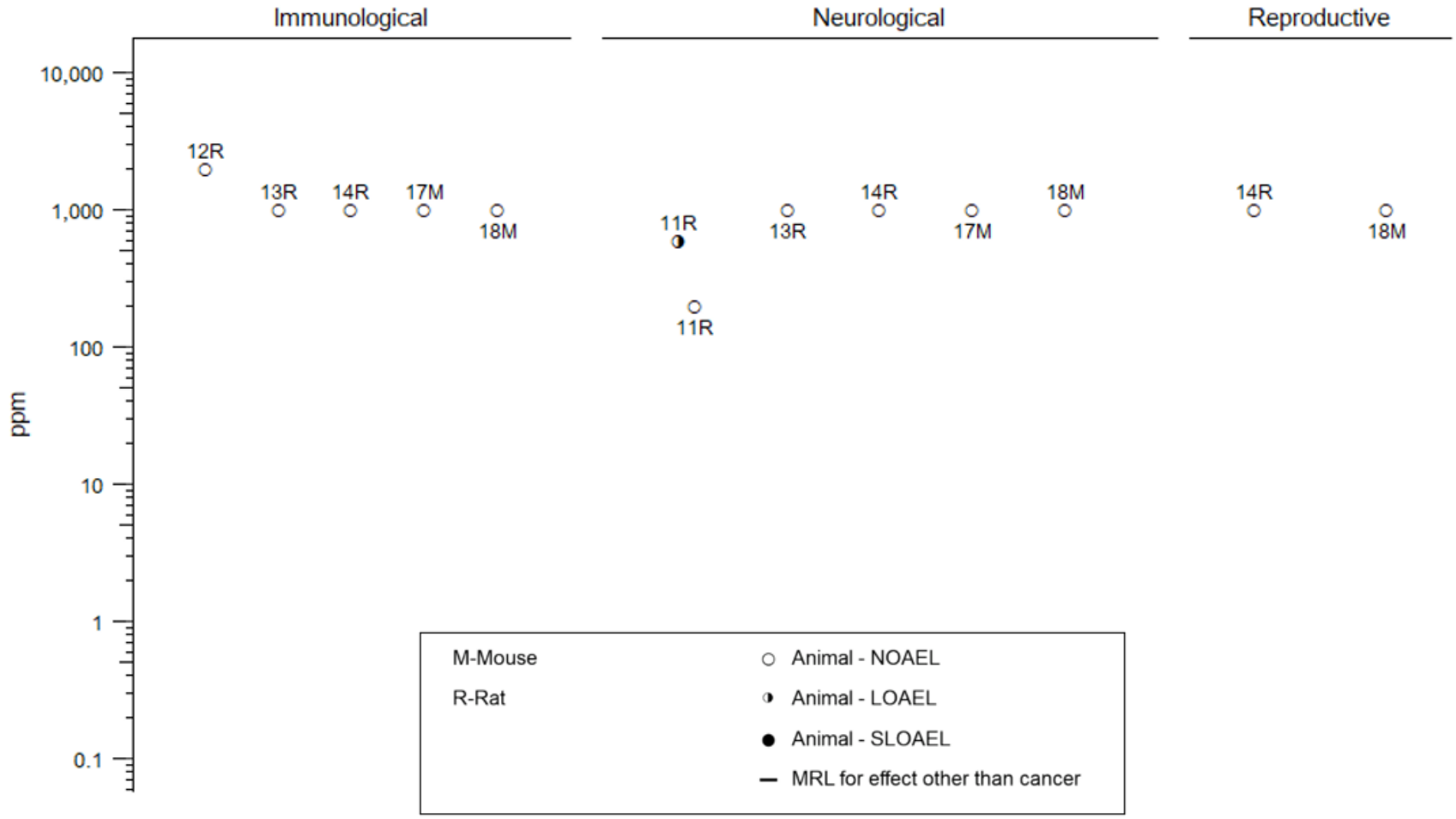


Figure 2-2. Levels of Significant Exposure to Vinyl Acetate – Inhalation Chronic (≥365 days)

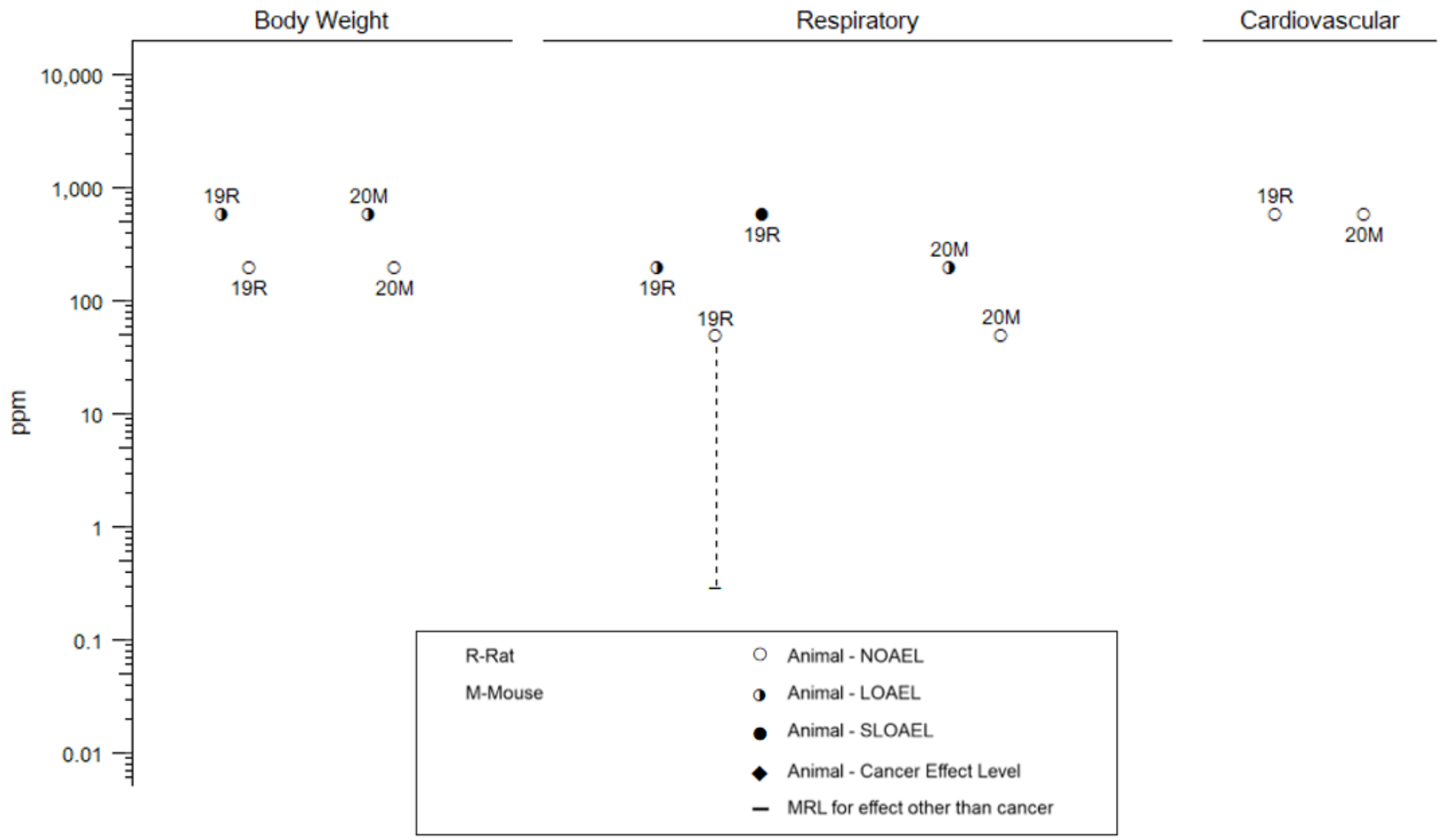


Figure 2-2. Levels of Significant Exposure to Vinyl Acetate – Inhalation Chronic (≥365 days)

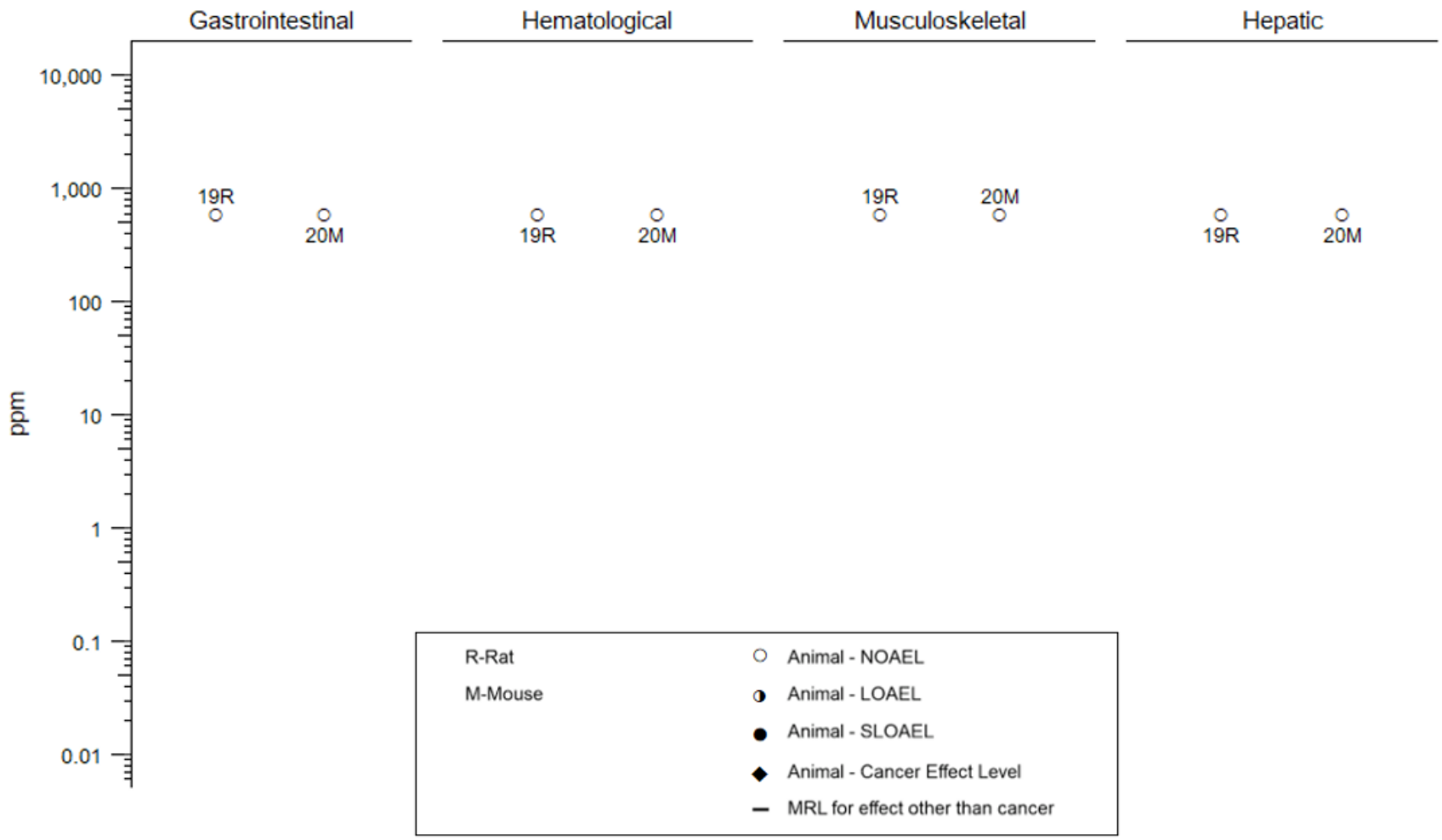


Figure 2-2. Levels of Significant Exposure to Vinyl Acetate – Inhalation Chronic (≥365 days)

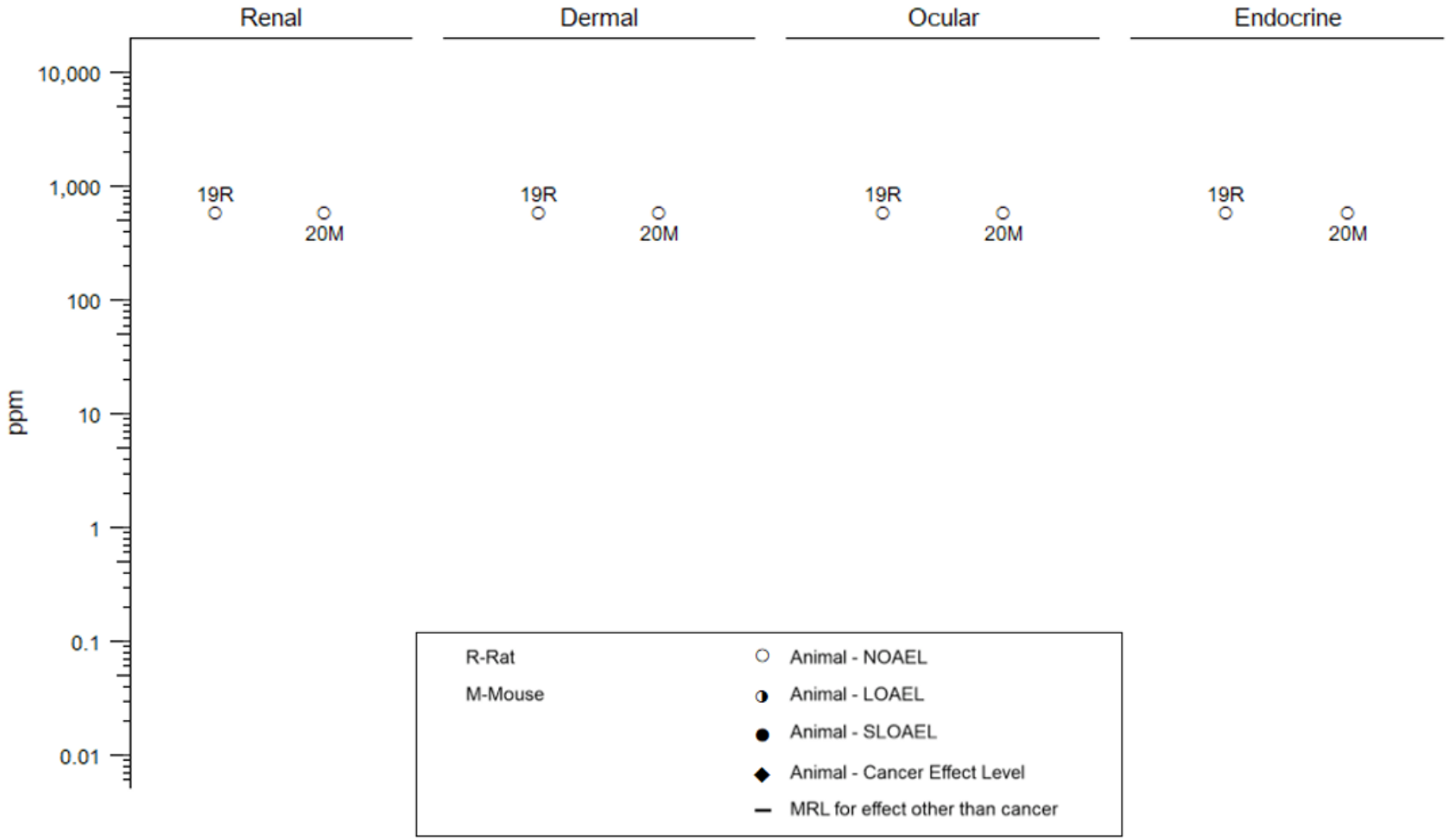
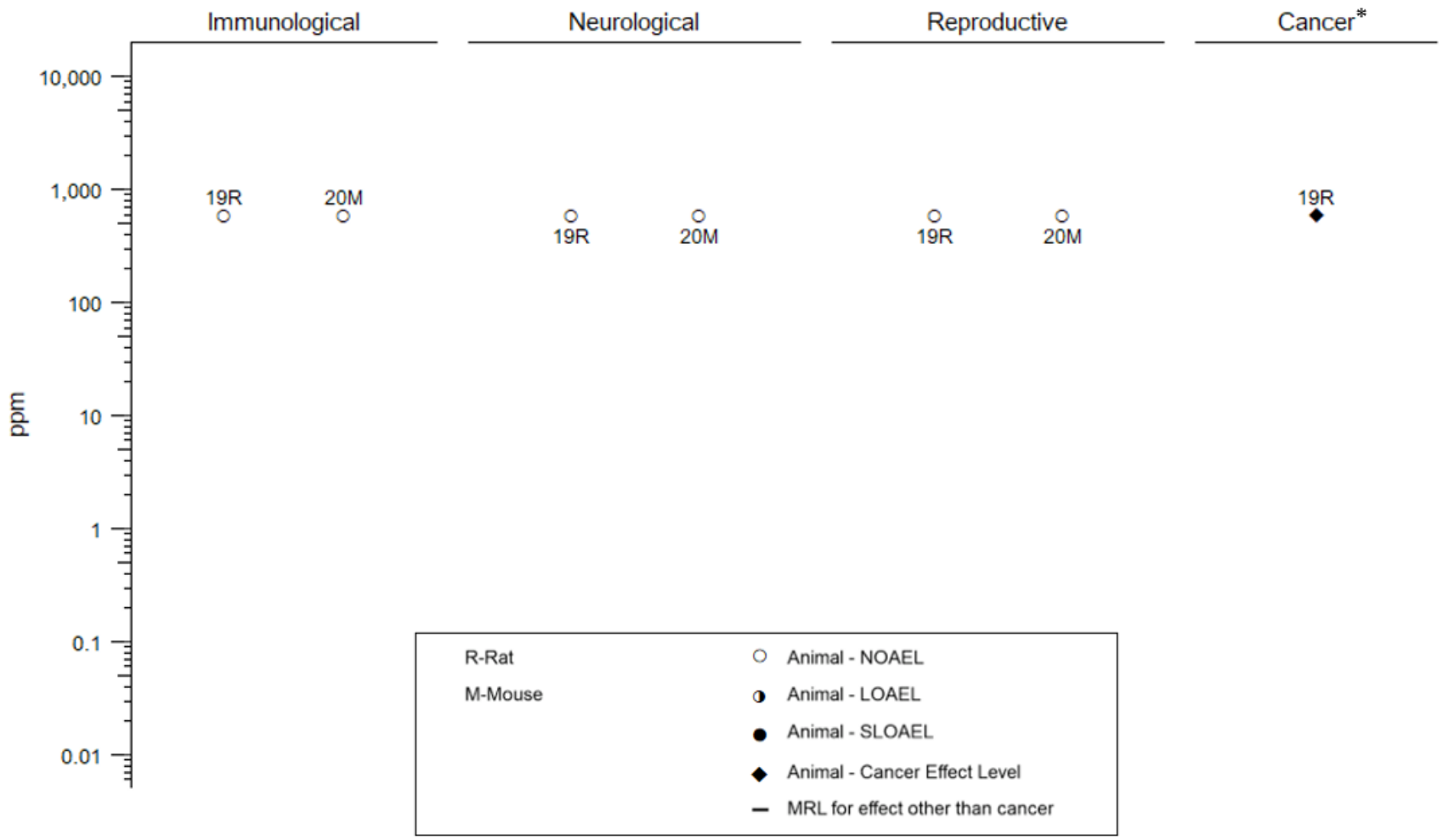


Figure 2-2. Levels of Significant Exposure to Vinyl Acetate – Inhalation Chronic (≥365 days)



*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 endpoint.

Table 2-2. Levels of Significant Exposure to Vinyl Acetate – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE									
Hurtt et al. 1995									
1	Rat (Sprague-Dawley) 21–23 F	10 days GDs 6–15 (W)	0, 28, 124, 477	CS, BW, WI, GN, HP, RX, DX	Bd wt Repro Develop	477 477 477			
Smyth and Carpenter 1948									
2	Rat (Sherman) 6 NS	Once (NS)	Not reported	LE	Death			2,920	LD_{50}
Valentine et al. 2002									
3	Rat (Fischer-344) 5 M	8 days (W)	0, 81, 350, 660, 1,400	CS, BW, FI, WI, BI, HP	Bd wt Gastro	1,400 1,400			
Valentine et al. 2002									
4	Rat (Fischer-344) 5 M	1 day (W)	0, 81, 350, 660, 1,400	CS, BW, FI, WI, BI, HP	Bd wt Gastro	1,400 1,400			
Valentine et al. 2002									
5	Mouse (BDF1) 5 M	8 days (W)	0, 250, 1,200, 2,300, 5,300	CS, BW, FI, WI, BI, HP	Bd wt Gastro	5,300 5,300			
Valentine et al. 2002									
6	Mouse (BDF1) 5 M	1 day (W)	0, 250, 1,200, 2,300, 5,300	CS, BW, FI, WI, BI, HP	Bd wt Gastro	5,300 5,300			

Table 2-2. Levels of Significant Exposure to Vinyl Acetate – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
INTERMEDIATE EXPOSURE									
Hazleton 1979d									
7	Rat (Sprague-Dawley) 5 M, 5 F	4 weeks (W)	M: 0, 8/849, 29, 139, 628 F: 0, 9/929, 34, 146, 755	BW, FI, WI, GN, OW, HP	Bd wt	628 M 755 F			
					Resp	628 M 755 F			
					Cardio	628 M 755 F			
					Gastro	628 M 755 F			
					Hemato	628 M 755 F			
					Hepatic	628 M 755 F			
					Renal	628 M 755 F			
					Immuno	628 M 755 F			
					Neuro	628 M 755 F			
[Note: The low-dose males received 8 mg/kg/day for 3 weeks and 849 mg/kg/day for 1 week; TWA dose of 218 mg/kg/day. The low-dose females received 9 mg/kg/day for 3 weeks and 929 mg/kg/day for 1 week; TWA dose of 239 mg/kg/day]									
Hazleton 1980f									
8	Rat (Sprague-Dawley) 10 M, 10 F	3 months (W)	M: 0, 31, 163, 684 F: 0, 36, 193, 810	CS, BW, WI, BC, UR, GN, OW, HP	Bd wt	684 M 810 F			
					Resp	684 M 810 F			
					Cardio	684 M 810 F			
					Gastro	684 M 810 F			

Table 2-2. Levels of Significant Exposure to Vinyl Acetate – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Hemato	684 M 810 F			
					Hepatic	684 M 810 F			
					Renal	684 M 810 F			
					Ocular	684 M 810 F			
					Immuno	684 M 810 F			
					Neuro	684 M 810 F			
					Repro	684 M 810 F			
Mebus et al. 1995									
9	Rat (Sprague-Dawley) F0: 18 M, 36 F F1: 25 M, 25 F	14–18 weeks per generation; 2 generations (W)	M: 0, 23, 108, 471 F: 0, 36, 165, 697	BW, WI, HP, RX, DX	Bd wt	471 M 36 F		165 F	37% decrease in F1 body weight gain during lactation with 14% decreased in water intake
					Resp	471 M 697 F			
					Endocr	471 M 697 F			
					Repro	471 M 697 F			
					Develop	165		697	10% decrease in F1 weanling body weight on PND 21 with decreased maternal water intake
Valentine et al. 2002									
10	Rat (Fischer-344) 5 M	29 days (W)	0, 81, 350, 660, 1,400	CS, BW, FI, WI, BI, HP	Bd wt	1,400			
					Gastro	1,400			

Table 2-2. Levels of Significant Exposure to Vinyl Acetate – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Valentine et al. 2002									
11	Rat (Fischer-344) 5 M	92 days (W)	0, 81, 350, 660, 1,400	CS, BW, FI, WI, BI, HP	Bd wt	1,400			
					Gastro	1,400			
Hazleton 1979d									
12	Mouse (CD-1) 5 M, 5 F	4 weeks (W)	M: 0, 10/1,651, 28, 178, 1,040	BW, FI, WI, GN, OW, HP	Bd wt	178 M	1,040 M		13% decrease in body weight on day 26 with 9% decrease in water intake on days 1–14
						1,023 F			
			F: 0, 11/2,115, 31, 215, 1,023		Resp	1,023			
					Cardio	1,023			
					Gastro	1,023			
					Hemato	1,023			
					Hepatic	1,023			
					Renal	1,023			
					Immuno	1,023			
					Neuro	1,023			
[Note: The low-dose males received 10 mg/kg/day for 3 weeks and 1,651 mg/kg/day for 1 week; TWA dose of 420 mg/kg/day. The low-dose females received 11 mg/kg/day for 3 weeks and 2,115 mg/kg/day for 1 week; TWA dose of 537 mg/kg/day.]									
Hazleton 1980e									
13	Mouse (CD-1) 10 M, 10 F	13 weeks (W)	0, 42, 203, 1,016	CS, BW, FI, WI, BC, GN, OW, HP	Bd wt	1,016			
					Resp	1,016			
					Cardio	1,016			
					Gastro	1,016			
					Hemato	1,016			
					Hepatic	1,016			
					Renal	1,016			
					Immuno	1,016			
					Neuro	1,016			
					Repro	1,016			

Table 2-2. Levels of Significant Exposure to Vinyl Acetate – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Valentine et al. 2002									
14	Mouse (BDF1) 5 M	29 days (W)	0, 250, 1,200, 2,300, 5,300	CS, BW, FI, WI, BI, HP	Bd wt	5,300			
					Gastro	5,300			
Valentine et al. 2002									
15	Mouse (BDF1) 5 M	92 days (W)	0, 250, 1,200, 2,300, 5,300	CS, BW, FI, WI, BI, HP	Bd wt	5,300			
					Gastro	2,300			
CHRONIC EXPOSURE									
Belpoggi et al. 2002									
16	Rat (Wistar) F0: 13–14 M, 37 F F1: 64–86 M, 64–86 F	104 weeks 2 generations (W)	0, 130, 640	CS, BW, HP	Death			640 M	18–32% decreased survival in F0 males between exposure weeks 55 and 93
					Bd wt	640			
					Cancer			640	CEL: precursor lesions (dysplasia) and tumors of the upper gastrointestinal tract (oral cavity and lips, tongue, esophagus, forestomach); uterine tumors
Bogdanffy et al. 1994b									
17	Rat (Sprague-Dawley) 60 M, 60 F	104 weeks (W)	M: 0, 10, 47, 202 F: 0, 16, 76, 302	CS, BW, FI, WI, BC, UR OW, HP	Bd wt	47 M	202 M		16% decreased in terminal body weight in males with decrease in food (7–12%) and water (18–34%) intake throughout exposure period
						76 F	302 F		11% decreased in terminal body weight in males with decrease in water intake (19–34%) intake throughout exposure period
					Resp	202 M 302 F			
					Cardio	202 M 302 F			

Table 2-2. Levels of Significant Exposure to Vinyl Acetate – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Gastro	202 M 302 F			
					Hemato	202 M 302 F			
					Musc/skel	202 M 302 F			
					Hepatic	202 M 302 F			
					Renal	202 M 302 F			
					Dermal	202 M 302 F			
					Ocular	202 M 302 F			
					Endocr	202 M 302 F			
					Immuno	202 M 302 F			
					Neuro	202 M 302 F			
					Repro	202 M 302 F			
[Note: exposure began *in utero*]									
Minardi et al. 2002									
18	Rat (Sprague-Dawley) F0: 13–14 M, 37 F F1: 53–107 M, 57–99 F	104 weeks 2 generations (W)	0, 120, 620	CS, BW, HP	Bd wt	620			
					Cancer			120	CEL: precursor lesions (dysplasia) and tumors of the upper gastrointestinal tract (oral cavity and lips, tongue, esophagus, forestomach)

Table 2-2. Levels of Significant Exposure to Vinyl Acetate – Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Maltoni et al. 1997									
19	Mouse (Swiss) F0: 13–14 M, 37 F F1: 37–49 M, 44–48 F	78 weeks 2 generations (W)	0, 240, 1,200	CS, HP	Death			240 M	10–17% decrease in survival of F0 males between exposure weeks 23 and 55
					Cancer			1,200	CEL: precursor lesions (dysplasia) and tumors of the upper gastrointestinal tract (oral cavity, tongue, esophagus, forestomach)

[a]The number corresponds to entries in Figure 2-3; differences in levels of health effects and cancer effects between male and females are not indicated in Figure 2-3. Where such differences exist, only the levels of effect for the most sensitive sex are presented.

BC = blood chemistry; Bd wt or BW = body weight; BI = biochemical changes; Cardio = cardiovascular; CEL = cancer effect level; CS = clinical signs; Develop = developmental; DX = developmental effects; Endocr = endocrine; F = female(s); FI = food intake; Gastro = gastrointestinal; GD = gestation day; GN = gross necropsy; Hemato = hematological; HP = histopathology; Immuno = immunological; LD_{50} = dose producing 50% death; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); Musc/skel = muscular/skeletal; Neuro = neurological; NOAEL = no-observed-adverse-effect level; NS = not specified; OW = organ weight; PND = postnatal day; Repro = reproductive; Resp = respiratory; TWA = time-weighted average; UR = urinalysis; (W) = water; WI = water intake

Figure 2-3. Levels of Significant Exposure to Vinyl Acetate – Oral Acute (≤14 days)

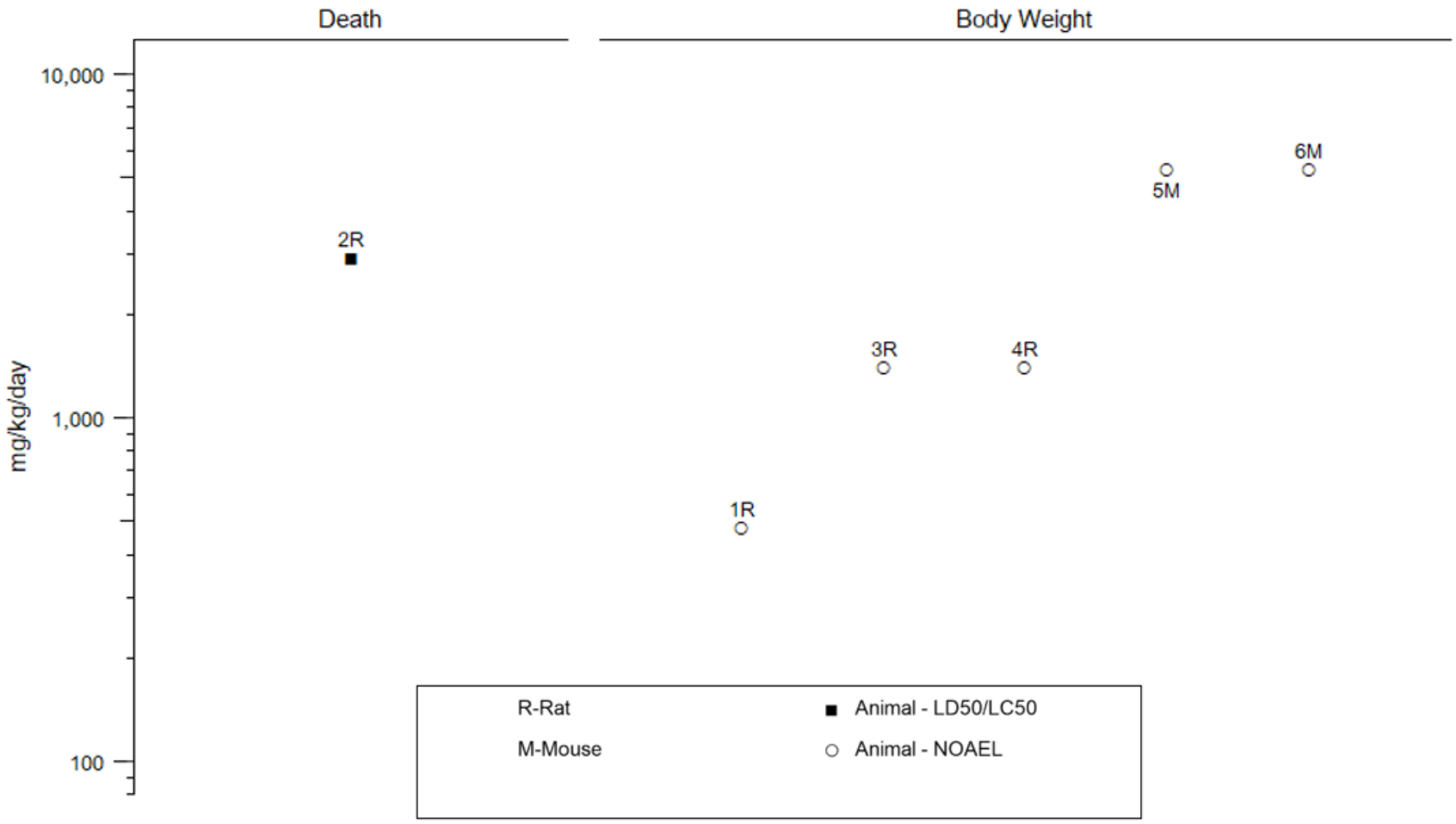


Figure 2-3. Levels of Significant Exposure to Vinyl Acetate – Oral Acute (≤14 days)

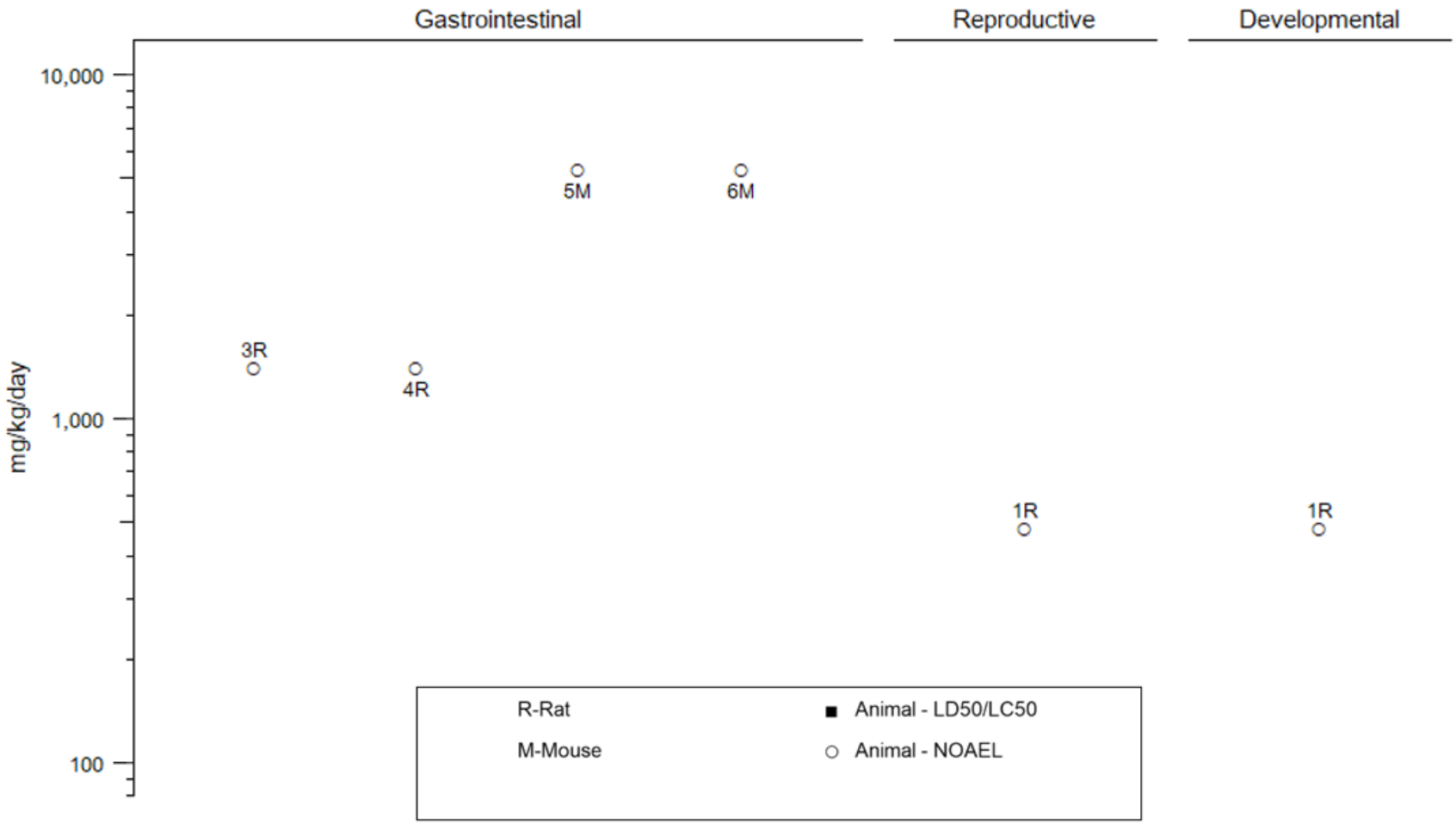


Figure 2-3. Levels of Significant Exposure to Vinyl Acetate – Oral Intermediate (15–364 days)

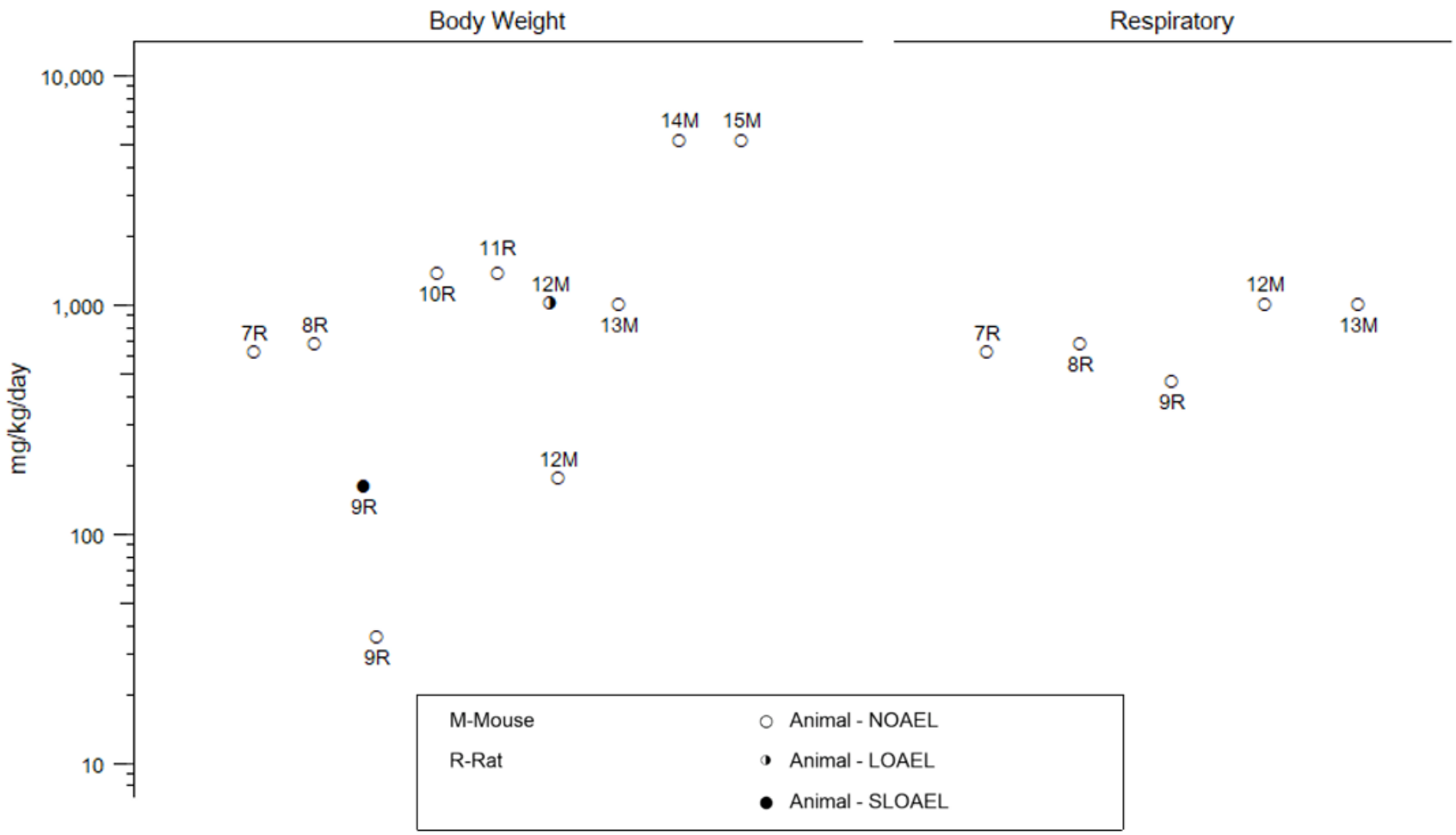


Figure 2-3. Levels of Significant Exposure to Vinyl Acetate – Oral Intermediate (15–364 days)

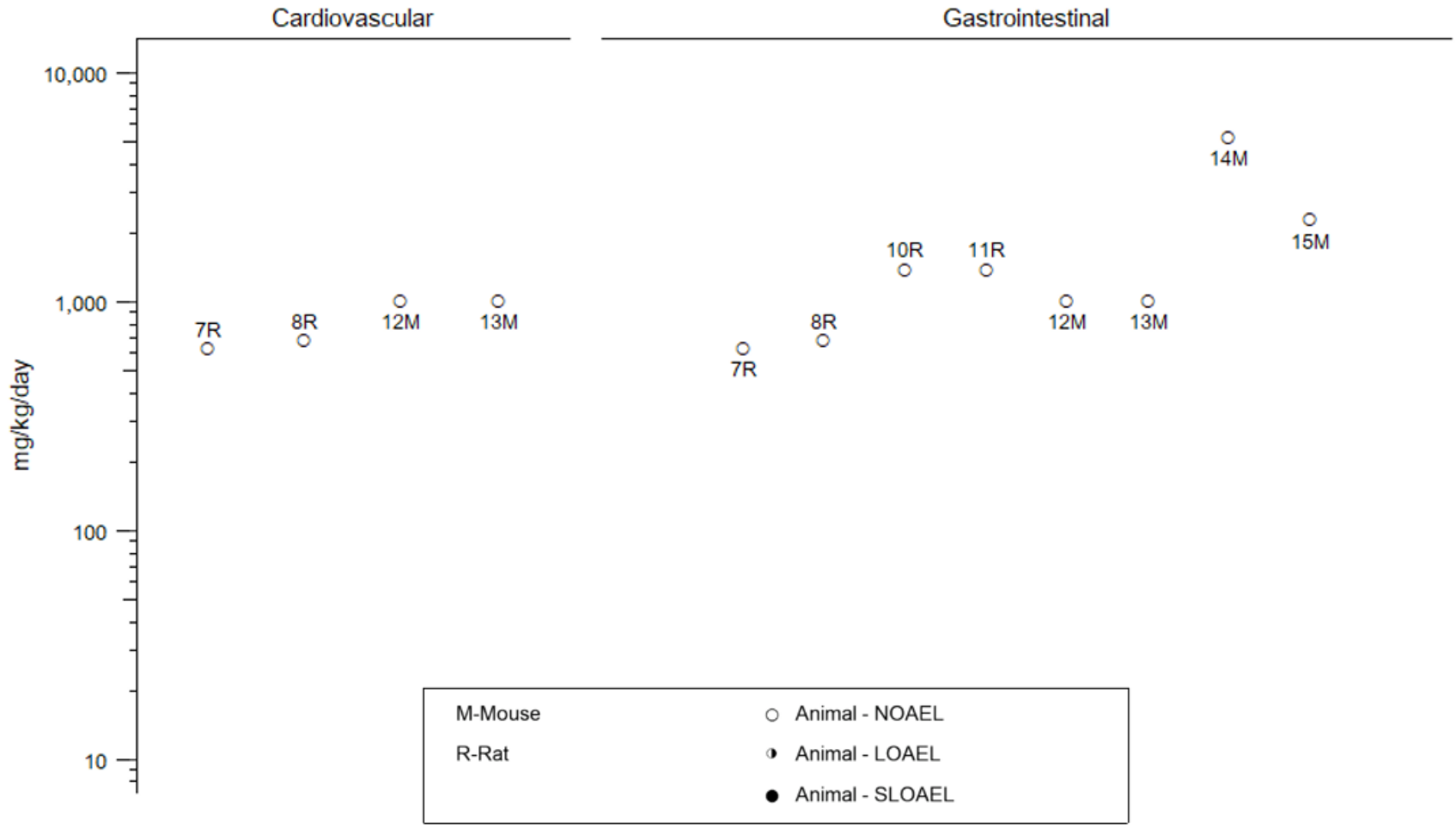


Figure 2-3. Levels of Significant Exposure to Vinyl Acetate – Oral Intermediate (15–364 days)

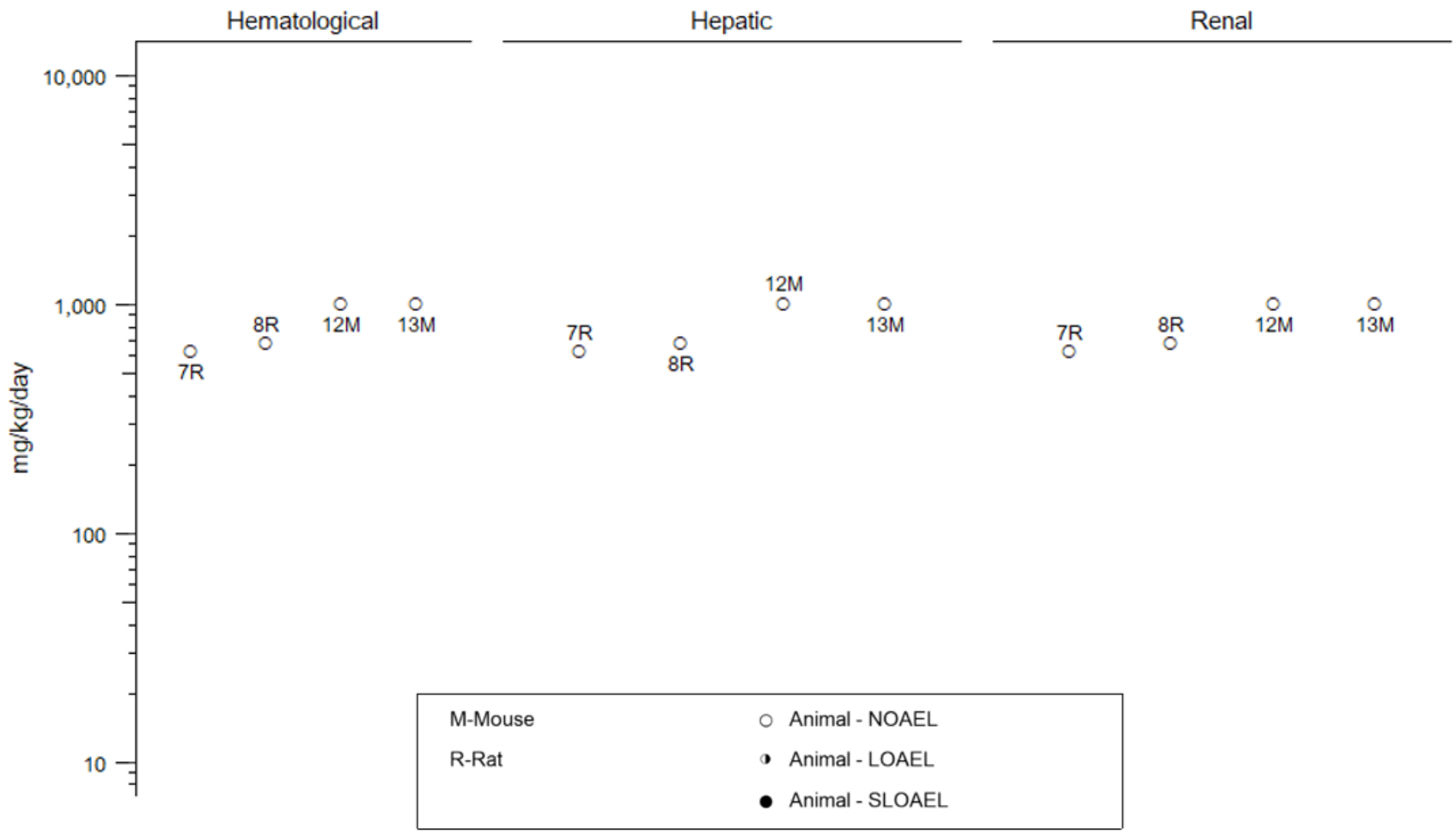


Figure 2-3. Levels of Significant Exposure to Vinyl Acetate – Oral Intermediate (15–364 days)

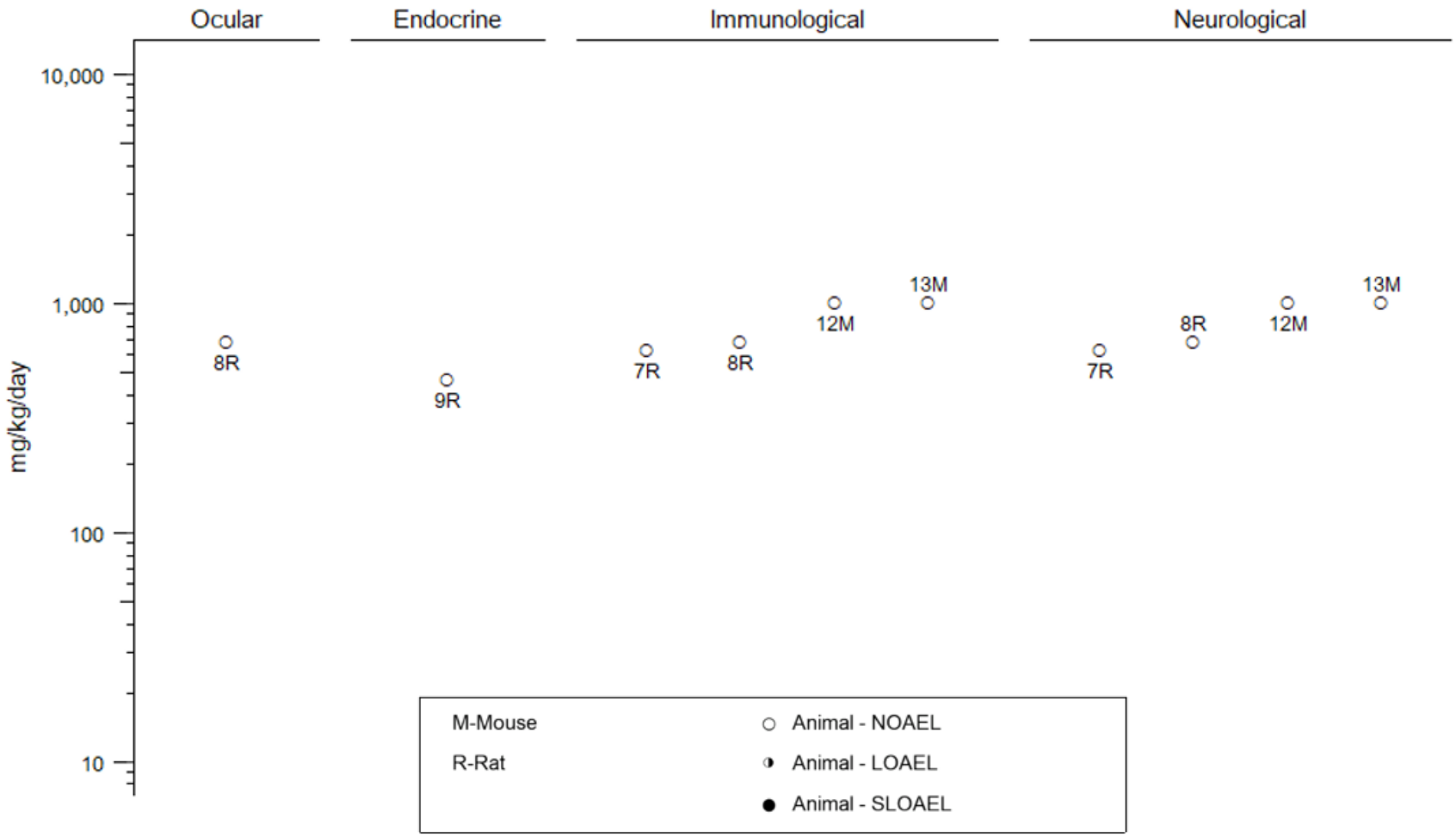


Figure 2-3. Levels of Significant Exposure to Vinyl Acetate – Oral Intermediate (15–364 days)

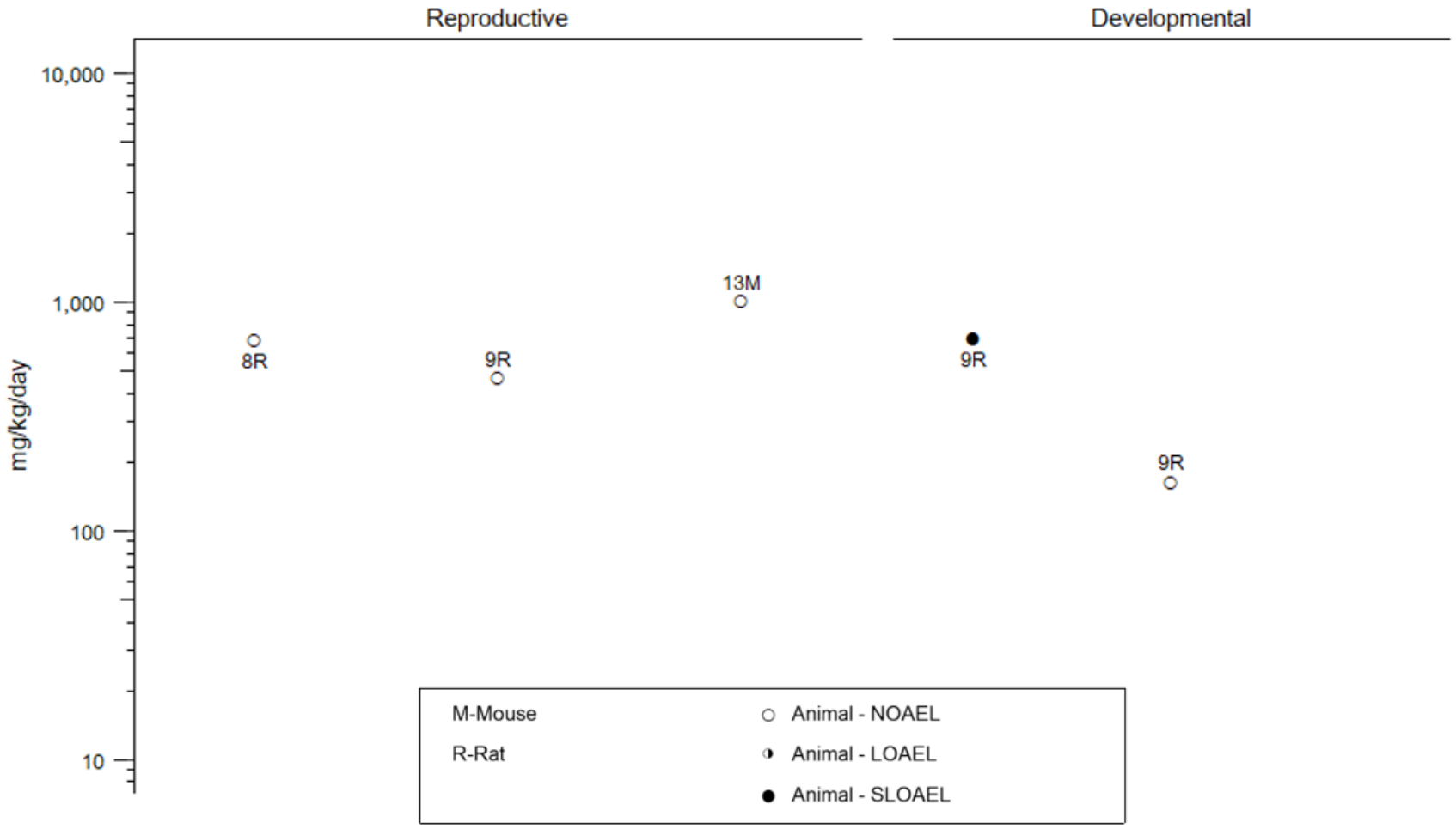


Figure 2-3. Levels of Significant Exposure to Vinyl Acetate – Oral Chronic (≥365 days)

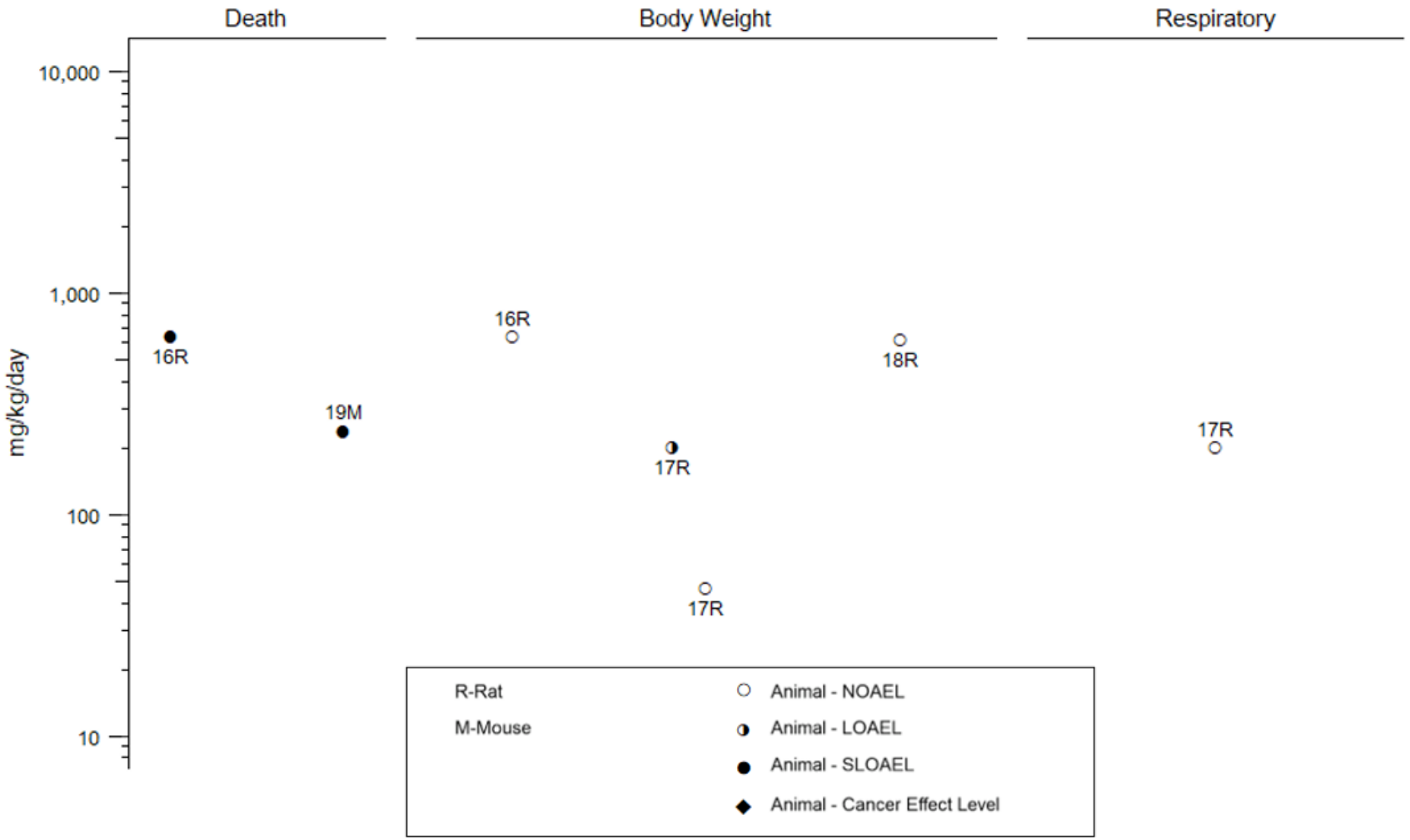


Figure 2-3. Levels of Significant Exposure to Vinyl Acetate – Oral Chronic (≥365 days)

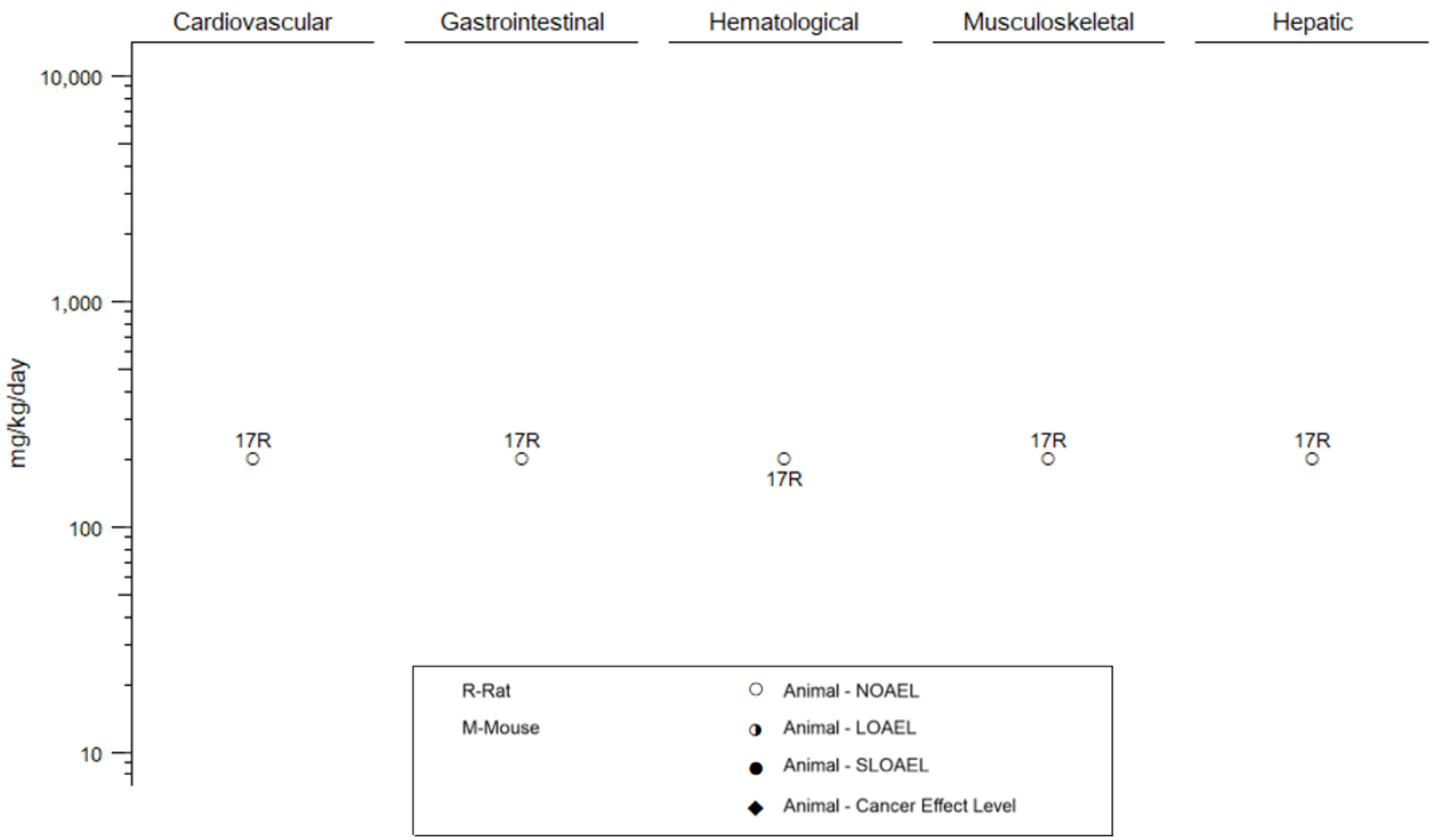


Figure 2-3. Levels of Significant Exposure to Vinyl Acetate – Oral Chronic (≥365 days)

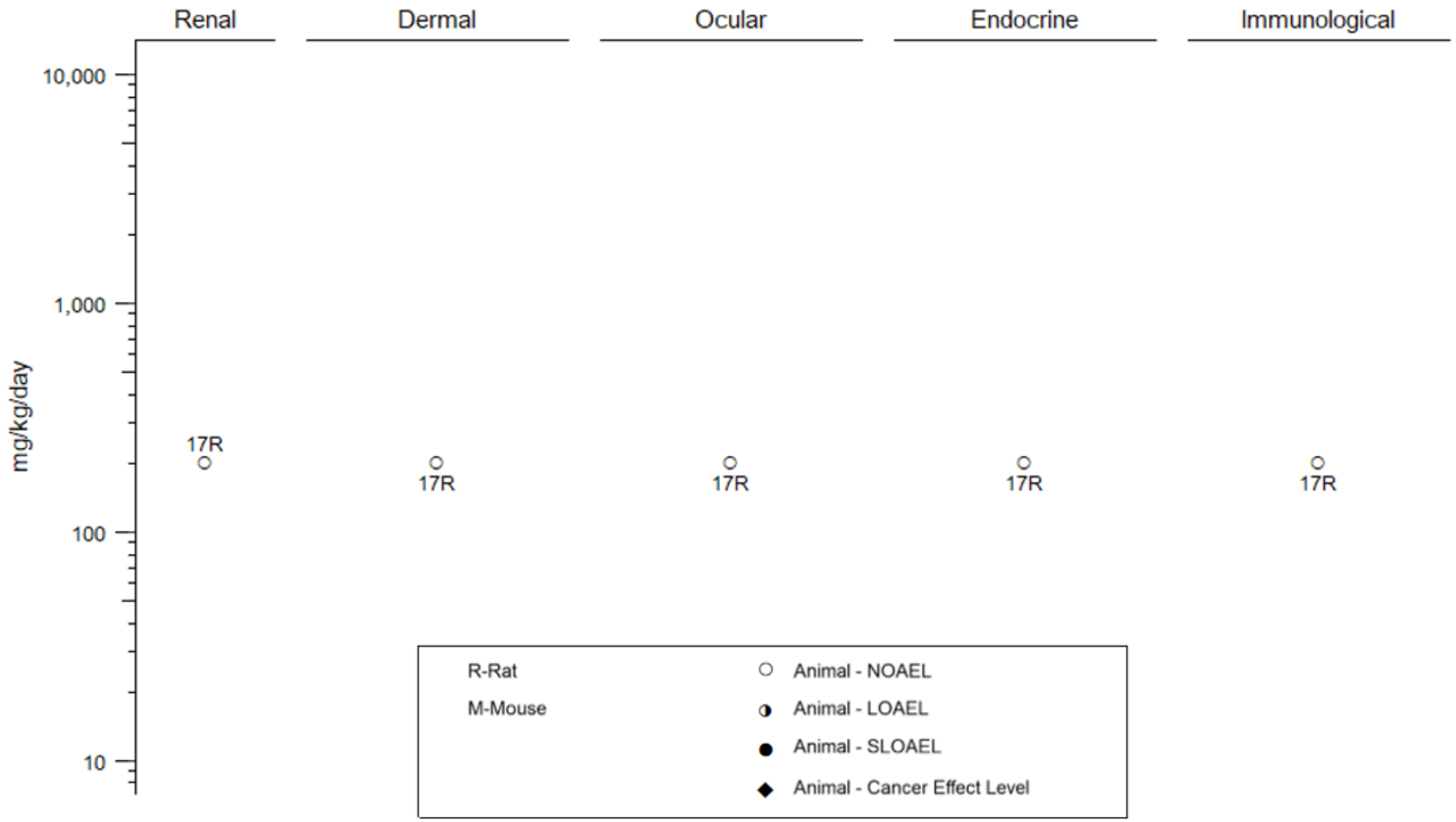
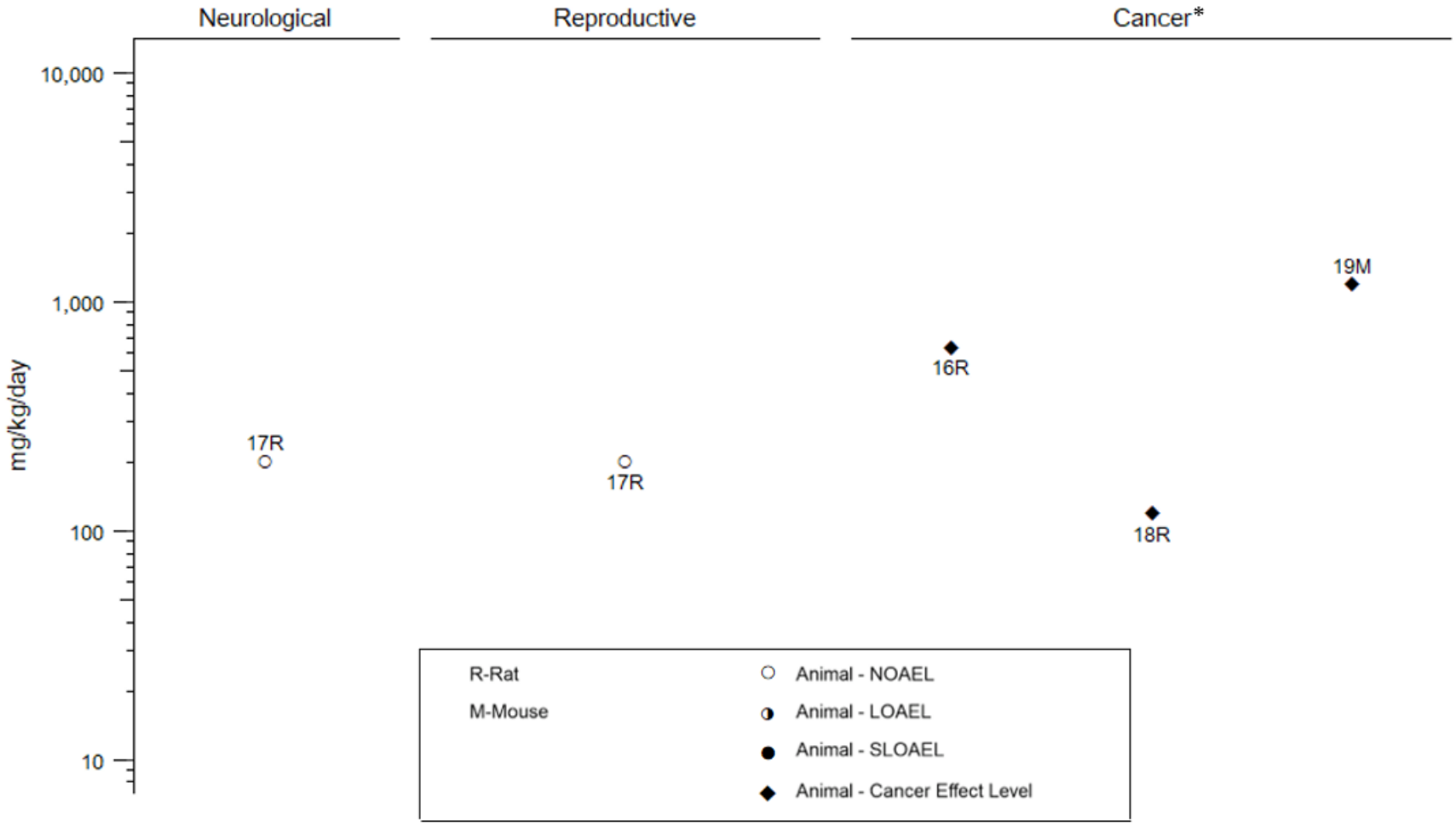


Figure 2-3. Levels of Significant Exposure to Vinyl Acetate – Oral Chronic (≥365 days)



*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 endpoint.

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

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE								
Gruvberger et al. 1998								
Human 87 NS	2 days	1% petroleum solution	CS, IX	Dermal Immuno	1% 1%			
Tanaka and Lucas 1984								
Human 6–11 M	48–72 hours	2% aqueous solution	CS, IX	Dermal Immuno	2% 2%			
Celanese Chemical 1972								
Rabbit (New Zealand) 6 NS	4–72 hours under occluded conditions (clipped intact or abraded skin)	0.5 mL (undiluted)	CS	Dermal		0.5 mL		Slight edema, non-corrosive
Smyth and Carpenter 1948								
Rabbit (NS) 6 NS	24 hours	Undiluted	LE	Death			2.5 mL/kg	LD_{50}
Morris 1995								
Guinea pig (Hartley) 4 NS	6 hours under occluded conditions (clipped intact skin)	0, 1, 2.5, 5, 10, 25, 50, 100% acetone solution	CS	Dermal	50%	100%		Slight irritation
Morris 1995								
Guinea pig (Hartley) 5–10 M, 5–10 F	Induction: 3 weeks, 3 days/week 6 hours/day under occluded conditions (clipped intact skin) Challenge: 12 days later	Induction: 100% Challenge: 25% acetone solution	CS, BW, IX	Bd wt Immuno	100%	25%		Slight sensitization (Grade 1: slight confluent or moderate patchy erythema with challenge)

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

Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
INTERMEDIATE EXPOSURE								
Gage 1970								
Rat (Wistar) 4 M, 4 F	15 days 6 hours/day	0, 100, 250, 630, 2,000 ppm in air	CS	Ocular	630 ppm	2,000 ppm		Nasal and eye irritation

Bd wt or BW = body weight; CS = clinical signs; Immuno = immunological; F = female(s); IX = immune function; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); NOAEL = no-observed-adverse-effect level; NS = not specified

2.2 DEATH

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

In animal inhalation studies, reported 4-hour inhalation median lethal concentration (LC_{50}) values for vinyl acetate were 3,680 ppm in rats, 1,460 ppm in mice, 5,210 ppm in guinea pigs, and 2,760 ppm in rabbits (Union Carbide 1973). All of these species exhibited labored breathing and clonic convulsions prior to death, and lung damage was reported to be the cause of death in all instances. In a review of acute toxicity data available in the Registry of Toxic Effects of Chemical Substances (RTECS) database, Kennedy and Graepel (1991) identified an LC_{50} value of 4,000 ppm in rats. Carpenter et al. (1949) also categorized 4,000 ppm as an exposure level that killed "2/6, 3/6, or 4/6 rats" without providing additional details or exact mortality incidence.

In longer-duration inhalation studies, no significant effects on survival were observed in either rats or mice following exposure to concentrations up to 1,000.2 ppm for 4 weeks (Hazleton 1979b, Hazleton 1979c), rats following exposure to 998.9 ppm for 3 months (Hazleton 1980c), or rats or mice exposed to 594.7 ppm for 104 weeks (Bogdanffy et al. 1994a; Hazleton 1988). However, 9/20 mice exposed to 998.6 ppm of vinyl acetate for 3 months died, while only 2/20 control mice died (Hazleton 1980b). All deaths occurred during the orbital sinus blood sampling procedure. The study author suggested that exposure to 998.6 ppm may have increased animal susceptibility to the anesthesia used (Hazleton 1980b).

Smyth and Carpenter (1948) determined an oral median lethal dose (LD_{50}) value of 2,920 mg/kg for vinyl acetate in rats; the cause of death was not reported. An oral LD_{50} value of 2,500 mg/kg in rats was identified in a review of acute toxicity data available in the RTECS database (Kennedy and Graepel 1991). Decreased survival was not observed in intermediate-duration drinking water studies at doses up to 810 mg/kg/day in rats or 1,023 mg/kg/day in mice (Hazleton 1979d, 1980e, 1980f). In a study in Wistar rats with chronic-duration exposure over 2 generations, an 18–32% decrease in survival was observed in F0 males after 55–93 weeks of exposure to 640 mg/kg/day via drinking water; survival was comparable in F0 males at the end of exposure (104 weeks) and in F0 females and F1 offspring throughout the study (Belpoggi et al. 2002). A similar finding was reported in a companion study in Swiss mice, with a 10–17% decrease in survival in F0 males after 23–55 weeks of exposure to ≥240 mg/kg/day via drinking water (Maltoni et al. 1997). Again, survival was comparable in F0 males at the end of exposure (78 weeks) and F0 females and F1 offspring throughout the study. In contrast, no exposure-related changes in survival were observed in similarly exposed F344 rats at drinking water

doses up to 620 mg/kg/day over 2 generations (Minardi et al. 2002) or Sprague-Dawley rats at drinking water doses up to 302 mg/kg/day for 104 weeks (Bogdanffy et al. 1994b).

The reported 24-hour dermal LD_{50} value in rabbits for vinyl acetate is 2.5 mL/kg (Smyth and Carpenter 1948).

2.3 BODY WEIGHT

No studies were located regarding body weight effects in humans after exposure to vinyl acetate.

In inhalation studies in animals, decreases in body weight and/or body weight gain have been consistently observed in rats and mice. Effects were observed in rats at acute-duration exposures ≥1,005 ppm (Bogdanffy et al. 1997; Hazleton 1980d; Hurtt et al. 1995), rats and mice at intermediate-duration exposures ≥998.9 ppm (Bogdanffy et al. 1997; Hazleton 1979b, 1980b, 1980c), and rats and mice at chronic-duration exposures of 594.7 ppm (Bogdanffy et al. 1994a; Hazleton 1988). 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. Body weight effects were 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 (Bogdanffy et al. 1994a). In acute- and intermediate-duration inhalation studies by Krieger et al. (2020), body weight decreases were only observed at concentrations associated with decreased food intake (≥604.8 ppm).

Decreases in body weight have also been observed after exposure to vinyl acetate in drinking water; however, findings are less consistent than observed in inhalation studies. Significant reductions in body weight and/or weight gain were reported in male mice exposed to 1,040 mg/kg/day for 4 weeks (Hazleton 1979d), rats chronically exposed to doses ranging from 202–302 mg/kg/day following *in utero* exposure (Bogdanffy et al. 1994b), and F0 and F1 rat dams during lactation in a 2-generation study at 697 and ≥165 mg/kg/day, respectively (Mebus et al. 1995). In all studies, body weight effects were accompanied by reduced water consumption during some or all of the exposure period (presumably due to palatability issues). Male rats chronically exposed via drinking water also showed decreases in food intake. Therefore, decreased water and/or food intake may have contributed to observed body weight effects. Other available drinking water studies do not report body weight effects at acute- or intermediate-duration doses up to 1,400 mg/kg/day in rats or 5,300 mg/kg/day in mice (Hazleton 1979d, 1980e, 1980f; Hurtt et

al. 1995; Valentine et al. 2002), or at chronic-duration doses up to 640 mg/kg/day in rats (Belpoggi et al. 2002; Minardi et al. 2002).

2.4 RESPIRATORY

Human and animal studies indicate that vinyl acetate is a respiratory irritant, and respiratory tract damage is characteristic of inhalation exposure to vinyl acetate in animals. Taken together, the results of the acute-, intermediate-, and chronic-duration inhalation exposure experiments indicate that the extrathoracic region appears to be the primary site of vinyl acetate-induced lesions at lower exposure concentrations, particularly the olfactory epithelium of the nasal cavity. The pulmonary region is also affected at higher exposure levels. Observed effects are attributed to portal-of-entry effects due to rapid hydrolysis of vinyl acetate into acetaldehyde and acetic acid following contact with mucosal surfaces, resulting in chronic irritation (reviewed by Bogdanffy et al. 1999; Bogdanffy et al. 2001; Bogdanffy et al. 2004; Slikker et al. 2004; see Section 2.21, Mechanisms of Toxicity for further details). No studies were located regarding respiratory effects in humans after oral or dermal exposure to vinyl acetate. In animals, the lung is not a target of oral exposure to vinyl acetate and dermal data are limited to a single acute-duration lethality study reporting lung congestion in animals that died.

Studies in small groups of humans (3–9/group) show that acute-duration exposure to vinyl acetate vapor can cause minimal and transient irritation of the nose and/or throat at acute exposure levels as low as 4 ppm in volunteers and workers (Deese and Joyner 1969; Union Carbide 1973). During the course of an occupational survey study, Deese and Joyner (1969) evaluated subjective complaints of odor and respiratory irritation in three individuals (a study author, a laboratory technician, and a factory worker) in three locations of a factory during air sampling for intervals ranging from 20 to 120 minutes. During the sampling periods, exposure levels were 4.2–9.9 ppm in Production Unit A, 2.7–9.5 ppm in Production Unit B, and 0.4–21.6 ppm in Production Unit C. Vinyl acetate odor was detected by at least one of three individuals at all exposure levels (≥0.4 ppm), with “marked” odor at 21.6 ppm. Hoarseness and/or cough was observed in three of three individuals at 21.6 ppm. Respiratory irritation was not consistently observed at <10 ppm (Deese and Joyner 1969). In a controlled exposure experiment in volunteers, complaints of odor and respiratory irritation were evaluated in subjects exposed to concentrations ranging from 0.6 to 20 ppm for 2 minutes or from 20 to 72 ppm for up to 4 hours (Union Carbide 1973). No odor detection or respiratory irritation was observed at 0.6 ppm; odor was detected but vinyl acetate was not irritating at 1.3 ppm. Irritation was reported in one or two (of nine) volunteers after exposure to 4–20 ppm for 2 minutes. At longer durations and higher concentrations, volunteers reported irritation after

exposure to 20 ppm for 3 hours (one of three) or 72 ppm for 30 minutes (four of four). All volunteers (four of four) reported olfactory irritation after 4 hours at 20 ppm, 2 hours at 34 ppm, or 30 minutes at 72 ppm. Consistent with these findings, increased breathing rate was observed after nose-only exposure to 10 ppm for 3–5 minutes in two volunteers during a physiologically based pharmacokinetic (PBPK) model validation study (Hinderliter et al. 2005). While these studies suggest that vinyl acetate is non-irritating at concentrations <3 ppm, potentially irritating between 4 and 34 ppm, and irritating at ≥72 ppm, reliable NOAEL/LOAEL determinations for these studies could not be identified due to the small group numbers, limited reporting, and/or variable or unreported exposure durations. Due to the aforementioned limitations, the Deese and Joyner (1969), Hinderliter et al. (2005), and Union Carbide (1973) human results were not included in LSE tables.

Limited human data indicate that long-term occupational exposure to low air levels of vinyl acetate can be irritating to the respiratory tract and may cause mild impairment in pulmonary function. In an occupational health survey, 21 male chemical operators exposed to vinyl acetate for a mean of 15.2 years were compared to 21 matched unexposed controls by thorough multiphasic screening examinations (Deese and Joyner 1969). Air samples obtained at several locations in the plant 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. No major differences were found between the exposed and unexposed workers with respect to any of the respiratory parameters studied, including complete physical examinations, chest x-ray, and spirometry. In a questionnaire, 6/21 exposed workers indicated that vinyl acetate was irritating to the nose, throat, and/or eyes during the workday under “normal” conditions; three of the workers specifically noted eye irritation, and other irritation complaints were unspecified.

In a cross-sectional study of 40 carpet manufacturers exposed to vinyl acetate for an average of 9.40 years, increased rates of self-reported pulmonary symptoms (cough, phlegm, wet cough, wheezing, dyspnea, chest tightness, chest cold) were reported, compared to 40 unexposed referents (Khoshakhlagh et al. 2023). However, the study authors did not disclose the time period (e.g., the past week, past month) during which subjects had these symptoms. Exposed workers also showed decreased pulmonary function measurements (forced vital capacity, forced expiratory volume, peak expiratory flow) compared to referents; the study authors did not report if spirometry was conducted before, during, or after a work shift. Vinyl acetate concentrations in breathing zones of exposed workers for different jobs ranged from 0.02 to 11.71 ppm; the average concentration±standard deviation across all workers was 3.61±3.18 ppm (Khoshakhlagh et al. 2023).

As with the acute-duration studies, several limitations of the occupational studies preclude identification of reliable NOAEL/LOAEL values. The predominant limitation in both studies is lack of discussion or statistical control for concurrent exposure to other chemicals in the workplace that may contribute to observed respiratory effects. Additional limitations include a small number of subjects and lack of statistical analyses in the study by Deese and Joyner (1969) and the omission of key study design details (e.g., timing of spirometry measurements) and wide variability of exposure levels with no attempt of linear regression analysis in the cross-sectional study by Khoshakhlagh et al. (2023). Therefore, these studies are also excluded from the LSE table.

As discussed in Section 2.2 (Death), acute-duration lethality studies in laboratory animals reported respiratory tract damage as the cause of death in rats, mice, guinea pigs, and rabbits acutely exposed to vinyl acetate for up to 4 hours (Union Carbide 1973). Gasping and labored breathing were usually observed prior to death at ≥820 ppm in mice and ≥3,680 ppm in rats, rabbits, and guinea pigs. Necropsy in rabbits and guinea pigs revealed excess pleural fluid and lung congestion and/or hemorrhage.

In an acute-duration study, Bogdanffy et al. (1997) examined five sections of the nasal cavity in rats following exposure to vinyl acetate for 1 or 5 days (6 hours/day). Mild-to-moderate degeneration and/or necrosis of the olfactory epithelium was observed in all rats exposed once to ≥598.5; no nasal lesions were observed at 0 or 199.6 ppm. After 5 days of intermittent exposure to ≥598.5 ppm, a few degenerative and necrotic lesions of minimal severity were observed, but all rats showed mild-to-severe olfactory epithelium regenerative hyperplasia. After both durations, the severity of the olfactory epithelium lesions was greatest in the anterior regions of the nasal cavity (Levels 2 and 3), compared to the posterior regions (Levels 4 and 5); olfactory epithelium is not found in the outermost nasal region (Level 1). Bogdanffy et al. (1997) also reported elevated cell proliferation in the nasal epithelium following a single inhalation exposure, but not after the 5-day exposure protocol.

Similar findings were reported in an acute-duration study by Krieger et al. (2020) that examined four regions of the nasal cavity in rats following exposure to vinyl acetate for 1 or 5 days (6 hours/day). Slight-to-marked necrosis/degeneration of the proximal olfactory epithelium were observed in the majority of rats exposed once to ≥604.8 ppm; no nasal lesions were observed at ≤201.6 ppm. Inflammatory lesions were characterized by cell death and exfoliation. After 5 days, lesions in the majority of rats exposed to ≥604.8 ppm for 6 hours/day were generally classified as atrophic, rather than degenerative; however, some necrosis was observed in atrophied tissues. Atrophic and necrotic findings after 5 days also showed a concentration-related increase in severity, progressing from slight to marked.

Mild respiratory metaplasia was also observed in the more distal nasal regions in three of six rats exposed to 1,009.7 ppm for 5 days. Krieger et al. (2020) also reported increased cellular proliferation in the olfactory epithelium of the dorsal meatus at ≥604.8 ppm following the 1- or 5-day exposure periods; however, this was only confirmed using one of two experimental methods (Ki-67 nuclear staining; bromodeoxyuridine [BrdU] staining was uninterpretable due to methodological issues). There was some evidence of increased cellular proliferation at 5 days at 50.4 ppm; however, no clear effect was observed at 201.6 ppm, indicating no concentration-related changes in cellular proliferation at ≤201.6 ppm (Krieger et al. 2020).

Respiratory irritation and distress have also been reported in several intermediate-duration studies in rats and mice exposed to concentrations ≥497.6 ppm for ≥4 weeks (Hazleton 1979b, 1979c, 1980b, 1980c) and in rats exposed to 2,000 ppm for 15 days (Gage 1970). Signs and symptoms included nasal irritation (i.e., sneezing progressing with increasing severity to a nasal discharge and bloody exudate) and respiratory difficulty (i.e., as rapid shallow breathing progressing to labored and slow breathing).

At sacrifice, numerous upper respiratory lesions have been observed in rodents following intermediate-duration exposure to vinyl acetate, including the nasal epithelium, trachea, and lungs. Lesions observed in the nasal cavity in rats include olfactory epithelium regenerative hyperplasia, olfactory epithelial degeneration/necrosis, and nerve bundle degeneration/atrophy at ≥598.5 ppm (Bogdanffy et al. 1997) and atrophy and necrosis/degeneration of the olfactory epithelium with respiratory metaplasia at ≥604.8 ppm (Krieger et al. 2020). Krieger et al. (2020) also reported cellular proliferation of olfactory epithelium, ethmoturbinate, and dorsal meatus; however, this was only confirmed using one of two experimental methods (Ki-67 nuclear staining; BrdU staining was uninterpretable due to methodological issues). Nasal lesions in mice following intermediate-duration inhalation exposure include focal and diffuse rhinitis with associated exudation and transudation into the nasal passages at 998.6 ppm (Hazleton 1980b). Low incidences of metaplasia and hyperplasia of the trachea and mild multifocal bronchitis were also reported in mice at 998.6 ppm (Hazleton 1980b). Lesions observed in the lungs of rats include focal histiocytic alveolitis at 998.9 ppm (Hazleton 1980c) and the presence of excess macrophages in the lungs in rats at 2,000 ppm (Gage 1970). Elevated lung weights, presumably due to lung congestion, have also been reported in mice at 998.9 ppm (Hazleton 1980b).

Chronic-duration 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 (Bogdanffy et al. 1994a; Hazleton 1988). Histopathological changes in the upper respiratory tract were observed in

mice and rats exposed to ≥200.5 ppm and were consistent with chronic irritation. Observed nonneoplastic lesions in the nasal cavity at ≥200.5 ppm included olfactory epithelial atrophy, olfactory epithelial squamous metaplasia, olfactory epithelial regeneration, olfactory epithelial inflammatory cell infiltrate, epithelial nest-like infolds, olfactory epithelial leukocytic exudate, basal cell hyperplasia, turbinate leukocytic exudate, and submucosal inflammatory cell infiltrate in the rats and inflammatory exudate, submucosal gland hyperplasia, olfactory epithelial atrophy, squamous metaplasia, and replacement of olfactory by respiratory epithelium in mice. In rats, nonneoplastic lesions in the lungs were observed at 594.7 ppm (bronchial exfoliation, intraluminal fibrous projections, pigmented macrophages, peribronchiolar/ perivascular lymphoid aggregates), and lung weights were significantly increased in all exposed female rats at terminal sacrifice. In mice, exposure-related lesions in the lung included accumulation of alveolar macrophages and bronchial gland dilatation at ≥200.5 ppm and accumulation of alveolar macrophages, intraalveolar eosinophilic material, accumulation of brown-pigmented macrophages, intraluminal fibroepithelial projections, and bronchial/bronchiolar epithelial flattening and/or exfoliation and disorganization at 594.7 ppm. Epithelial hyperplasia of the trachea/bronchi was also observed in mice at 594.7 ppm.

Pulmonary changes have not been observed in animals following oral exposure. No changes in lung weight or histology were found in drinking water studies in rats or mice exposed to intermediate-duration doses up to 810 or 1,023 mg/kg/day, respectively (Hazleton 1979d, 1980e, 1980f; Mebus et al. 1995), or in rats exposed to chronic-duration doses up 302 mg/kg/day (Bogdanffy et al. 1994b). Additionally, no exposure-related nonneoplastic lung lesions were observed in F0 or F1 rats or mice exposed to doses up to 640 mg/kg/day for 104 weeks or 1,200 mg/kg/day for 78 weeks, respectively, and then allowed to live until natural death (Belpoggi et al. 2002; Maltoni et al. 1997; Minardi et al. 2002). However, due to long (and unspecified) post-exposure periods in these 2-generation studies, the high doses cannot be considered reliable NOAELs due to potential recovery.

Lymphoid hyperplasia of the submucosa of the paranasal sinuses was reported for mice that received doses of 1,016 mg/kg/day via the drinking water for 3 months (Hazleton 1980e). However, the study authors attributed this to variation in histologic sectioning. Since this effect was not observed in the companion chronic-duration exposure study (Bogdanffy et al. 1994b), it is not clear if it was treatment-related, and its toxicological significance is not known.

2.5 CARDIOVASCULAR

In the occupational study by Deese and Joyner (1969) described in Section 2.4 (Respiratory), no changes were observed in cardiovascular endpoints of a physical examination (e.g., blood pressure) or an electrocardiogram in 21 exposed male workers, compared to unexposed workers. The mean exposure level was 8.6 ppm, and the mean duration of exposure was 15.2 years (Deese and Joyner 1969). As previously discussed, this study was not included in the LSE table due to numerous limitations. No additional studies evaluating potential cardiovascular effects in humans exposed to vinyl acetate were available.

No exposure-related cardiovascular effects have been observed in rats or mice following inhalation or oral exposure. No changes in cardiovascular histology or heart weight were observed following inhalation exposure to vinyl acetate at concentrations up to 1,000.2 ppm for 4 weeks, 998.9 ppm for 3 months, or 594.7 ppm for 104 weeks (Bogdanffy et al. 1994a; Hazleton 1979b, 1979c, 1980b, 1980c, 1988). Similarly, no changes in cardiovascular histology or heart weight were observed following intermediate-duration exposure to drinking water doses up to 810 mg/kg/day in rats or 1,023 mg/kg/day in mice (Hazleton 1979d, 1980e, 1980f), or chronic-duration drinking water doses up to 302 mg/kg/day in rats (Bogdanffy et al. 1994b). Additionally, no exposure-related nonneoplastic cardiac lesions were observed in F0 or F1 rats or mice exposed to doses up to 640 mg/kg/day for 104 weeks or 1,200 mg/kg/day for 78 weeks, respectively, and then allowed to live until natural death (Belpoggi et al. 2002; Maltoni et al. 1997; Minardi et al. 2002). However, due to long (and unspecified) post-exposure periods in these 2-generation studies, the high doses cannot be considered reliable NOAELs due to potential recovery.

2.6 GASTROINTESTINAL

No studies were located regarding gastrointestinal effects in humans after 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 1,000.2 ppm for 4 weeks or 998.9 ppm for 3 months (Hazleton 1979b, 1979c, 1980b, 1980c) or 594.7 ppm for 104 weeks (Bogdanffy et al. 1994a; Hazleton 1988). Similarly, no exposure-related changes in the gastrointestinal tract were observed in acute- and intermediate-duration oral studies at doses up 1,400 mg/kg/day in rats or 5,300 mg/kg/day in mice (Hazleton 1979d, 1980e, 1980f; Valentine et al. 2002). Using bromodeoxyuridine (BrdU) to label dividing cells, one study reported evidence of increased cell proliferation in the oral mucosa in mice

exposed to doses ≥2,300 mg/kg/day for 92 days; however, the biological significance of this finding in the absence of evidence of histopathological changes under standard light microscopy is unclear (Valentine et al. 2002). In rats, there was only equivocal evidence of increased cell proliferation in the oral mucosa following exposure to doses up to 1,400 mg/kg/day for 92 days (proliferation indices increases were statistically significant, but <2-fold in magnitude). Increased cell proliferation was not observed in rats or mice at doses up to 1,400 or 5,300 mg/kg/day, respectively, for up to 29 days (Valentine et al. 2002). An increase in dark material was reported in the intestine of mice exposed to 998.9 ppm for 3 months (Hazleton 1980b) or 1,023 mg/kg/day for 3 weeks via drinking water (Hazleton 1979d). This substance was never identified in the studies and was not associated with any evidence of irritation; therefore, the biological significance of its occurrence is not known.

As discussed in Section 2.19 (Cancer), the gastrointestinal tract is a target for pre-neoplastic and neoplastic lesions in rats and mice following chronic-duration oral exposure to vinyl acetate (Belpoggi et al. 2002; Maltoni et al. 1997; Minardi et al. 2002). However, no exposure-related gastrointestinal lesions were observed in rats or mice following drinking water exposure to doses up to 302 mg/kg/day (Bogdanffy et al. 1994b). Additionally, no exposure-related non-neoplastic gastrointestinal lesions were observed in F0 or F1 rats or mice exposed to doses up to 640 mg/kg/day for 104 weeks or 1,200 mg/kg/day for 78 weeks, respectively, and then allowed to live until natural death (Belpoggi et al. 2002; Maltoni et al. 1997; Minardi et al. 2002). However, due to long (and unspecified) post-exposure periods in these 2-generation studies, the high doses cannot be considered reliable NOAELs due to potential recovery.

One chronic-duration oral study reported lesions of the upper gastrointestinal system in female rats (basal cell hyperplasia of the esophagus and stomach) and male and female mice (basal cell hyperplasia, squamous cell hyperplasia, and/or epithelial dysplasia of the oral cavity, larynx, esophagus, and forestomach) following chronic-duration drinking water exposure (Umeda et al. 2004); however, methodological deficiencies precluded accurate exposure assessment. Instead of mixing the drinking water solution daily, Umeda et al. (2004) mixed the solution twice weekly, reporting test solution stabilities of 72–80% for the rat study and 86–96% for the mouse study. In both studies, concentration-dependent increases in acetic acid concentration and decreases in water pH were reported over a 4-day period. The study authors estimated doses associated with reported effects in rats (575 mg/kg/day) and mice (≥989 mg/kg/day); however, it is unclear if the estimated doses account for the test solution stability or if acetic acid levels and decreased pH of the drinking water contributed to observed findings. Therefore, this study is not included in the LSE table.

2.7 HEMATOLOGICAL

In the occupational study by Deese and Joyner (1969) described in Section 2.4 (Respiratory), no changes were observed in hematological parameters in 21 male workers exposed to a mean level of 8.6 ppm, compared to unexposed workers. As previously discussed, this study was not included in the LSE table due to numerous limitations. No additional studies evaluating potential hematological effects in humans exposed to vinyl acetate were available.

No exposure-related hematological changes were observed in animal studies following inhalation or oral exposure. In inhalation studies, no consistent or biologically relevant changes in hematological parameters were found in rats at concentrations up to 2,000 ppm for 15 days (Gage 1970), rats or mice at concentrations up to 1,000.2 ppm for 4 weeks or 998.9 ppm for 3 months (Hazleton 1979b, 1979c, 1980b, 1980c), or rats or mice at concentrations up to 594.7 ppm for 104 weeks (Bogdanffy et al. 1994a; Hazleton 1988). Similarly, in drinking water studies, no changes in hematological parameters were observed following intermediate-duration exposure to doses up to 810 mg/kg/day in rats or 1,023 mg/kg/day in mice (Hazleton 1979d, 1980e, 1980f) or chronic-duration exposure to doses up to 302 mg/kg/day in rats (Bogdanffy et al. 1994b).

2.8 MUSCULOSKELETAL

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

In laboratory animals, no histological changes in muscle or bone were noted in rats or mice following inhalation exposure to vinyl acetate at concentrations up to 594.7 ppm for 104 weeks (Bogdanffy et al. 1994a; Hazleton 1988) or drinking water exposure to vinyl acetate at doses up to 302 mg/kg/day in rats (Bogdanffy et al. 1994b).

2.9 HEPATIC

In the occupational study by Deese and Joyner (1969) described in Section 2.4 (Respiratory), no changes were observed in selected blood parameters of liver function (e.g., alkaline phosphatase, cholesterol, total protein, albumin, or globulin levels) in 21 male workers exposed to vinyl acetate at a mean level of 8.6 ppm, compared to unexposed workers. As previously discussed, this study was not included in the

LSE table due to numerous limitations. No additional studies evaluating potential hepatic effects in humans exposed to vinyl acetate were available.

In inhalation studies, no exposure-related hepatic lesions have been observed in rats exposed to concentrations up to 2,000 ppm for 15 days (Gage 1970), in rats or mice at concentrations up to 1,000.2 ppm for 4 weeks or 998.9 ppm for 3 months (Hazleton 1979b, 1979c, 1980b, 1980c), or in rats or mice at concentrations up to 594.7 ppm for 104 weeks (Bogdanffy et al. 1994a; Hazleton 1988). While some sporadic changes in absolute and/or relative liver weight were observed in some of these studies, no significant, exposure-related findings were observed. No significant changes in serum enzymes indicative of hepatic dysfunction were noted in these studies.

In a 3-month oral study, pericholangitis (swelling around the bile ducts) was increased in male rats exposed to 684 mg/kg/day via drinking water (10/10) compared to controls (3/10); this lesion was found in 6/10 control females and 7/10 females exposed to the high dose (810 mg/kg/day) (Hazleton 1980f). Granulomatous hepatitis was also observed in 2/10 males at 684 mg/kg/day, compared with 0/10 controls; the incidence in both control and high-dose females was 2/10 rats. These findings were not accompanied by any changes in hepatic serum enzymes or liver weight, and the study authors concluded that these effects were not unequivocally related to exposure or clearly adverse. In other drinking water studies, no exposure-related changes in liver histology or hepatic enzyme levels were observed in rats exposed to doses up to 755 mg/kg/day for 4 weeks (Hazleton 1979d) or 302 mg/kg/day for 104 weeks (Bogdanffy et al. 1994b), or mice exposed to doses up to 1,023 mg/kg/day for 4 weeks (Hazleton 1979d) or 1,016 mg/kg/day for 13 weeks (Hazleton 1980e). As observed in the inhalation studies, some sporadic changes in absolute and/or relative liver weight were observed in these studies, but no significant, exposure-related findings were observed. Additionally, no exposure-related nonneoplastic hepatic lesions were observed in F0 or F1 rats or mice exposed to doses up to 640 mg/kg/day for 104 weeks or 1,200 mg/kg/day for 78 weeks, respectively, and then allowed to live until natural death (Belpoggi et al. 2002; Maltoni et al. 1997; Minardi et al. 2002). However, due to long (and unspecified) post-exposure periods in these 2-generation studies, the high doses cannot be considered reliable NOAELs due to potential recovery.

2.10 RENAL

In the occupational study by Deese and Joyner (1969) described in Section 2.4 (Respiratory), no changes were observed in selected blood parameters of renal function (e.g., blood urea nitrogen [BUN], creatinine)

or urinalysis in 21 male workers exposed to vinyl acetate at a mean level of 8.6 ppm, compared to unexposed workers. As previously discussed, this study was not included in the LSE table due to numerous limitations. No additional studies evaluating potential renal effects in humans exposed to vinyl acetate were available.

No exposure-related renal effects were noted in rats or mice following inhalation or oral exposure. In inhalation studies, no changes in kidney histology or weight were found in rats at concentrations up to 2,000 ppm for 15 days (Gage 1970), in rats or mice at concentrations up to 1,000.2 ppm for 4 weeks or 998.9 ppm for 3 months (Hazleton 1979b, 1979c, 1980b, 1980c), or in rats or mice at concentrations up to 594.7 ppm for 104 weeks (Bogdanffy et al. 1994a; Hazleton 1988). Similarly, in drinking water studies, no changes in kidney histology were observed following intermediate-duration exposure to doses up to 810 mg/kg/day in rats or 1,023 mg/kg/day in mice (Hazleton 1979d, 1980e, 1980f) or chronic-duration exposure to doses up to 302 mg/kg/day in rats (Bogdanffy et al. 1994b). Additionally, no exposure-related nonneoplastic changes in kidney histology were observed in F0 or F1 rats or mice exposed to doses up to 640 mg/kg/day for 104 weeks or 1,200 mg/kg/day for 78 weeks, respectively, and then allowed to live until natural death (Belpoggi et al. 2002; Maltoni et al. 1997; Minardi et al. 2002). However, due to long (and unspecified) post-exposure periods in these 2-generation studies, the high doses cannot be considered reliable NOAELs due to potential recovery. While some sporadic changes in absolute and/or relative kidney weight were observed in some of these studies, no significant, exposure-related findings were observed. Furthermore, no consistent exposure-related changes in renal clinical chemistry were observed in these studies. Decreases in BUN were sporadically observed in both rats and mice in inhalation studies, but these changes were generally within the range of historical controls, not dose-related, and not consistently observed across all sampling times.

Urine from rats intermittently exposed to 998.9 ppm vinyl acetate for 3 months via inhalation (5 days/week, 6 hours/day) was decreased in volume and more concentrated when compared to controls (Hazleton 1980c). Reduced urine volume was also observed in rats intermittently exposed to 594.7 ppm of vinyl acetate for 104 weeks (Bogdanffy et al. 1994a; Hazleton 1988). The study authors attributed this effect to reduced water intake in these animals. In another study, no changes in urine parameters were observed in rats intermittently exposed to concentrations up to 2,000 ppm for 15 days (Gage 1970). More concentrated and darker colored urine was also observed in female rats receiving a dose of 810 mg/kg/day vinyl acetate in the drinking water for 3 months; however, this effect was attributed to reduced water intake due to the unpalatability of the drinking water solution (Hazleton 1980f). No changes in urinalysis

parameters were found in rats administered vinyl acetate in the drinking water at doses of up to 755 mg/kg/day for 4 weeks (Hazleton 1979d).

2.11 DERMAL

In patch test studies, no irritation was observed in workers with occupational exposure to vinyl acetate (and other chemicals) after a 48- or 72-hour exposure to 1–2% vinyl acetate solution (Gruvberger et al. 1998; Tanaka and Lucas 1984).

Occupational case reports show that some workers may develop blisters following dermal contact with vinyl acetate, particularly on the thin skin of the finger web and the underside of the wrist, and that continued contact (e.g., clothing wet with the chemical) might result in severe irritation or blistering of the skin (Union Carbide 1958). In the occupational health survey by Deese and Joyner (1969) described in Section 2.4 (Respiratory), 18/21 male chemical operators did not complain of any dermatitis or skin burns associated with dermal exposure to mean vinyl acetate air concentrations of 8.6 ppm. One operator complained of dermatitis, a second complained of "dryness of the hands," and a third answered the survey with a question mark. None of the 21 matched unexposed controls complained of skin issues. While these occupational studies suggest that skin exposure to vinyl acetate vapor or liquid may cause dermal effects, reliable NOAEL/LOAEL determinations for these studies could not be identified due to the small group numbers, limited reporting, and/or variable or unreported exposure durations. Therefore, Deese and Joyner (1969) and Union Carbide (1958) were not included in the LSE tables.

Slight edema of both intact and abraded skin was observed in rabbits following application of 0.5 mL of undiluted vinyl acetate; vinyl acetate was determined to be non-corrosive (Celanese Chemical 1972). Based on these results, the study authors classified vinyl acetate as noncorrosive to the skin. In guinea pigs, a 0.3 mL volume of undiluted chemical was slightly irritating when applied to clipped skin in 2/4 test animals; no irritation was observed at concentrations ≤50% (Morris 1995).

No histopathological changes were observed in the skin of rats or mice following inhalation exposure to vinyl acetate at concentrations up to 594.7 ppm for 104 weeks (Bogdanffy et al. 1994a; Hazleton 1988) or drinking water exposure to vinyl acetate at doses up to 302 mg/kg/day in rats (Bogdanffy et al. 1994b).

2.12 OCULAR

Eye irritation has been reported in individuals after acute-duration exposures to vinyl acetate vapor. In the acute-duration occupational exposure study described in Section 2.4 (Respiratory), subjective reports of eye irritation were recorded following exposure to vinyl acetate at concentrations ranging from 0.4 to 21.6 ppm for up to 2 hours (Deese and Joyner 1969). All individuals (three of three) exposed to 21.6 ppm complained of eye irritation that "would be intolerable over an extended period." At lower concentrations, no irritation was observed at ≤4.2 ppm or between 7.6 and 9.9 ppm; however, one of three individuals exposed to 5.7 or 6.8 ppm reported slight eye irritation. In a controlled exposure experiment in volunteers, complaints of eye irritation were evaluated in subjects exposed to concentrations ranging from 0.6 to 20 ppm for 2 minutes or from 20 to 72 ppm for up to 4 hours (Union Carbide 1973). No eye irritation was observed at 0.6 ppm. Irritation was reported in one or two (of nine) volunteers after exposure to 4–20 ppm for 2 minutes. At longer durations and higher concentrations, no eye irritation was reported in volunteers exposed to 20 ppm for 4 hours or 34 ppm for 2 hours. However, volunteers exposed to 72 ppm for 30 minutes complained of eye irritation that persisted for up to 60 minutes after exposure (Union Carbide 1973). In the chronic-duration occupational study by Deese and Joyner (1969) described in Section 2.4 (Respiratory), 6/21 exposed male workers indicated that vinyl acetate was irritating to their eyes, nose, or throat; three of these workers specifically indicated that it was irritating to their eyes. The mean exposure level was 8.6 ppm and the mean duration of exposure was 15.2 years (Deese and Joyner 1969). As previously discussed, these human studies were not included in the LSE table due to numerous limitations precluding identification of a reliable NOAEL/LOAEL value, including small number of subjects, lack of control for confounding factors, and lack of statistical analyses.

Eye irritation was also noted in animals exposed to 2,000 ppm vinyl acetate in air for 15 days (Gage 1970). No histopathological changes were observed in the eyes of rats or mice following inhalation exposure to vinyl acetate at concentrations up to 594.7 ppm for 104 weeks (Bogdanffy et al. 1994a; Hazleton 1988) or drinking water exposure to vinyl acetate at doses up to 302 mg/kg/day in rats (Bogdanffy et al. 1994b). No ocular abnormalities were detected in ophthalmoscopic examinations in rats exposed to air concentrations up to 998.9 ppm for 6 hours/day, 5 days/week for 3 months (Hazleton 1980c) or drinking water doses up to 810 mg/kg/day for 12 weeks (Hazleton 1980f).

2.13 ENDOCRINE

No studies were located regarding endocrine system effects in humans after exposure to vinyl acetate.

No studies evaluating endocrine function in laboratory animals were identified. In intermediate- and chronic-duration inhalation studies, no exposure-related changes in endocrine organ weight or histology were noted in rats exposed to concentrations up to 2,000 ppm for 15 days (Gage 1970) or rats or mice exposed to concentrations up to 594.7 ppm for 104 weeks (Bogdanffy et al. 1994a; Hazleton 1988). In oral studies, no exposure-related changes in endocrine organ weight or histology were reported in rats following chronic-duration exposure to doses up to 302 mg/kg/day (Bogdanffy et al. 1994b). In a 2-generation study in rats, no histopathological lesions were observed in the pituitary gland at doses up to 697 mg/kg/day (Mebus et al. 1995). Additionally, no exposure-related nonneoplastic changes in endocrine organ histology were observed in F0 or F1 rats or mice exposed to doses up to 640 mg/kg/day for 104 weeks or 1,200 mg/kg/day for 78 weeks, respectively, and then allowed to live until natural death (Belpoggi et al. 2002; Maltoni et al. 1997; Minardi et al. 2002). However, due to long (and unspecified) post-exposure periods in these 2-generation studies, the high doses cannot be considered reliable NOAELs due to potential recovery.

2.14 IMMUNOLOGICAL

In patch test studies, no evidence of skin sensitization has been observed in workers with occupational exposure to vinyl acetate (Gruvberger et al. 1998; Tanaka and Lucas 1984). However, vinyl acetate was a slight sensitizer in guinea pigs when challenged with 25% solution approximately 2 weeks after an initial exposure to undiluted vinyl acetate (Morris 1995).

No animal inhalation or oral studies evaluating the function of the immune system were available. Reductions in relative thymus and/or spleen weight were consistently noted in rats and mice exposed to vinyl acetate via inhalation for 4 weeks and 3 months at exposure concentrations of 998.6–1,000.2 ppm; however, no gross or histopathological effects were noted in these organs (Hazleton 1979b, 1979c, 1980b, 1980c). A lack of histopathological effects in the spleen was also reported in rats exposed to concentrations up to 2,000 ppm for 15 days (Gage 1970). Similarly, changes in thymus and/or spleen weight were noted in some intermediate-duration drinking water studies in mice (Hazleton 1979d, 1980e, 1980f). However, changes were not always dose-related and were not accompanied by histopathological lesions. The biological significance of organ weight changes in some intermediate-duration inhalation and oral studies in the absence of histopathological effects is not known; therefore, organ weight changes were not used to establish NOAEL/LOAEL values in these studies.

In chronic-duration animal studies, no exposure-related pattern in immune organ weight or histology were observed in rats or mice following exposure to inhalation concentrations up to 594.7 ppm for up to 104 weeks (Bogdanffy et al. 1994a; Hazleton 1988) or rats administered oral doses up to 302 mg/kg/day for 104 weeks (Bogdanffy et al. 1994b). Additionally, no exposure-related nonneoplastic changes in immune organ or bone marrow histology were observed in F0 or F1 rats or mice exposed to doses up to 640 mg/kg/day for 104 weeks or 1,200 mg/kg/day for 78 weeks, respectively, and then allowed to live until natural death (Belpoggi et al. 2002; Maltoni et al. 1997; Minardi et al. 2002). However, due to long (and unspecified) post-exposure periods in these 2-generation studies, the high doses cannot be considered reliable NOAELs due to potential recovery.

2.15 NEUROLOGICAL

In the occupational study by Deese and Joyner (1969) described in Section 2.4 (Respiratory), no changes were observed in visual acuity or tonometry (glaucoma testing) in 21 male workers exposed to vinyl acetate at a mean level of 8.6 ppm, compared to unexposed workers. As previously discussed, this study was not included in the LSE table due to numerous limitations. No additional studies evaluating potential neurological effects in humans exposed to vinyl acetate were available.

In acute-duration inhalation lethality studies, labored breathing, impaired coordination, and convulsions were observed at lethal exposure levels ≥1,640 ppm in mice, ≥3,280 ppm in rats and guinea pigs, and 6,560 ppm in rabbits (Union Carbide 1973). Clinical signs of neurotoxicity were not reported in animals that survived and observed findings prior to death likely reflected systemic toxicity rather than a primary effect of vinyl acetate on the nervous system (death was attributed to lung damage in all cases).

Intermittent, non-specific clinical signs of toxicity (hunched posture, ruffled fur) were qualitatively reported in rats and mice following intermediate-duration exposure to vinyl acetate at ≥497.6 ppm (Hazleton 1979b, 1979c, 1980b, 1980c). These clinical signs were also noted intermittently throughout the chronic-duration studies in all exposure groups, including control animals, with no apparent exposure-related trends (Bogdanffy et al. 1994a; Hazleton 1988). Therefore, these transient behavioral effects are considered to be caused by the poor health of the animals rather than a primary effect of vinyl acetate on the nervous system. These signs were not accompanied by exposure-related changes in brain weight or gross and/or histopathological lesions in the nervous system. No studies designed to evaluate neurological function and/or behavior following inhalation exposure were identified.

As discussed in Section 2.4 (Respiratory), damage to the olfactory epithelium of the nasal cavity is a consistent finding in acute-, intermediate-, and chronic-duration inhalation studies (Bogdanffy et al. 1994a, 1997; Hazleton 1988). One of these studies also reported degeneration and atrophy of nerve bundles in the olfactory epithelium in rats following exposure to ≥598.5 ppm for 4 weeks (Bogdanffy et al. 1997). However, damage to the nerve bundles was not observed in rats or mice exposed to concentrations up to 998.9 ppm for 3 months (Hazleton 1980b, 1980c) or 594.7 ppm for 104 weeks (Bogdanffy et al. 1994a; Hazleton 1988).

In oral studies, no clinical signs of neurotoxicity or exposure-related changes in brain weight or nervous tissue histology were reported in rats or mice at intermediate-duration doses up to 810 or 1,023 mg/kg/day, respectively (Hazleton 1979d, 1980e, 1980f), or in rats at chronic-duration doses up to 302 mg/kg/day (Bogdanffy et al. 1994b). Additionally, no exposure-related nonneoplastic changes in brain histology were observed in F0 or F1 rats or mice exposed to doses up to 640 mg/kg/day for 104 weeks or 1,200 mg/kg/day for 78 weeks, respectively, and then allowed to live until natural death (Belpoggi et al. 2002; Maltoni et al. 1997; Minardi et al. 2002). However, due to long (and unspecified) post-exposure periods in these 2-generation studies, the high doses cannot be considered reliable NOAELs due to potential recovery.

2.16 REPRODUCTIVE

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

No exposure-related changes in reproductive endpoints in rats were observed following inhalation or oral exposure. No changes in pregnancy outcomes or gross or histopathological findings in the reproductive organs were observed in rat dams following inhalation exposure to concentrations up to 1,005 ppm on gestation days (GDs) 6–15 (Hazleton 1980d; Hurtt et al. 1995) or oral exposure to drinking water doses up to 477 mg/kg/day on GD 6–15 (Hurtt et al. 1995). In a 2-generation drinking-water study in rats, a slight reduction in the number of pregnancies was observed in the F1 female rats exposed to approximately 697 mg/kg/day (19/24 treated animals became pregnant as opposed to 24/25 of the controls) (Mebus et al. 1995). This reduction was attributed to poor male mating performance based on a marginal reduction in the mating index when F1 males exposed to approximately 471 mg/kg/day were mated with untreated females (19/25), compared with controls (34/36). However, this difference was not statistically significant and was not accompanied by a decreased fertility index. Additionally, 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, and no histopathological changes in reproductive organs were observed. Therefore, the highest dose (471 mg/kg/day in males and 697 mg/kg/day in females) is considered a reproductive NOAEL.

In inhalation and oral studies that did not assess reproductive function, no exposure-related changes in reproductive organ weight or histology were observed. In inhalation studies, no changes in the reproductive organs were observed in male or female rats or mice exposed to concentrations up to 998.9 ppm for 3 months (Hazleton 1980b, 1980c) or 594.7 ppm for 104 weeks (Bogdanffy et al. 1994a; Hazleton 1988). In oral studies, no reproductive organ changes were observed at intermediate-duration exposure up to 810 mg/kg/day in rats or 1,016 mg/kg/day in mice (Hazleton 1980e, 1980f) or chronic-duration exposure up to 302 mg/kg/day in rats (Bogdanffy et al. 1994b). Additionally, no exposure-related changes in reproductive organ nonneoplastic histology were observed in F0 or F1 rats or mice exposed to doses up to 640 mg/kg/day for 104 weeks or 1,200 mg/kg/day for 78 weeks, respectively, and then allowed to live until natural death (Belpoggi et al. 2002; Maltoni et al. 1997; Minardi et al. 2002). However, due to long (and unspecified) post-exposure periods in these 2-generation studies, the high doses cannot be considered reliable NOAELs due to potential recovery.

2.17 DEVELOPMENTAL

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

The potential developmental effects of vinyl acetate were evaluated in rats following inhalation or oral exposure on GDs 6–15 (Hazleton 1980d; Hurtt et al. 1995). Neither embryolethality nor teratogenicity were observed on GD 20 at inhalation concentrations up to 1,005 ppm or drinking water concentrations up to 5,000 ppm (477 mg/kg/day). In the inhalation study, fetuses of dams exposed to 1,005 ppm showed significant growth retardation (e.g., significant decreases in mean litter weight, mean fetal weight, and mean fetal crown/rump length) and a significant increase in the incidence of minor skeletal fetal defects/variants (e.g., delayed ossification), compared with controls. These findings could be secondary to maternal toxicity, as dams exposed to 1,005 ppm exhibited a significant 9–12% reduction in body weight gain on GDs 10–20. No exposure-related changes in fetal growth or development were observed in the oral gestational study at maternal doses up to 477 mg/kg/day; a lack of maternal toxicity was also reported at this dose.

In a 2-generation study in rats, F1 pup weight at weaning on postnatal day (PND) 21 was significantly decreased by 10% following maternal exposure to drinking water concentrations of 5,000 ppm (time-weighted dose of 697 mg/kg/day) prior to mating and throughout gestation and lactation (Mebus et al. 1995). As observed in the inhalation gestational study, this effect may be attributable to the significant 40% decrease in body weight gain observed in F0 dams during lactation at 669 mg/kg/day. No exposure-related changes were observed in F2 offspring body weight, despite a 37% decrease in F1 dam body weight gain during lactation. Body weight effects in both F0 and F1 dams were associated with significant decreases in water intake. Since all body weight effects in both generations may be secondary to unpalatability of the test substance at 5,000 ppm in drinking water, adversity of body weight effects in dams could not be determined.

2.18 OTHER NONCANCER

Chronic dacryoadenitis (inflammation) and lymphoid hyperplasia of the submucosa of the Harderian gland were observed in mice administered 1,016 mg/kg/day vinyl acetate in the drinking water for 13 weeks (Hazleton 1980e). The study authors attributed this effect to variation in histologic sectioning and the toxicological significance of this finding is not known. In toxicokinetic studies in rodents, the Harderian gland was found to have the highest concentration of radiolabel in the body following the administration of radiolabeled vinyl acetate (Hazleton 1979a, 1980a). This high concentration of radiolabel may be associated with the chronic dacryoadenitis seen in mice. Since Harderian glands are not present in humans, the relevance of this finding to human health is not known.

2.19 CANCER

In a large cohort of male workers from two chemical companies (n=29,139 workers), a nested case-control design was used to assess the potential association between exposure to 21 specific chemicals and 52 chemical activity groups (Union Carbide 1989). Using this design, no increased risk of lymphatic or hematopoietic tissue cancer was observed in workers “ever” exposed to vinyl acetate compared with those “never” exposed to vinyl acetate. The odds ratios (ORs) for non-Hodgkin’s lymphoma, myeloma, nonlymphocytic leukemia, and lymphocytic leukemia for vinyl acetate were 1.2 (7 cases), 1.6 (3 cases), 0.5 (2 cases), and 1.8 (2 cases), respectively. The number of workers ever exposed to vinyl acetate was not reported. Very little can be determined from this study due to multiple chemical exposures and lack of control for confounding factors. No additional studies evaluating potential associations between vinyl acetate exposure and cancer in humans were available.

Studies in animals indicate that vinyl acetate causes route-specific tumors due to portal-of-entry effects, with exposure-related neoplastic lesions in the upper respiratory system in rats following chronic-duration inhalation exposure and in the oral cavity and upper gastrointestinal tract of rats and mice following chronic-duration drinking water exposure. These findings are summarized below. Evidence for neoplastic effects at sites distant from the site of administration are limited. Observed portal-of-entry effects are attributed to rapid hydrolysis of vinyl acetate following contact with mucosal surfaces; hydrolysis products include acetaldehyde, a known genotoxicant, and acetic acid, which lowers cellular pH, resulting in cellular damage and subsequent proliferation (reviewed by Albertini 2013; Bogdanffy 2002; Bogdanffy and Valentine 2003; Bogdanffy et al. 1999, 2001, 2004; Slikker et al. 2004; see Section 2.21, Mechanisms of Toxicity for further details).

In a chronic-duration inhalation bioassay in rats, the total incidence of nasal tumors (combined) was significantly elevated in male rats at 594.7 ppm (7/59) compared with control (0/59) and nonsignificantly elevated in females (4/59 compared with 0/59 controls) (Bogdanffy et al. 1994a; Hazleton 1988). Nasal tumors observed in males exposed to 594.7 ppm included inverted papilloma, two squamous cell carcinomas, and carcinoma *in situ*; total incidences of benign and malignant nasal tumors were 4/59 and 3/59, respectively. Only squamous cell carcinoma was observed in females. At 200.5 ppm, one male had a nasal papilloma. No nasal cavity tumors were observed in control rats or those exposed to 49.4 ppm vinyl acetate. Effects to the larynx of rats was confined to a single squamous carcinoma in a female rat exposed to 594.7 ppm. No tumors were seen in the lungs of rats, and no treatment-related tumors were observed outside the respiratory system. In similarly exposed mice, neoplastic findings were limited to a single squamous cell lung carcinoma in a male rat at 594.7 ppm and a single adenocarcinoma in a control male; no tumors were reported in female mice (Bogdanffy et al. 1994a; Hazleton 1988).

Squamous cell dysplasia and carcinoma of the oral cavity, tongue, esophagus, and/or forestomach have been reported in a series of studies that exposed Sprague-Dawley rats, Wistar rats, and Swiss mice to vinyl acetate in drinking water over 2 generations (Belpoggi et al. 2002; Maltoni et al. 1997; Minardi et al. 2002). Exposure included breeding males and females and their offspring; exposure began on GD 12 when breeders (F0 animals) were approximately 17 weeks old and continued for 104 weeks in rats and 78 weeks in mice. At sacrifice, a complete histopathological examination was conducted, including multiple levels in the oral cavity. In Sprague-Dawley rats, the incidence of squamous cell carcinoma was significantly increased in the oral cavity of F1 offspring at 620 mg/kg/day and the forestomach in F1 males at ≥120 mg/kg/day and F1 females at 620 mg/kg/day (Minardi et al. 2002). Significant neoplastic

findings in Wistar rats included increased incidence of squamous cell carcinoma of the oral cavity in F1 males and females at 640 mg/kg/day (Belpoggi et al. 2002). In Swiss mice, the study authors reported increases in squamous cell carcinoma of the oral cavity, tongue, esophagus, and forestomach and forestomach acanthoma; however, statistics were not performed by the study authors (Maltoni et al. 1997). Based on statistics performed for this review (GraphPad, Fisher's Exact Test), incidences were significantly increased at 1,200 mg/kg/day for incidence of squamous cell carcinoma of the esophagus in F0 females and the oral cavity, tongue, esophagus, and forestomach in F1 offspring as well as forestomach acanthoma in F1 females. When squamous cell carcinomas and their precursor lesions (squamous cell dysplasia) of the upper gastrointestinal tract were combined for analysis, a statistically significant increase was seen in male and female Sprague-Dawley rats from both generations at 120 and 620 mg/kg/day (Minardi et al. 2002) and male and female Wistar rats from both generations at 640 mg/kg/day and F0 female Wistar rats at 130 mg/kg/day (Belpoggi et al. 2002). The study authors did not conduct combined statistical analysis of mouse data, and the reported data were inadequate for independent statistical analysis.

In contrast to the oral studies discussed above, Bogdanffy et al. (1994b) did not report any statistically significant increases in gastrointestinal neoplastic lesions in Sprague-Dawley rats exposed to vinyl acetate in drinking water at doses up to 302 mg/kg/day for 104 weeks following *in utero* exposure. Only 2/60 males exposed to 302 mg/kg/day developed squamous cell carcinoma of the oral cavity; however, this study did not evaluate multiple histopathological sections of the oral cavity, as was done in the previously discussed oral bioassays. Additionally, while the administered dose appears to be higher than the CEL of 120 mg/kg/day reported for Sprague-Dawley rats by Minardi et al. (2002), it is lower than the CEL of 640 mg/kg/day identified in Wistar rats by Belpoggi et al. (2002); therefore, the dosing in the Bogdanffy et al. (1994b) study may not have been high enough. In support, no noncancer effects were reported by Bogdanffy et al. (1994b) other than weight loss associated with decreased water and food intake, which was attributed to unpalatability of the test substance. This suggests that this study may not have achieved the maximum tolerated dose necessary to evaluate potential carcinogenic effects of vinyl acetate.

Minardi et al. (2002) suggested some evidence for Zymbal gland, lymphatic, lung and liver tumors, but based on statistics performed for this review (GraphPad, Fisher's Exact Test), these were not significantly increased. The study authors concluded that vinyl acetate is a multi-site tumor but statistical findings are more consistent with portal-of-entry effects only.

One standard 2-year chronic-duration oral study also reported neoplastic lesions of the upper gastrointestinal system in male rats (oral cavity squamous cell carcinoma) and male and female mice (squamous cell papilloma and carcinoma of the oral cavity, esophagus, and forestomach) following chronic-duration drinking water exposure (Umeda et al. 2004); however, methodological deficiencies precluded accurate exposure assessment. Instead of mixing the drinking water solution daily, Umeda et al. (2004) mixed the solution twice weekly, reporting test solution stabilities of 72–80% for the rat study and 86–96% for the mouse study. In both studies, concentration-dependent increases in acetic acid concentration and decreases in water pH were reported over a 4-day period. The study authors estimated doses associated with reported effects in rats (442 mg/kg/day) and mice (≥989 mg/kg/day); however, it is unclear if the estimated doses account for the test solution stability or if acetic acid levels and decreased pH of the drinking water contributed to observed findings. Therefore, this study is not included in the LSE table.

The only other potential site of carcinogenicity identified in the oral bioassays discussed above is the uterus in Wistar rats (Belpoggi et al. 2002). In that study, uterine carcinoma was significantly increased in F1 females, and the combined incidence of uterine carcinoma and sarcoma was significantly increased in F0 and F1 females at 640 mg/kg/day, the dose associated with gastrointestinal tumors (Belpoggi et al. 2002). Adenocarcinomas of the uterus were also reported in F344 rats exposed to 143 mg/kg/day via drinking water for 100 weeks (Lijinsky and Reuber 1983). The uterine carcinomas were large, malignant invasive neoplasms that are extremely unusual, which supports that these tumors may be related to vinyl acetate exposure. Other potentially exposure-related tumors reported by Lijinsky and Reuber (1983) include neoplastic nodules of the liver (significant increase in females at 143 mg/kg/day; nonsignificant increase in males at ≥36 mg/kg/day) and C-cell adenomas of the thyroid in females (significant increase at 143 mg/kg/day). However, findings from the Lijinsky and Reuber (1983) study should be interpreted with caution due to several limitations, including small animal groups (20/sex/group), potential contaminants in the commercial grade vinyl acetate of undetermined purity, and reported instability of vinyl acetate in drinking water (that was mixed weekly). The study by Lijinsky and Reuber (1983) is not included in the LSE table since an accurate dose estimate cannot be determined; the study authors suggested that doses were likely half of nominal dose due to weekly decomposition in the drinking water.

IARC has determined that vinyl acetate is possibly carcinogenic to humans (Group 2B) based on inadequate evidence in humans and limited evidence in experimental animals (IARC 1995). The EPA (IRIS 1990) and HHS (NTP 2021) have not evaluated the potential for vinyl acetate to cause cancer in humans.

2.20 GENOTOXICITY

Available evidence indicates that vinyl acetate is not mutagenetic in bacterial systems but may cause mutagenicity in mammalian cells. There is also strong evidence that vinyl acetate is clastogenic and interacts directly with deoxyribonucleic acid (DNA) in mammalian cells; however, findings in *in vivo* studies are mixed. Observed genotoxic effects are generally attributed to the vinyl acetate hydrolysis product acetaldehyde, which is a known genotoxic compound. The results of *in vitro* and *in vivo* genotoxicity studies with vinyl acetate are summarized in Tables 2-4 and 2-5, respectively.

Table 2-4. Genotoxicity of Vinyl Acetate *In Vitro*

		Results		
Species (test system)	Endpoint	With activation	Without activation	Reference
Prokaryotic organisms				
Salmonella typhimurium TA100, TA1530	Gene mutation	–	–	Bartsch et al. 1976
S. typhimurium TA98, TA100, TA1535, TA1537	Gene mutation	–	–	Florin et al. 1980
S. typhimurium TA98, TA100, TA1535, TA1537, TA1538	Gene mutation	–	–	Lijinsky and Andrews 1980
S. typhimurium TA97, TA98, TA100, TA1535,	Gene mutation	–	–	NTP 2017b
S. typhimurium TA97, TA98, TA100	Gene mutation	–	–	Brams et al. 1987
S. typhimurium TA1530, TA100	Gene mutation	–	–	Bartsch et al. 1979
S. typhimurium TA100	Gene mutation	–	–	Barbin et al. 1978
S. typhimurium TA102, TA2638	Gene mutation	–	–	Watanabe et al. 1998
S. typhimurium TA102	Gene mutation	–	No data	Jung et al. 1992; Muller et al. 1993
Escherichia coli WP2, WP2 *uvrA*	Gene mutation	–	–	Watanabe et al. 1998
E. coli PQ37	DNA damage (SOS induction)	–	–	Brams et al. 1987
Mammalian cells				
Cultured human TK6 cells[a]	Gene mutation (*Tk* locus)	+	+	Budinsky et al. 2013
Cultured human TK6 cells[a]	Gene mutation (*HPRT* locus)	–	No data	Budinsky et al. 2013

Table 2-4. Genotoxicity of Vinyl Acetate *In Vitro*

		Results		
Species (test system)	Endpoint	With activation	Without activation	Reference
Cultured human lymphocytes	Micronuclei	No data	+	Maki-Paakkanen and Norppa 1987
Cultured human lymphocytes	Micronuclei	No data	+	Norppa et al. 1988
Cultured human TK6 cells[a]	Micronuclei	+	–	Budinsky et al. 2013
Cultured human lymphocytes	Chromosomal aberrations	No data	+	Jantunen et al. 1986
Cultured human lymphocytes	Chromosomal aberrations	No data	+	Norppa et al. 1985
Cultured human lymphocytes	Chromosomal aberrations	No data	+	Mustonen et al. 1986
Cultured human lymphocytes	Sister chromatid exchange	No data	+	He and Lambert 1985
Cultured human lymphocytes	Sister chromatid exchange	No data	+	Norppa et al. 1985
Cultured human lymphocytes	Sister chromatid exchange	No data	+	Sipi et al. 1992
Cultured hamster ovary cells	Sister chromatid exchange	+	+	Norppa et al. 1985
Cultured human lymphocytes	DNA damage	No data	–	Lambert et al. 1985
Cultured human lymphocytes	DNA cross-links	No data	+	Lambert et al. 1985
Rat nasal epithelial cells	DNA cross-links	No data	+	Kuykendall et al. 1993
Cultured hamster fetal cells	Adenovirus transformation	No data	+	Casto 1980, 1981
Acellular systems				
pUC13 plasmid DNA, calf thymus histones	DNA cross-links	+	No data	Kuykendall and Bogdanffy 1992

[a]For this study, cells were cultured either in the presence of heat-inactivated horse serum (high capacity for hydrolysis of vinyl acetate to acetaldehyde) or heat-inactivated fetal bovine serum (low capacity for hydrolysis of vinyl acetate to acetaldehyde); horse serum results are in the “with activation” column, bovine serum results are in the “without activation” column.

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

Table 2-5. Genotoxicity of Vinyl Acetate *In Vivo*

Species (exposure route)	Endpoint	Results	Reference
Mammals			
Rat (inhalation, 4 or 13 weeks)	Micronuclei in bone marrow erythrocytes	–	Hazleton 1979c, 1980c
Mouse (inhalation, 4 or 13 weeks)	Micronuclei in bone marrow erythrocytes	–	Hazleton 1979b, 1980b
Mouse (intraperitoneal, once)	Micronuclei in spermatogonial cells	–	Lahdetie 1988
Mouse (oral, 4 weeks)	Micronuclei in bone marrow erythrocytes	±	Hazleton 1979d
Mouse (oral, 13 weeks)	Micronuclei in bone marrow erythrocytes	–	Hazleton 1980e
at (oral, 4 or 13 weeks)	Micronuclei in bone marrow erythrocytes	–	Hazleton 1979b, 1980f
Rat (intraperitoneal, once)	Micronuclei in polychromatic erythrocytes	+	NTP 2017a
Mouse (intraperitoneal, once)	Micronuclei in polychromatic erythrocytes	+	Maki-Paakkanen and Norppa 1987
Mouse (intraperitoneal, once)	Micronuclei in polychromatic erythrocytes	+	Norppa et al. 1988
Mouse (intraperitoneal, once)	Sister chromatid exchange in bone marrow	+	Takeshita et al. 1986
Rat (inhalation, 14 days)	DNA adducts in nasal respiratory and olfactory epithelia	+	Hsiao et al. 2022
Rat (inhalation, 6 hours)	DNA adducts in nasal respiratory and olfactory epithelia	+	Liu et al. 2021
Rat (inhalation, 4 hours)	DNA adducts in hepatocytes	–	Simon et al. 1985b
Rat (oral, once)	DNA adducts in hepatocytes	–	Simon et al. 1985b

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

Mutagenicity. Numerous studies indicate that vinyl acetate is not mutagenic in bacterial systems with or without metabolic activation (Barbin et al. 1978; Bartsch et al. 1976, 1979; Brams et al. 1987; Florin et al. 1980; Jung et al. 1992; Lijinsky and Andrews 1980; Muller et al. 1993; NTP 2017b; Watanabe et al. 1998). However, vinyl acetate has been shown to cause mutations in human TK6 cells under conditions favoring hydrolysis of vinyl acetate into acetaldehyde and acetic acid (Budinsky et al. 2013).

Clastogenicity. Several studies report clastogenic effects in cultured human lymphocytes and whole blood, including dose-dependent increases in the induction of chromosomal aberrations (Jantunen et al. 1986; Mustonen et al. 1986; Norppa et al. 1985), sister chromatid exchanges (He and Lambert 1985; Norppa et al. 1985; Sipi et al. 1992), and micronuclei (Maki-Paakkanen and Norppa 1987; Norppa et al. 1988). In human TK6 cells, vinyl acetate induced micronuclei under conditions favoring hydrolysis of vinyl acetate into acetaldehyde and acetic acid (Budinsky et al. 2013). 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). Observed effects have been attributed to the hydrolysis product of vinyl acetate, acetaldehyde (Albertini 2013; Sipi et al. 1992). Additionally, decreased pH associated with generation of acetic acid may contribute to some of the observed *in vitro* clastogenic effects.

In vivo, the group mean incidence of bone marrow erythrocytes containing micronuclei was increased in mice exposed to high doses (1,023–1,040 mg/kg/day) in their drinking water for 4 weeks; however, all micronuclei counts were within the expected range of spontaneous occurrence (Hazleton 1979d). Bone marrow micronuclei were not induced in mice orally exposed to similar doses (up to 1,016 mg/kg/day) for 13 weeks (Hazleton 1980e) or rats orally exposed to doses up to 755 or 810 mg/kg/day for 4 or 13 weeks, respectively (Hazleton 1979d, 1980f). In inhalation studies, micronuclei were not induced in the bone marrow of rats or mice exposed to concentrations up to approximately 1,000 ppm for 4 or 13 weeks (Hazleton 1979b, 1979c, 1980b, 1980c).

Following a single intraperitoneal exposure, vinyl acetate induced a dose-dependent increase in micronucleated polychromatic erythrocytes in rat or mouse bone marrow cells (Maki-Paakkanen and Norppa 1987; Norppa et al. 1988; NTP 2017a) and a small dose-related increase in sister chromatid exchanges in the bone marrow cells of hepatectomized and non-hepatectomized mice (Takeshita et al. 1986). However, vinyl acetate did not induce micronuclei in spermatogonial cells of mice following intraperitoneal injection (Lahdetie 1988). The discrepant results between oral, inhalation, and intraperitoneal studies are likely due to route of administration since vinyl acetate is associated with portal-of-entry effects only (Albertini 2013); other contributing factors may include the tissue distribution of vinyl acetate, tissue-specific carboxylesterase activity, and/or species differences.

DNA Interactions and Damage. Vinyl acetate has caused DNA cross-linking in cultured human lymphocytes (Lambert et al. 1985), rat nasal epithelial tissue (Kuykendall et al. 1993), and pUC13 plasmid DNA (Kuykendall and Bogdanffy 1992). Co-incubation with a carboxylesterase inhibitor decreased DNA cross-linking in nasal tissue and plasmids, indicating that hydrolysis of vinyl acetate generates genotoxic metabolites (Kuykendall et al. 1993; Kuykendall and Bogdanffy 1992). It is likely that the genotoxic agent is the hydrolysis product acetaldehyde; however, lowering of culture pH due to acetic acid production may contribute to observed effects *in vitro* (Kuykendall et al. 1993; Kuykendall and Bogdanffy 1992). In other *in vitro* studies, vinyl acetate did not cause DNA damage in the *Escherichia coli* SOS chromotest (Brams et al. 1987) or single-strand breaks in human lymphocytes (Lambert et al. 1985).

In rats, radiolabeled DNA adducts were identified in nasal respiratory and olfactory epithelial cells following exposure to vinyl acetate for 6 hours (Liu et al. 2021) and 14 days (Hsiao et al. 2022). Since acetaldehyde is produced endogenously by living cells during normal metabolism, presence of radiolabel was critical to provide evidence that the observed N^2-ethyl-dG adducts were exogenous in nature, rather than detection of endogenous acetaldehyde adducts. The number of exogenous DNA adducts was >2-fold higher in the nasal respiratory epithelium, compared to the olfactory epithelium (Liu et al. 2021). In the 14-day study, when the dose increased by 12-fold, the DNA adducts increased by ~38.5- and 262-fold in the respiratory and olfactory epithelia, respectively (Hsiao et al. 2022). In another *in vivo* study, vinyl acetate did not produce specific DNA-adducts in rat liver following treatment via inhalation or gavage (Simon et al. 1985b).

2.21 MECHANISMS OF TOXICITY

Several reviews have described the proposed mechanisms of toxicity underlying portal-of-entry tissue damage and subsequent tumor formation in tissues of the upper respiratory system and gastrointestinal tracts of rats and mice following inhalation and oral exposure, respectively (Albertini 2013; Bogdanffy and Valentine 2003; Bogdanffy et al. 1999, 2001, 2004; Slikker et al. 2004). Collectively, these reviews propose the following mechanistic steps following portal-of-entry absorption of vinyl acetate:

1. Rapid hydrolysis of vinyl acetate by carboxylesterase in epithelial tissues in the upper respiratory and gastrointestinal tract result in the production acetaldehyde and acetic acid (see Section 3.1, Toxicokinetics for more details)
2. Proton accumulation and intracellular acidification, resulting in cytotoxicity and cell death
3. Restorative and/or mitogenic cell proliferation
4. Mutagenesis (spontaneous and induced by acetaldehyde-mediated DNA-protein crosslinks)
5. Neoplastic transformation

Hydrolysis of vinyl acetate by carboxylesterase has been shown to be a key step in this mechanistic pathway. Both acetic acid-mediated cytotoxicity and acetaldehyde-mediated DNA-crosslinks in rat nasal explants were attenuated following pretreatment with the carboxylesterase inhibitor bis(p-nitrophenyl)phosphate (BNPP) (Kuykendall et al. 1993). Similarly, pretreatment of mouse oral buccal epithelial cells and rat nasal epithelial cells and tissue explant cultures with BNPP reduced acetic acid-mediated intracellular acidification (Lantz et al. 2003; Nakamoto et al. 2005).

Intracellular acidification has been proposed to be the most sensitive precursor event and indicator of vinyl acetate toxicity (Bogdanffy and Valentine 2003; Bogdanffy et al. 1999, 2001, 2004; Slikker et al. 2004). Since intracellular pH is tightly maintained by homeostatic mechanisms, intracellular acidification and subsequent cytotoxicity and cell proliferation do not occur until a sufficiently high threshold concentration of acetic acid/proton is met. Additional data indicate that metabolic formation of acetaldehyde alone, without intracellular acidification, is inadequate to induce tumor formation. Taken together, mechanistic information along with observed toxicological data indicate that tumor formation is a threshold effect for vinyl acetate. The proposed mechanistic steps are supported by mode-of-action based kinetic modeling of nasal tumors in rats (Bogdanffy and Valentine 2003; Bogdanffy et al. 1999). While no such model exists for oral exposure, the mode of action is expected to be analogous (Bogdanffy and Valentine 2003).

An alternate mechanism of carcinogenicity could occur if vinyl acetate was metabolized by the microsomal P450 system to its corresponding epoxide, which could produce the same products of DNA alkylation as vinyl chloride and vinyl carbamate (Laib and Bolt 1986). However, 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 1986). These results suggest that vinyl acetate is not likely epoxidized by the microsomal P450 system to an ultimate carcinogenic metabolite in the liver. In support, pretreatment of isolated nasal cavities from rats with the cytochrome P450 2E1 (CYP2E1) inhibitor diallyl sulfide did not alter the rate of vinyl acetate extraction from the test chamber, while pretreatment with the carboxylesterase inhibitor BNPP reduced extraction by approximate 41% (Bogdanffy et al. 1999).

CHAPTER 3. TOXICOKINETICS, SUSCEPTIBLE POPULATIONS, BIOMARKERS, CHEMICAL INTERACTIONS

3.1 TOXICOKINETICS

Toxicokinetic data are available from *in vivo* animal studies and *in vitro* studies regarding the absorption, distribution, metabolism, and excretion of vinyl acetate. Available data are summarized below.

- Vinyl acetate is rapidly and effectively absorbed via the inhalation and oral route. Absorption data following dermal exposure are not available. However, vinyl acetate is expected to be absorbed to some degree based on lethality reported in a single rabbit study following exposure to a highly concentrated dermal dose.

- Vinyl acetate is rapidly and widely distributed, with the highest concentration in the Harderian gland, salivary glands, lacrimal glands, gastrointestinal mucosa, and respiratory tract.

- Vinyl acetate is rapidly hydrolyzed by carboxylesterases to form acetaldehyde and acetic acid. Under physiological conditions, acetic acid is highly ionized into acetate, which is incorporated into the "2 carbon pool" of normal body metabolism and eventually forms carbon dioxide (CO_2) as the major breakdown product.

- Vinyl acetate is eliminated rapidly from the body, primarily through expired air as CO_2.

- Available *in vivo* and *in vitro* data have been utilized to develop PBPK models to simulate the kinetics of vinyl acetate uptake and metabolism in the nasal cavity in rats and humans.

3.1.1 Absorption

No studies were located regarding the absorption of vinyl acetate in humans after exposure via any route.

Studies in rats indicate that vinyl acetate is rapidly and effectively absorbed via the inhalation route. 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 (Hazleton 1979a). 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).

Animal studies indicate that vinyl acetate is also quickly and effectively absorbed via the oral route. 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).

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). No further details regarding dermal absorption in laboratory animals are available.

3.1.2 Distribution

No studies were located regarding the distribution of vinyl acetate in humans following exposure via any route or animals following dermal exposure.

Studies in male and female rats show that radioactivity is immediately and widely distributed throughout the body after inhalation exposure to 1,000 ppm ^{14}C-VA (Hazleton 1979a). The salivary glands, lacrimal glands, Harderian glands, gastrointestinal mucosa, nasoturbinates, kidneys, and certain portions of the larynges had the highest concentrations of the radiolabel. The brain, spinal cord, liver, fat, and bone marrow also had readily detectable levels of radioactivity. Low levels in the heart, blood, testes, and skeletal muscle were also observed. Whole-body autoradiographs obtained at 1 and 6 hours after exposure showed 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 3-1. As can be seen in Table 3-1, 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 distribution pattern were found at 1, 6, and 72 hours after exposure.

Table 3-1. Distribution of Radioactivity in Rats Immediately After Inhalation of 750 ppm [^{14}C]-Vinyl Acetate for 6 Hours

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	2,045
Heart	82
Ileum	393
Kidney	204
Liver	204
Lungs	270
Residual carcass	72
Submaxillary salivary gland	341
Skeletal muscle	61
Stomach	210

Source: Hazleton 1980a

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 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;

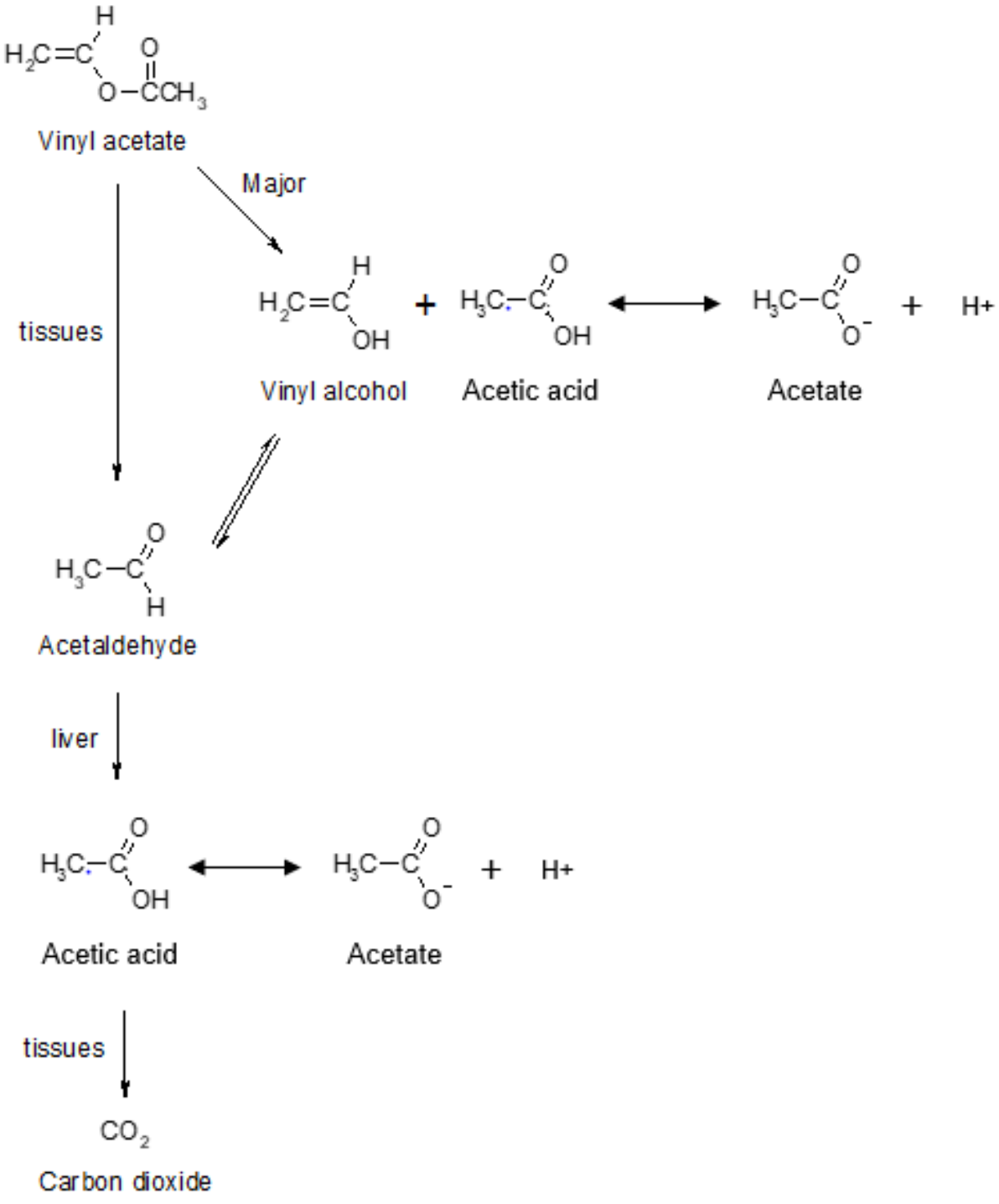
females had higher concentration in the ovaries than did males in the testes. A similar distribution pattern was seen in mice of both sexes administered a single oral dose of 5,000 ppm of ^{14}C-VA as an aqueous solution (Hazleton 1980a). In this study, the highest concentrations of radioactivity were found in Harderian glands, salivary and lingual glands, gastrointestinal mucosa, liver, and brown fat. 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. 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.

3.1.3 Metabolism

The metabolism of vinyl acetate has been studied in humans (Bogdanffy et al. 1998; Hinderliter et al. 2005), animals (Hazleton 1979a, 1980a; Holub and Tarkowski 1982; Morris et al. 2002; Simon et al. 1985a), and *in vitro* studies (Bogdanffy and Taylor 1993; Bogdanffy et al. 1998, 1999; Boyland and Chasseaud 1967; Fedtke and Wiegand 1990; Morris et al. 2002). Metabolism of vinyl acetate, particularly at the portal of entry, has also been thoroughly reviewed (Andersen and Sarangapani 1999; Andersen et al. 2002; Bogdanffy et al. 2001; Plowchalk et al. 1997; Slikker et al. 2004). Collectively, these studies show that vinyl acetate quickly undergoes hydrolysis in the body through several intermediate steps to form the principal end products, CO_2, 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. A summary of the proposed metabolic pathways for vinyl acetate is discussed below and presented in Figure 3-1.

The primary metabolic pathway for vinyl acetate is rapid hydrolysis into acetic acid and the unstable intermediate vinyl alcohol via a high-affinity carboxylesterase pathway (Andersen et al. 2002; Bogdanffy et al. 1999, 2001; Plowchalk et al. 1997; Slikker et al. 2004). Vinyl alcohol is rapidly converted to acetaldehyde, and acetic acid is extensively ionized into acetate under physiological conditions. *In vivo* and *in vitro* experiments have shown that the carboxylesterases in epithelial cells in the respiratory tract of rats and humans and the oral mucosa of rats and mice are capable of metabolizing vinyl acetate, although hydrolysis activity is approximately 100-fold lower in oral mucosal cells compared with nasal mucosal cells (Bogdanffy and Taylor 1993; Bogdanffy et al. 1998, 1999; Hinderliter et al. 2005; Morris et al. 2002). These findings indicate that metabolism of vinyl acetate is expected to occur at the portal of entry, although blood and liver cells are also capable of hydrolyzing vinyl acetate into acetaldehyde and acetate via esterases (Fedtke and Wiegand 1990; Hazleton 1979a, 1980a; Simon et al. 1985a). In the liver,

Figure 3-1. Proposed Primary Metabolic Pathway for Vinyl Acetate



acetaldehyde can be further metabolized into acetate. This in turn is incorporated into the "2 carbon pool" of normal body metabolism and eventually forms CO_2 as the major breakdown 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). Following inhalation exposure, zero-order kinetics were observed at higher concentrations (800–1,400 ppm) and first-order kinetics at lower concentrations (Simon et al. 1985a). This indicates that the metabolic pathways of vinyl acetate are saturable at high levels.

In vitro studies show that the half-lives for conversion of vinyl acetate to acetaldehyde in rat plasma to be 57, 58, and 57 seconds at concentrations of 25, 50, or 100 ppm, respectively. Using rat whole blood, the half-lives of vinyl acetate were found to be 112, 121, and 141 seconds at the same conditions, respectively. In rat liver homogenates, the half-lives were 50, 97, and 167 seconds, again at the same concentrations, respectively. Similar half-lives were seen in mouse plasma, whole blood, and liver homogenates. Furthermore, even with diluted preparations of plasma, whole blood, and liver homogenates, the hydrolysis of vinyl acetate is very rapid (Hazleton 1979a). A later *in vitro* study using human blood and plasma found that the hydrolysis of vinyl acetate proceeded at a similar rate as reported for the rat and mouse (Hazleton 1980a). However, different results were reported by Fedtke and Wiegand (1990) using 200 µM vinyl acetate added to rat and human blood. They reported that the half-life of vinyl acetate elimination in human whole blood was 4.1 minutes as compared to <1 minute in rat whole blood (Fedtke and Wiegand 1990). The majority of the hydrolysis was found to occur in the red blood cells rather than the plasma of human blood. The half-life in plasma was 62 minutes as compared to 5.5 minutes in red blood cells. However, in rat plasma, the half-life of vinyl acetate elimination was 1.2 minutes as compared to 5.6 minutes in rat red blood cells. While these results differ from those reported above with regard to the location of the hydrolytic enzymes in the blood across species, they do confirm that hydrolysis is the predominant route of metabolism for vinyl acetate in both human and rat blood.

Further *in vitro* metabolic studies show that vinyl acetate added to preparations of rat liver supernatant did conjugate (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 Chasseaud 1967, 1970). Rats exposed for 5 hours/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 (Holub and Tarkowski 1982).

According to the study 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). However, Bogdanffy et al. (1999) concluded that the lack of observed glutathione depletion following exposure indicates that glutathione conjugation is not a major metabolic pathway for vinyl acetate.

Based on analogy to vinyl chloride and vinyl carbamate, it is possible that vinyl acetate could be metabolized into its corresponding epoxide form by cytochrome P450 (CYP450) enzymes; however, evidence of epoxide formation has not been identified following *in vivo* exposure to vinyl acetate (Laib and Bolt 1986; Simon et al. 1985a). Furthermore, inhibition of CYP2E1 using diallyl sulfide did not affect the pharmacological uptake of vinyl acetate by rat nasal explants, but inhibition of carboxylesterases with BNPP decreased uptake by approximately 60% (Bogdanffy et al. 1999). Taken together, these studies do not indicate that metabolism by CYP450 is a major metabolic pathway for vinyl acetate.

3.1.4 Excretion

No studies were located regarding the excretion of vinyl acetate in humans following exposure via any route.

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 CO_2 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.

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 gavage (Hazleton 1980a). During the 6 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 CO_2.

3.1.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Models are simplified representations of a system with the intent of reproducing or simulating its structure, function, and behavior. PBPK models are more firmly grounded in principles of biology and biochemistry. They use mathematical descriptions of the processes determining uptake and disposition of chemical substances as a function of their physicochemical, biochemical, and physiological characteristics (Andersen and Krishnan 1994; Clewell 1995; Mumtaz et al. 2012a; Sweeney and Gearhart 2020). PBPK models have been developed for both organic and inorganic pollutants (Ruiz et al. 2011) and are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Mumtaz et al. 2012b; Ruiz et al. 2011; Sweeney and Gearhart 2020; Tan et al. 2020). PBPK models can also be used to more accurately extrapolate from animal to human, high dose to low dose, route to route, and various exposure scenarios and to study pollutant mixtures (El-Masri et al. 2004). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic endpoints (Clewell 1995).

Research on PBPK models for vinyl acetate have focused on simulating characteristics of the anatomy and physiology of the rodent and human that are thought to contribute to interspecies differences in dose-response relationships for nasal lesions (Andersen and Sarangapani 1999; Andersen et al. 2002). Important features of vinyl acetate-induced nasal lesions and vinyl acetate kinetics that are relevant to

interspecies extrapolation include: (1) regional gradients of nasal lesions, with more severe lesions occurring in the anterior regions (Bogdanffy et al. 1994a); (2) nearly 100% first-pass extraction of vinyl acetate from inspired air at low concentrations which saturates at higher concentrations (Plowchalk et al. 1997); and (3) intracellular acidification resulting from metabolism of vinyl acetate to acetic acid (Bogdanffy 2002).

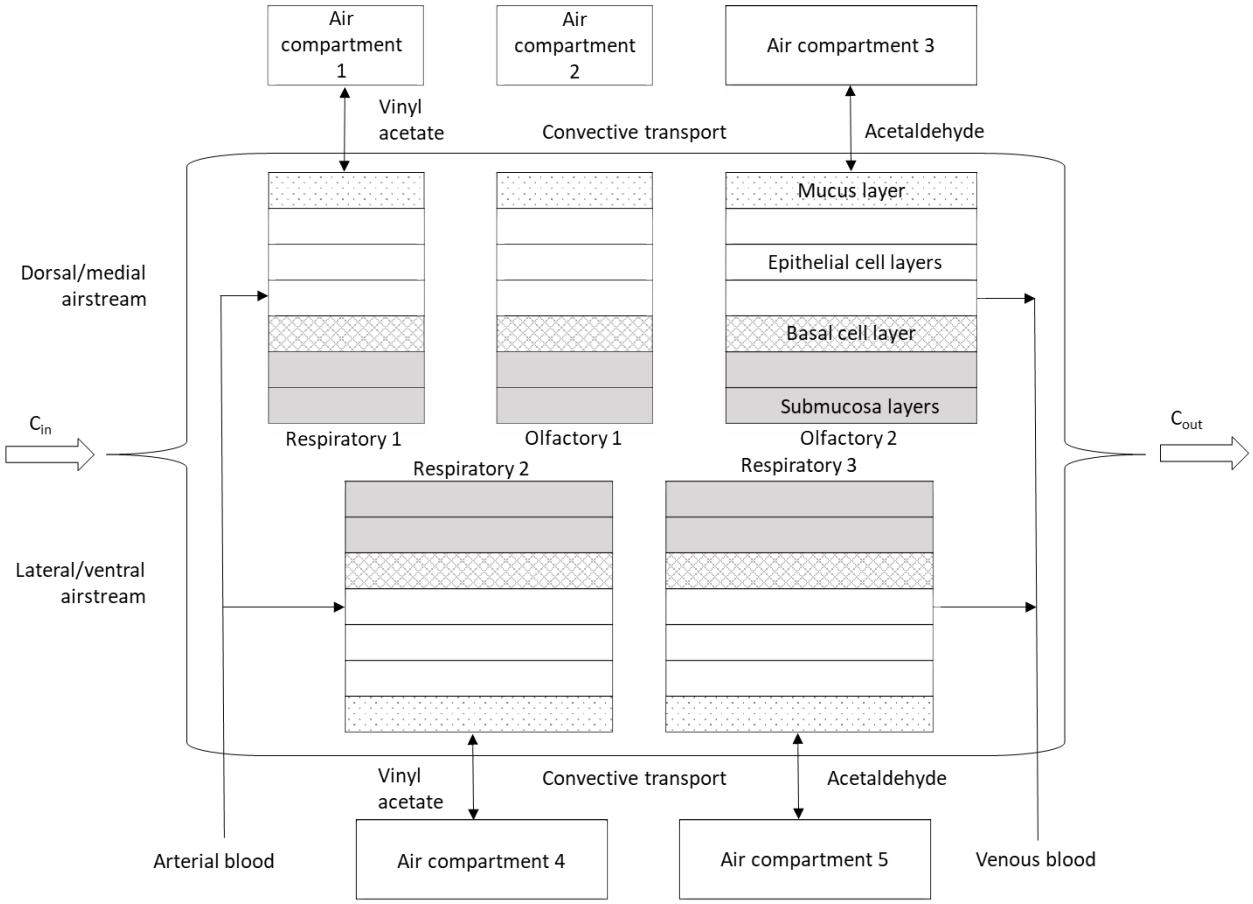
Several models have been developed to simulate the kinetics of vinyl acetate uptake and metabolism in the nasal cavity (Andersen and Sarangapani 1999; Bogdanffy et al. 1999; Plowchalk et al. 1997; Morris et al. 1993). Two models are described in detail in the following discussion because they provide a means to simulate the nasal cavities of rats (Bogdanffy et al. 1999; Plowchalk et al. 1997) and humans (Bogdanffy et al. 1999); and have been evaluated with experimental observations other than those used in model calibration (Bogdanffy et al. 1999; Hinderliter et al. 2005). The models have been applied to predicting nasal tissue dosimetry and interspecies extrapolation of dosimetry in rats to humans (Andersen et al. 2002; Bogdanffy et al. 1999). These models have several features that are important for predicting vinyl acetate dosimetry in the nasal cavity: (1) convective delivery of vinyl acetate to the mucus surface layer of olfactory and respiratory tissues; (2) diffusion of vinyl acetate into progressively deeper layers of olfactory and respiratory tissues; (3) saturable metabolism of vinyl acetate to acetic acid and acetaldehyde; (4) systemic absorption of vinyl acetate and metabolites from submucosal layers; and (5) acidification of olfactory and respiratory tissues resulting from release of protons in the formation of acetic acid.

Bogdanffy et al. (1999; Plowchalk et al. 1997) Model

Description. Bogdanffy et al. (1999) modified the Plowchalk et al. (1997) model to create models of the kinetics of vinyl acetate uptake and metabolism in the nasal cavity of rats and humans. Two major changes were made from the Plowchalk et al. (1997) rat model. The number of compartments was increased from three to five by including an additional dorsal/medial olfactory tissue compartment, and an additional lateral/ventral respiratory tissue compartment (Figure 3-2). Flow-limited exchange of vinyl acetate and its metabolites at the air-mucus layer interface was replaced with diffusion limited exchange.

The Bogdanffy et al. (1999) model divides the nasal tissues into compartments representing: (1) dorsal medial respiratory tissue; (2) dorsal/medial olfactory tissue; and (3) lateral/ventral respiratory tissue. The rat model includes two dorsal medial olfactory tissue compartments; the human model includes a single dorsal medial olfactory tissue compartment. Each tissue compartment is represented by layered

Figure 3-2. PBPK Model of the Rat Nasal Cavity Used to Compute Vinyl Acetate Extraction and Acetaldehyde Exhalation Under Steady-State Conditions*



*The generated structure of the human model is identical to that of the rat, with the exception of having only one olfactory tissue compartment.

Source: Bogdanffy et al. (1999), by permission of Oxford University Press

subcompartments that provide a diffusion pathway for vinyl acetate and its metabolites between the surface mucus layer and deeper epithelial, basal cell, and submucosal layers. Inhaled vinyl acetate deposits in the surface mucus layer of each tissue compartment and then diffuses to deeper subcompartments where it is cleared by metabolism and absorption to blood. The model simulates two air flow patterns in the nasal cavity. A dorsal/medial flow contacts the dorsal olfactory and respiratory compartments and a lateral/ventral flow that contacts the lateral ventral respiratory tissue. Vinyl acetate and its volatile metabolites are assumed to be homogeneously distributed in the air flows and move through the nasal cavity by convection. Exchanges between chemicals in air and the mucus surface layer is assumed to occur by diffusion, governed by the air-mucus concertation gradient, the mucus surface area, a mass transfer coefficient (cm/hour) and a tissue:air partition coefficient. Exchange between tissue subcompartments is governed by diffusion coefficients (cm^2/hour) and the concentration gradient between subcompartments. Metabolism is simulated as Michaelis-Menten processes (V_{max}, K_M), with parameter values assigned to carboxylesterase, acetyl-CoA synthetase, and aldehyde dehydrogenase for each tissue subcompartment. Absorption of vinyl acetate and metabolites from the submucosa is assumed to be flow-limited and governed by the mass of each chemical in the submucosa and blood flow rate to the submucosa. The partition coefficients that govern exchange between air and the mucus surface layer are 29 for vinyl acetate, 140 for acetaldehyde, and 80,000 for acetic acid. These values promote release of acetaldehyde to air and trapping of acetic acid in tissues. The model includes parameters to simulate the change in intracellular pH (free hydrogen ion concentration, H^+) in olfactory and respiratory tissues. This is achieved by simulating the production of H^+ in the conversion of vinyl acetate to acetic acid and removal of intracellular H^+ from facilitated H^+/Na^+ exchange. The rate of formation of H^+ is governed by the rate of formation of acetic acid from vinyl acetate which results in 3 moles of H^+ per mole of vinyl acetate consumed. Rate of H^+/Na^+ exchange is simulated from a Hill equation for the saturable exchange (V_{max}, K_M, Hill coefficient).

Parameter Estimates and Calibration. Distribution of metabolism enzymes to tissue subcompartments was based on studies of the histochemical localization of the enzymes in nasal tissue (Plowchalk et al. 1997). A high affinity carboxylesterase activity (K_M 4.7 µg/mL) was attributed to the mucus surface layer. Lower affinity carboxylesterase activities (K_M 40–50 µg/mL) were attributed to the respiratory and olfactory epithelium, and submucosa. Acetyl-CoA synthetase activities were attributed to the respiratory and olfactory epithelium, and submucosa. Aldehyde dehydrogenase activity was limited to the respiratory and olfactory epithelia. Parameters for carboxylesterase and aldehyde dehydrogenase were obtained from studies of whole tissues and were scaled (V_{max}) to tissue compartment surface areas (Bogdanffy et al. 1998). Parameters for acetyl-CoA synthetase were based on studies of rat liver and

were assumed to be the same for nasal tissues. Values for humans were scaled based on surface area of the nasal tissues (Knowles et al. 1974). Tissue:air partition coefficients for vinyl acetate acetaldehyde were obtained from gas uptake studies (Plowchalk et al. 1997), and the partition coefficient from acetic acid was from Hine and Mookerjee (1975). Diffusion coefficients for vinyl acetate, acetaldehyde, and acetic acid were estimated by Morris et al. (1993). Parameters for the Hill equation used to simulate H^+/Na^+ exchange were based on studies of H^+/Na^+ exchange in human leukocytes (Frelin et al. 1988).

Evaluation. The rat model was evaluated against observations made in rats exposed nose-only to vinyl acetate (Bogdanffy et al. 1999). Air containing vinyl acetate (75–1,500 ppm) was drawn through the nasal cavity of rats and air exiting through the nasopharynx was collected from a nasopharyngeal cannula. This configuration allowed measurements of first-pass extraction and metabolism of vinyl chloride within the nasal cavity. Values for the metabolism parameters for carboxylesterase were calibrated to fit observations from rats exposed at an air flow rate of 100 mL/minute and then the model was evaluated against observations made at 50 and 200 mL/minute. The calibrated model predicted the observed concentration-dependent extraction of vinyl acetate from the inhaled air at all three air flow rates. The model also predicted the concentrations of acetaldehyde in nasopharyngeal air observed at 50 and 100 mL/minute, but overpredicted concentrations at 200 mL/minute.

The Bogdanffy et al. (1999) human model was evaluated against data from an experimental study conducted in humans (Hinderliter et al. 2005). Five adult subjects inhaled, nose-only, vinyl acetate (labeled with ^{13}C at the 1 and 2 positions) from an exposure bag. A nasopharyngeal probe was inserted to allow collection of air exiting the nasal cavity at the nasopharynx. Subjects inhaled vinyl acetate at concentrations of 1, 5, or 10 ppm for periods of 3–5 minutes, at rest or during light exercise. Agreement between observations and model predictions was assessed from the Pearson's correlation coefficient (r) for the observed and predicted nasopharyngeal concentrations of vinyl acetate and acetaldehyde. Without adjustment of model parameter values from those reported in Bogdanffy et al. (1999), the correlation coefficient was 0.9 for vinyl acetate and 0.6 for aldehyde. The experimental design could not control for increases in breathing frequency that accompanied exposures (e.g., doubling with exposure to 10 ppm). When exposures were simulated at inspired air flows of 0.5 or 2 times the default value (7.5 L/minute), the observed mean nasopharyngeal concentrations of vinyl acetate and acetaldehyde fell within the ranges predicted for the range of air flows. Nasopharyngeal concentrations of vinyl acetate were uniformly lower than the inspired concentrations, indicating extraction of vinyl acetate, and increased in proportion to the inspired concentration, suggesting the extraction was not saturated at the exposures studied.

Applications to Dosimetry. Bogdanffy et al. (1999) applied the model to simulating doses of vinyl acetate, acetaldehyde, acetic acid, and intracellular free hydrogen ion to the olfactory epithelium of the rat and human exposed to the same concentrations of vinyl acetate. In both humans and rats, the internal external concentration-epithelium dose relationship was predicted to be nonlinear at exposure concentrations >200 ppm. At exposure concentrations of 200 or 600 ppm, steady-state olfactory tissue concentrations of vinyl acetate, acetaldehyde, and acetic acid were predicted to be higher in humans compared to rats.

3.1.6 Animal-to-Human Extrapolations

The toxicokinetics of inhaled vinyl acetate in humans are similar to those that have been observed in rats and mice, although some differences may occur due to differences in carboxylesterase distribution and/or activity. As described in section 3.1.5, steady-state olfactory tissue concentrations of vinyl acetate, acetaldehyde, and acetic acid were predicted to be higher in humans compared to rats given the same external exposure levels (Bogdanffy et al. 1999). In nasal tissue explants, carboxylesterase activity is about 3 times higher in rat respiratory tissues than human tissues, but roughly equivalent in rat and human olfactory tissues (Bogdanffy et al. 1998). However, K_m values were similar between species and nasal tissue regions (0.04–0.05 mg/mL) (Bogdanffy et al. 1998).

Additional species-specific properties of the respiratory system also impact animal-to-human extrapolations. In addition to differences in physiology (e.g., carboxylesterase distribution and/or activity), there are differences in upper airway morphology between rodents and humans resulting in a higher ratio of the nasal passage surface area to ventilation volume in rodents, compared to humans (EPA 1994). PBPK models evaluating nasal effects of vinyl acetate exposure account for these differences in morphology in dosimetric calculations (Bogdanffy et al. 1997). However, PBPK models do not account for situations in which nasal exposure would be lower when ventilation in the human occurs from a mix of nasal and oral breathing (e.g., during moderate to heavy exercise or in people who habitually breathe through their mouth) (ICRP 1994). This introduces some uncertainty in animal-to-human extrapolations since rodents are obligate nasal breathers (EPA 1994). Additionally, the available PBPK models were developed for adult rodents and humas. In order to extrapolate across life stages, all parameters (e.g., ventilation rate) would have to be reevaluated and assigned values that represent specific pre-adult ages (e.g., infants, children).

While no oral toxicokinetic data are available in humans, data in laboratory animals indicate that toxicokinetics are similar between routes and species. Oral tissue carboxylesterase activities were similar between rats and mice (0.5–0.9 mM) (Morris et al. 2002).

3.2 CHILDREN AND OTHER POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Children may be more or less susceptible than adults to health effects from exposure to hazardous substances and the relationship may change with developmental age.

This section also discusses unusually susceptible populations. A susceptible population may exhibit different or enhanced responses to certain chemicals than most persons exposed to the same level of these chemicals in the environment. Factors involved with increased susceptibility may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters can reduce detoxification or excretion or compromise organ function.

Populations at greater exposure risk to unusually high exposure levels to vinyl acetate are discussed in Section 5.7, Populations with Potentially High Exposures.

Available literature does not specifically identify any populations with confirmed unusual or increased susceptibility to the health effects of vinyl acetate. However, based on reported irritative properties of vinyl acetate, certain groups may be more susceptible to health effects of vinyl acetate exposure. For example, individuals with pre-existing health problems in the upper respiratory tract, eyes, and possibly the skin may be unusually susceptible to the irritative effects associated with exposure to vinyl acetate. Preplacement medical examinations to identify such conditions have been recommended for people who may be occupationally exposed to vinyl acetate (NIOSH 1978). Smokers may also 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).

Certain genetic variants in the human population may confer increased susceptibility to the toxic effects of vinyl acetate since toxic effects are presumably mediated via metabolites (acetaldehyde and acetic acid; see Section 2.21 for more details). Since hydrolysis of vinyl acetate is carboxylesterase-dependent, identified genetic variants of carboxylesterase that alter enzymatic function could potentially increase susceptibility to toxic effects (Fukami et al. 2008; Yamada et al. 2010; Zhu et al. 2008); however, data regarding human carboxylesterase and vinyl acetate metabolism are limited to a single study reporting a small range of activity in nasal epithelial cells from eight male and one female Caucasian donors (Bogdanffy et al. 1998). Individuals with certain aldehyde dehydrogenase (ALDH2) polymorphisms that reduce the rate of acetaldehyde metabolism may also have increased susceptibility to toxic effects. However, a PBPK model incorporating ALDH2 polymorphisms predicted that the impact of polymorphisms would be negligible in human olfactory tissue (Teeguarden et al. 2008).

It is unclear if the developing fetus or neonate are uniquely susceptible to toxic effects of vinyl acetate, as all available studies report developmental effects at exposure levels associated with parental toxicity (Hazleton 1980d; Hurtt et al. 1995; Mebus et al. 1995).

3.3 BIOMARKERS OF EXPOSURE AND EFFECT

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 2006). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. Biomarkers of exposure to vinyl acetate are discussed in Section 3.3.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that (depending on magnitude) can be recognized as an established or potential health impairment or disease (NAS/NRC 2006). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effect caused by vinyl acetate are discussed in Section 3.3.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.2, Children and Other Populations that are Unusually Susceptible.

3.3.1 Biomarkers of Exposure

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, 1980a; Simon et al. 1985a). Acetaldehyde is subsequently metabolized to acetate in the liver. Acetate enters normal metabolic pathways and is broken down to CO_2, 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 difficult to determine which metabolites were due to vinyl acetate exposure and which were present as a result of normal metabolic processes. No other biomarkers (specific or otherwise) have been identified to indicate exposure to vinyl acetate.

3.3.2 Biomarkers of Effect

Numerous positive genotoxic endpoints 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. Intracellular acidification in nasal tissue has been proposed as the most sensitive measure of vinyl acetate toxicity (Bogdanffy and Valentine 2003; Bogdanffy et al. 1999, 2001, 2004). Again, this effect cannot be considered a specific biomarker of effects caused by vinyl acetate because intracellular acidification is a proposed mechanism for several other known nasal toxicants, including numerous aldehydes and esters (Bogdanffy et al. 1990).

3.4 INTERACTIONS WITH OTHER CHEMICALS

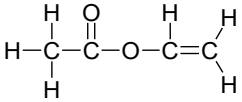
There are no chemicals known that influence the toxicity of vinyl acetate in the body.

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Information regarding the chemical identity of vinyl acetate, also commonly referred to as ethenyl acetate (International Union of Pure and Applied Chemistry [IUPAC] name) or ethenyl ethanoate is presented in Table 4-1. It is the acetate ester of vinyl alcohol.

Table 4-1. Chemical Identity of Vinyl Acetate

Characteristic	Information	Reference
Chemical name	Vinyl acetate	NLM 2022
Synonym(s) and registered trade name(s)	Acetic acid, ethenyl ester; acetic acid ethylene ester; acetic acid, vinyl ester; 1-acetoxyethylene; ethanoic acid; ethenyl ester; ethenyl acetate; ethenyl ethanoate; vinyl A monomer; vinyl ethanoate; VAC; vinyl acetate HQ; VYAC; ZESET T	NLM 2022
Chemical formula	$C_4H_6O_2$	NLM 2022
SMILES	CC(=O)OC=C	NLM 2022
Chemical structure		NLM 2022
CAS Registry Number	108-05-4	NLM 2022
InChIKey	XTXRWKRVRITETP-UHFFFAOYSA-N	NLM 2022
InChI	1S/C4H6O2/c1-3-6-4(2)5/h3H,1H2,2H3	NLM 2022

CAS = Chemical Abstracts Service; SMILES = simplified molecular-input line-entry system

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Vinyl acetate is a flammable, volatile colorless liquid. Pure vinyl acetate that is not produced with inhibitors may polymerize on exposure to light. Information regarding physical and chemical properties of vinyl acetate is presented in Table 4-2.

Table 4-2. Physical and Chemical Properties of Vinyl Acetate

Property	Information	Reference
Molecular weight	86.09 g/mol	Windholz 1983
Color	Colorless	U.S. Coast Guard 1978
Physical state	Liquid (polymerizes into a transparent, colorless solid in light)	Windholz 1983 NLM 2022
Melting point	-93.2°C	NLM 2022
Boiling point	72–73°C	NLM 2022
Density at 20 °C	0.932 (20/4°C)	NLM 2022
Relative vapor density (air=1)	3.0	NLM 2022
Odor	Sweet smell in small quantities, pleasant fruity characteristic	U.S. Coast Guard 1978
Odor threshold:		
Water	0.88 ppm (w/v) 0.25 ppm	Amoore and Hautala 1983 Goeva 1966
Air	0.5 ppm (v/v) 0.12 ppm	Amoore and Hautala 1983 U.S. Coast Guard 1978
Solubility:		
Water at 20 °C	2.0×10^4 mg/L 1 g/50 mL	EPA 2012 Windholz 1983
Organic solvents	10% solubility in alcohol, ether, and benzene	NLM 2022
Partition coefficients:		
Log K_{ow}	0.21–0.73	Fujisawa and Masuhara 1981; Howard 1989
Log K_{oc}	0.75 (estimated, MCI Method) 1.3 (estimated, K_{ow} Method)	EPA 2012
Vapor pressure at 20 °C	83 mmHg at 20°C 115 mmHg at 25°C 140 mmHg at 30°C	Verschueren 1983
Henry's law constant at 25 °C	5.11×10^{-4} atm-m^3/mol^{-1} (calculated)[a]	NLM 2022
Autoignition temperature	402°C 426.6°C	NFPA 1994 Hawley 1981
Flashpoint	-8°C (closed cup); -1.1°C (Tag open cup)	Hawley 1981; Windholz 1983
Flammability limits	2.6–13.4% by volume	NFPA 1994
Conversion factors	1 ppm=3.52 mg/m^3 1 mg/m^3=0.28 ppm	
Explosive limits[b]	2.6–13.4%	NLM 2022

[a]Henry's law constant = vapor pressure/water solubility.
[b]Explosive in water and air.

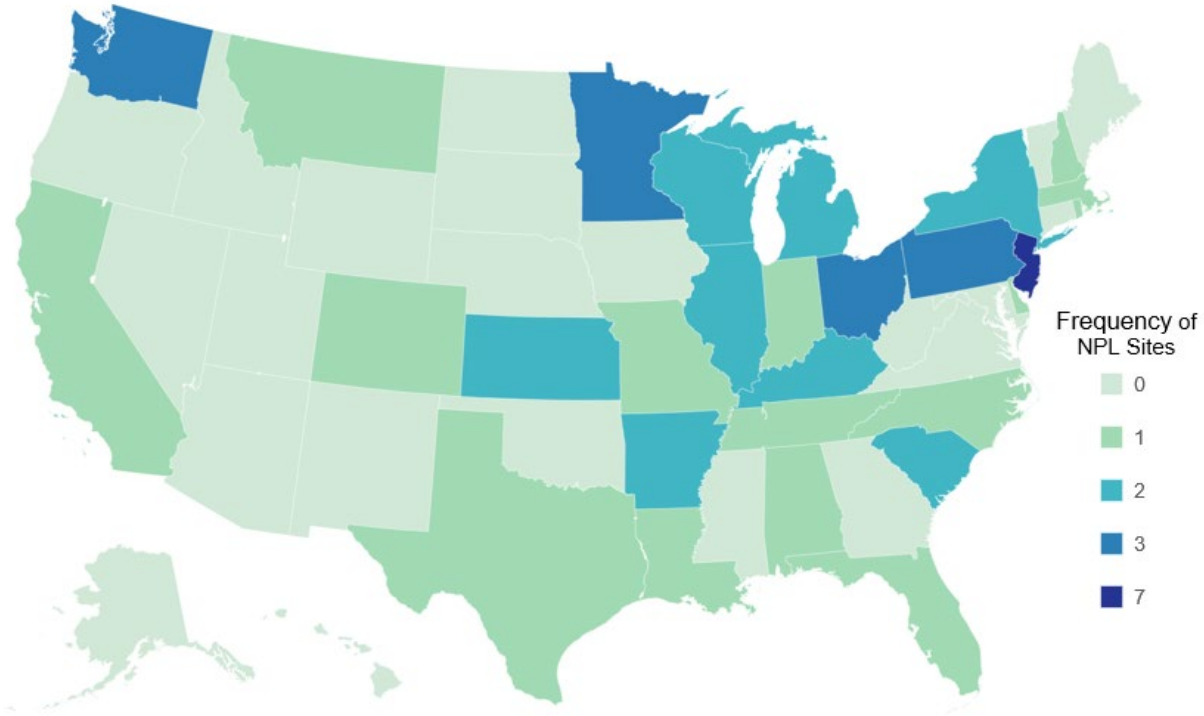
w/v = percent "weight in volume;" v/v = percent "volume in volume"

CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Vinyl acetate has been identified in at least 51 of the 1,868 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2022a). However, the number of sites in which vinyl acetate has been evaluated is not known. The number of sites in each state is shown in Figure 5-1. Of these sites, 50 are located within the United States, 1 is located in Puerto Rico (not shown).

Figure 5-1. Number of NPL Sites with Vinyl Acetate Contamination



Source: ATSDR 2022a

- Workplace exposure via inhalation or dermal contact appears to be the most important source of human exposure to vinyl acetate.

- The general population is most likely exposed to low levels of vinyl acetate through inhalation of contaminated ambient air and cigarette smoke, inhalation of contaminated indoor air from vapor intrusion or vaporization from water (during domestic water use activities) or products containing the compound (e.g., glues and paints), dermal contact with products containing the compound (e.g., glues and paints), and ingestion of low levels of residual vinyl acetate monomers in food

(that may have migrated from plastic food wraps) or food items containing the compound as a starch modifier.

- Low levels of vinyl acetate have been detected in outdoor air. Vinyl acetate has been infrequently detected in surface water and groundwater. Vinyl acetate was detected infrequently and at low levels in the air of residence and office buildings. No biomonitoring data for levels in food or drinking water were located.

- Vinyl acetate is highly water soluble and volatile. It is principally released to the atmosphere as a result of emissions from manufacturing, processing, and storage facilities. Vinyl acetate partitions to the atmosphere, surface water, and groundwater.

- Vinyl acetate undergoes indirect photolysis with an atmospheric lifetime of up to 6 days and undergoes hydrolysis with a half-life of around 7 days. Limited available evidence supports the potential for biodegradation.

5.2 PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.2.1 Production

The manufacturing process most widely used to produce vinyl acetate is the vapor phase process, an oxidative reaction in which ethylene is bubbled through acetic acid at 120°C in the presence of palladium chloride catalyst (Daniels 1983; IARC 1995). Impurities found in the reaction have been reported at <1% (for one manufacturer) and have included acetaldehyde, ethyl acetate, and methyl acetate. Alternative catalysts include salts of rhodium, gold, platinum, ruthenium, vanadium, and iridium (Daniels 1983; Leonard 1970; Llewellyn and Williams 1972). A liquid-phase process can also be used to produce vinyl acetate by bubbling acetylene through a mixture of mercurous sulfate and anhydrous acetic acid (IARC 1995; Leonard 1970). A less important commercial manufacturing process for vinyl acetate involves the reaction between acetaldehyde and acetic anhydride. The intermediate species, ethylidene diacetate, undergoes pyrolytic cleavage to vinyl acetate and acetic acid (Daniels 1983; Leonard 1970). Vinyl acetate can also be synthesized in high yields by reacting vinyl chloride with sodium acetate in solution at 50–75°C, using palladium chloride as a catalyst (Daniels 1983).

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

benzoquinones, nitrobenzenes, diphenyls, toluenes, anthracene, phenanthrene, naphthalene, and others (U.S. Coast Guard 1974).

Table 5-1 summarizes information on companies that reported the production, import, or use of vinyl acetate for the Toxics Release Inventory (TRI) in 2023 (TRI23 2024). TRI data should be used with caution since only certain types of industrial facilities are required to report. This is not an exhaustive list. In 2019, the following chemical companies manufactured vinyl acetate in the United States: H.B. Fuller Company at their facilities in Morris, Illinois; Celanese at their facilities in Bay City and Pasadena, Texas; Lyondell Chemical Company at their facilities in La Porte, Texas; Kuraray America, Inc. at their facilities in La Porte, Texas; Troy Corporation at their facilities in Phoenix, Arizona; and The Dow Chemical Company at their facilities in Texas City, Texas (EPA 2022a). Domestic production of vinyl acetate from 2016 to 2019 was between 1,000,000,000 and <5,000,000,000 pounds, annually (EPA 2022a).

Table 5-1. Facilities that Produce, Process, or Use Vinyl Acetate

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AL	3	100,000 (or N/A)	9,999,999 (or N/A)	6
AR	1	10,000	99,999	2, 3, 9, 12
CA	4	100 (or N/A)	9,999,999 (or N/A)	6, 7
CT	1	100,000	999,999	6
FL	1	1,000	9,999	7
GA	3	1,000,000 (or N/A)	9,999,999 (or N/A)	6
IA	1	100,000	999,999	1, 6, 13
IL	9	0 (or N/A)	9,999,999 (or N/A)	6, 10, 11
IN	1	1,000	9,999	14
KS	1	N/A	N/A	
KY	5	1,000 (or N/A)	49,999,999 (or N/A)	6, 10, 12
LA	5	10,000	9,999,999	6, 12, 14
MA	4	1,000	9,999,999	6, 7, 10, 12
MD	2	0 (or N/A)	99 (or N/A)	14
MI	1	100,000	999,999	6
MO	2	1,000	99,999	6, 7, 9
NC	6	10,000	999,999	6, 7
NE	2	1,000	99,999	9, 10, 12
NJ	4	10,000 (or N/A)	999,999 (or N/A)	6, 7
NV	1	N/A	N/A	
NY	1	10,000,000	49,999,999	6
OH	11	100 (or N/A)	9,999,999 (or N/A)	6, 7, 12
OR	1	1,000,000	9,999,999	6

Table 5-1. Facilities that Produce, Process, or Use Vinyl Acetate

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
PA	2	100,000	999,999	6
SC	10	10,000	49,999,999	6, 12
TN	4	100 (or N/A)	99,999 (or N/A)	6, 9, 12, 14
TX	36	0 (or N/A)	49,999,999 (or N/A)	1, 2, 3, 4, 5, 6, 7, 9, 10, 12, 13, 14
UT	1	1,000	9,999	9, 12
WI	1	1,000	9,999	7, 8
WV	1	N/A	N/A	

[a]Post office state abbreviations used.
[b]Amounts on site reported by facilities in each state. Facilities may report N/A (not applicable) instead of a numeric value "if the waste stream that contains or contained the EPCRA Section 313 chemical is not directed to the relevant environmental medium, or if leaks, spills, and fugitive emissions cannot occur" (EPA 2022b).
[c]Activities/uses:

1. Produce
2. Import
3. Used Processing
4. Sale/Distribution
5. Byproduct
6. Reactant
7. Formulation Component
8. Article Component
9. Repackaging
10. Chemical Processing Aid
11. Manufacture Aid
12. Ancillary
13. Manufacture Impurity
14. Process Impurity

EPCRA = Emergency Planning and Community Right-to-Know Act

Source: TRI23 2024 (Data are from 2023)

5.2.2 Import/Export

Only a small fraction of the vinyl acetate consumed in the United States is imported. Approximately 14,074,000 pounds of vinyl acetate were imported in 2023, 28,788,000 pounds were imported in 2022, and around 69,202,000 pounds of vinyl acetate were imported in 2021 (USITC 2024). In 2023, the United States imported vinyl acetate primarily from Singapore, Saudia Arabia, South Korea, and China.

Exports of vinyl acetate greatly exceed imports. The United States exported approximately 1,137,000,000 pounds in 2023; 1,093,000,000 pounds in 2022; and 1,172,000,000 pounds of vinyl acetate in 2021 (USITC 2024). Some of the top importers of American vinyl acetate were Belgium, Mexico, Canada, and Brazil.

5.2.3 Use

The primary use for vinyl acetate is as a monomer in the production of polyvinyl acetate, polyvinyl alcohol, and polyvinyl acetals (IARC 1995). Vinyl acetate is also polymerized with vinyl chloride to

produce ethylene-vinyl acetate (EVA) and polyvinyl chloride-acetate copolymers. Industrial uses for vinyl acetate reported in the 2020 CDR included use as an adhesion/cohesion promotor in adhesive manufacturing; a monomer in petrochemical manufacturing, paint and coating manufacturing, plastics and resin manufacturing, and adhesive manufacturing; and an intermediate in plastics and resin manufacturing. Consumer and commercial uses included use as an adhesive, intermediate, or monomer for packaging; an adhesive or intermediate in single- and two-component glues and adhesives; an intermediate in powder coatings, water-based paints, rubber foam, sporting equipment (e.g., ski boots, bicycle seats), and auto-related films; and an intermediate in construction and building materials (EPA 2022a). Vinyl acetate also has a few approved uses as a food additive (masticatory substance, solvent/vehicle) and polymerized vinyl acetate (e.g., EVA copolymers) are approved for use in food packaging (FDA 2022a, 2022b). EVA copolymers are also used in solar photovoltaic cells (Lee et al. 2008). Due to low toxicity and biocompatibility, EVA copolymers are also used to make medical devices, drug delivery systems, and implants; advances in 3D-printing technologies continue to expand these applications (Brandl et al. 2024; Moroni et al. 2023).

5.2.4 Disposal

Limited information on preferred disposal methods of vinyl acetate wastes in the United States is available.

The incineration method used in Japan, as reported in 1982 by the International Technical Information Institute, was to incinerate the compound by mixing it with a more flammable solvent and spraying it into a furnace (ITII 1982).

Landfill disposal of the polymerized solid may also be a common practice as criteria for vinyl acetate monitoring are included for municipal solid waste landfills under the Resource Conservation and Recovery Act (RCRA) (EPA 1991).

5.3 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2022b). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ ≥10 full-time employees; if their facility's North American Industry Classification System (NAICS) codes is covered

under EPCRA Section 313 or is a federal facility; and if their facility manufactures (defined to include importing) or processes any TRI chemical in excess of 25,000 pounds, or otherwise uses any TRI chemical in excess of 10,000 pounds, in a calendar year (EPA 2022b).

5.3.1 Air

Estimated releases of 858,455 pounds (~389 metric tons) of vinyl acetate to the atmosphere from 125 domestic manufacturing and processing facilities in 2023, accounted for about 72% of the estimated total environmental releases from facilities required to report to the TRI (TRI23 2024). These releases are summarized in Table 5-2.

Table 5-2. Releases to the Environment from Facilities that Produce, Process, or Use Vinyl Acetate[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AL	3	2,420	0[l]	0	0	0	2,420	0	2,420
AR	1	1	0	0	0	0	1	0	1
CA	4	4,565	580	0	1,937	0	4,574	2,509	7,082
CT	1	496	0	0	0	0	496	0	496
FL	1	423	0	0	43	0	423	43	466
GA	3	966	14	0	351	0	966	365	1,331
IL	9	17,503	512	0	500	100	17,503	1,112	18,615
IN	1	40	0	0	406	0	40	406	446
IA	1	7,622	0	0	0	0	7,622	0	7,622
KS	1	<RQ	<RQ	<RQ	<RQ	<RQ	<RQ	<RQ	<RQ
KY	5	53,722	0	0	0	0	61,022	0	61,022
LA	5	112,395	0	0	48,023	9	160,395	32	160,427
MD	2	38	0	0	125	0	38	125	163
MA	4	8,838	3,852	0	0	0	8,838	3,852	12,690
MI	1	196	0	0	0	0	196	0	196
MO	2	597	1	0	0	0	597	1	598
NE	2	1,517	0	0	9	0	1,517	9	1,526
NV	1	<RQ	<RQ	<RQ	<RQ	<RQ	<RQ	<RQ	<RQ
NJ	4	1,758	8	0	0	2,132	1,758	2,140	3,898
NY	1	9,554	0	0	0	0	9,554	0	9,554
NC	6	9,065	0	0	0	2,742	9,065	2,742	11,807
OH	11	55,895	1	0	12	2,121	55,895	2,134	58,028
OR	1	11,555	0	0	0	0	11,555	0	11,555

Table 5-2. Releases to the Environment from Facilities that Produce, Process, or Use Vinyl Acetate[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
PA	2	3,875	16	0	0	0	3,880	16	3,896
SC	10	135,854	1	0	3	26	135,854	30	135,884
TN	4	120	0	0	3,417	4	120	3,421	3,541
TX	36	394,250	129,123	115,377	11,845	1,062	513,220	139,350	652,569
UT	1	0	0	0	1	0	0	1	1
WV	1	<RQ	<RQ	<RQ	<RQ	<RQ	<RQ	<RQ	<RQ
WI	1	25,191	0	0	0	0	25,191	0	25,191
Total	125	858,455	134,107	115,377	66,672	8,196	1,032,739	158,286	1,191,025

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, wastewater treatment (metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II-V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other onsite landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown.
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off-site, including to POTWs.
[l]Due to reporting guidelines, a zero may represent that the facility or facilities in each state's row reported "0," and "NA," or left the cell blank in their Form R submission.

NA = not applicable; RF = reporting facilities; RQ = reportable quantity; UI = underground injection

Source: TRI23 2024 (Data are from 2023)

EPA's National Emission Inventory (NEI) database contains information regarding sources that emit criteria air pollutants (CAPs) and their precursors, and hazardous air pollutants (HAPs) for the 50 United States, Washington DC, Puerto Rico, and the U.S. Virgin Islands. Emissions are estimated from multiple sources, including state and local environmental agencies; the TRI database; computer models for on- and off-road emissions; and databases related to EPA's Maximum Achievable Control Technology (MACT) programs to reduce emissions of HAPs. Vinyl acetate emissions estimated from the 2020 inventory are summarized in Table 5-3.

Table 5-3. Vinyl Acetate Emissions Estimations from the 2020 National Emissions Inventory

Emission sector	Pounds of vinyl acetate emitted
Fires, prescribed fires	1,197,648
Industrial processes, chemical manufacturing	715,417
Solvent, industrial surface coating and solvent use	528,141
Solvent, consumer and commercial solvent use	343,560
Industrial processes, storage and transfer	160,023
Industrial processes, NEC	72,944
Industrial processes, pulp and paper	63,133
Industrial processes, cement manufacturing	27,015
Solvent, graphic arts	19,233
Waste disposal	17,187
Bulk gasoline terminals	10,777
Solvent, degreasing	9,460
Gas stations	1,379
Fuel combustion, industrial boilers, ICEs, coal	1,193
Fuel combustion, electric generation, coal	722
Industrial processes, petroleum refineries	307
Fuel combustion, electric generation, natural gas	211
Fuel combustion, industrial boilers, ICEs, oil	163
Fuel combustion, industrial boilers, ICEs, other	148
Fuel combustion, industrial boilers, ICEs, natural gas	122
Dust, construction dust	50
Solvent, non-industrial surface coating	39
Fuel combustion, commercial/institutional, natural gas	27
Fuel combustion, electric generation, biomass	10
Industrial processes, non-ferrous metals	5
Fuel combustion, commercial/institutional, biomass	2
Industrial processes, ferrous metals	2
Industrial processes, mining	0
Fuel combustion, industrial boilers, ICEs, biomass	0
Fuel combustion, residential, other	0
Fuel combustion, electric generation, oil	0
Fuel combustion, electric generation, other	0
Fuel combustion, commercial/institutional, other	0
Fuel combustion, commercial/institutional, coal	0

ICE = internal combustion engine; NEC = not elsewhere classified

Source: EPA 2020

5.3.2 Water

Estimated releases of 134,107 pounds (~60.8 metric tons) of vinyl acetate to surface water from 125 domestic manufacturing and processing facilities in 2023, accounted for about 11% of the estimated total environmental releases from facilities required to report to the TRI (TRI23 2024). These releases are summarized in Table 5-2.

Recent data on wastewater detections were not located.

5.3.3 Soil

Estimated releases of 66,672 pounds (~30.2 metric tons) of vinyl acetate to soil from 125 domestic manufacturing and processing facilities in 2023, accounted for about 5.5% of the estimated total environmental releases from facilities required to report to the TRI (TRI23 2024). Estimated releases of 115,377 pounds (~52.3 metric tons) of vinyl acetate via underground injection from 125 domestic manufacturing and processing facilities in 2023, constituting about 9.7% of the estimated total environmental releases from facilities required to report to the TRI (TRI23 2024). These releases are summarized in Table 5-2.

5.4 ENVIRONMENTAL FATE

5.4.1 Transport and Partitioning

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

Air. The reported vapor pressure for vinyl acetate is 83 mm Hg at 20°C (Verschueren 1983), indicating that it will exist primarily in the vapor phase when released to the ambient atmosphere. Removal of the compound from the atmosphere may occur during precipitation events, based on reported water solubilities of 1 g/50 mL and $2x10^4$ mg/L (EPA 2012; Windholz 1983). Its relatively short atmospheric half-life indicates that it will not undergo long-range transport.

Water. Using the vapor pressure and water solubility data presented in Table 4-2, a Henry's law constant value of $5.11x10^{-4}$ atm-m^3 mol^{-1} can be calculated. The magnitude of this value indicates that volatilization to the atmosphere will be an important transport process for vinyl acetate released to surface waters. Using this value and the methods reviewed by Thomas (1990), a volatilization half-life of about 4 hours at 20°C can be estimated for a river 1 meter deep flowing at a current of 1 m/second, with a wind velocity of 3 m/second.

Sediment and Soil. Based on the calculated Henry's law constant, vinyl acetate released to moist surface soils is also expected to volatilize to the atmosphere, but this may be limited by its high water solubility. Releases of vinyl acetate to subsurface soils may leach to and be transported in groundwater, depending upon site-specific hydrogeological conditions, if the compound is not transformed or degraded. Experimental partition coefficients (K_d) or n-octanol/water partition coefficient normalized to organic carbon (K_{oc}) were not available; however, estimated log K_{oc} values were 0.75 and 1.3 (Table 4-2), suggesting negligible sorption to soils and sediments. Negligible sorption of vinyl acetate is further supported by the high measured water solubility and low logarithm of the n-octanol/water partition coefficient (log K_{ow}).

Other Media. Experimental data for bioaccumulation of vinyl acetate were not located. The log K_{ow} can be used to estimate the potential for bioaccumulation. Log K_{ow} values for vinyl acetate have been reported to be 0.21 (Fujisawa and Masuhara 1981) and 0.73 (Howard 1989). The magnitude of these values indicates that bioconcentration and food chain biomagnification are not expected to be important processes for vinyl acetate.

5.4.2 Transformation and Degradation

Air. Vinyl acetate does not absorb ultraviolet light at wavelengths >250 nm (Daniels 1983); therefore, direct photolytic degradation of the compound in the troposphere is not expected to occur. However, vinyl acetate has been found to undergo rapid photochemical oxidation and polymerization in laboratory studies in the absence of inhibitor (NLM 2022). The average second-order rate constant for reaction with singlet molecular oxygen has been reported to be 0.82 L $mole^{-1}$ $second^{-1}$ (Datta and Rao 1979). In smog chamber studies with NOx concentrations representative of rural and urban atmospheres, the photooxidation half-life of vinyl acetate was determined to be 4.1–6.5 hours (Joshi et al. 1982). In a laboratory at room temperature, tropospheric lifetimes of vinyl acetate based on reactions with OH, NO_3,

and O_3 were estimated per reactant to be 6 hours, 6 days, and 5 days, respectively (Picquet-Varrault et al. 2010).

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

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

Vinyl acetate is readily biodegradable, suggesting that it will not be persistent in the environment under aerobic conditions. In an Organisation for Economic Cooperation and Development (OECD) 301C test guideline study of ready biodegradability, vinyl acetate achieved 90% degradation based on biological oxygen demand and 98% degradation based on total organic carbon after 28 days (NITE 2010). One hundred percent test substance loss was also observed, due in part to hydrolysis to acetic acid and acetaldehyde.

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

the nonenzymatic hydrolysis of the compound (12 versus 60 hours). Three bacteria strains isolated from soil were able to completely degrade vinyl acetate at concentrations of 47 and 124 g/m^3 after 5–12 hours under aerobic conditions (Greń et al. 2011). Buildup of acetaldehyde as an intermediate degradation product inhibited microbial growth at concentrations >10 g/m^3.

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

Other Media. No studies were located regarding the degradation or transformation of vinyl acetate in other media.

5.5 LEVELS IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to vinyl acetate depends, in part, on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of vinyl acetate in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on vinyl acetate levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable.

Table 5-4 shows the lowest limit of detections that are achieved by analytical analysis in environmental media. An overview summary of the range of concentrations detected in environmental media is presented in Table 5-5.

Table 5-4. Lowest Limit of Detection Based on Standards[a]

Media	Detection limit	Reference
Air	0.01–0.125 ppbv 1.0–19 µg/m^3 (0.28–5.4 ppbv; indoor)	EPA 2023a Montana DEQ 2012
Drinking water	0.031 ppb 11.8–23.0 ppb	Munch and Eichelberger 1992 EPA 1996
Surface water and groundwater	0.031 ppb 11.8–23.0 ppb	Munch and Eichelberger 1992 EPA 1996
Soil	4.8–24 ppb	WQP 2024

Table 5-4. Lowest Limit of Detection Based on Standards[a]

Media	Detection limit	Reference
Sediment	4.8–24 ppb	WQP 2024
Whole blood[b]	–	–

[a]Detection limits based on using appropriate preparation and analytics. These limits may not be possible in all situations.
[b]No analytical methods for detection of vinyl acetate in whole blood were located.

Table 5-5. Summary of Environmental Levels of Vinyl Acetate[a]

Media	Low	High	For more information
Outdoor air (ppbv)	0.010	4444	Section 5.5.1
Indoor air (ppbv)	1.9	9.1	Section 5.5.1
Surface water (ppb)	0.5	2	Section 5.5.2
Ground water (ppb)	0.5	100	Section 5.5.2
Drinking water[b]	–	–	
Food[b]	–	–	
Soil (ppb)	<LOD	580	Section 5.5.3
Sediment (ppb)	<LOD	<LOD	Section 5.5.3

[a]Unit conversion: ppb = µg/L (aqueous); = µg/kg (sediment and soil); ppbv = 24.45 concentration µg/m^3/86.09 g/mol (air). Summary values represent most recent ambient data available. Ranges do not reflect values below the limit of detection.
[b]No recent data were located.

LOD = level of detection

Detections of vinyl acetate in air, water, and soil at NPL sites are summarized in Table 5-6.

Table 5-6. Vinyl Acetate Levels in Water, Soil, and Air of National Priorities List (NPL) Sites

Medium	Median[a]	Geometric mean[a]	Geometric standard deviation[a]	Number of quantitative measurements	NPL sites
Water (ppb)	No data	No data	No data	No data	No data
Soil (ppb)	580	321	30.7	8	6
Air (ppbv)	45.4	444	51.8	3	3

[a]Concentrations found in ATSDR site documents from 1981 to 2022 for 1,868 NPL sites (ATSDR 2022a). Maximum concentrations were abstracted for types of environmental media for which exposure is likely. Pathways do not necessarily involve exposure or levels of concern.

5.5.1 Air

The national Air Quality System (AQS) database contains ambient air monitoring data for criteria gases, particulates, other toxics, and meteorological parameters collected by EPA, state, local, and tribal air pollution control agencies from monitors throughout the country. Table 5-7 shows the yearly mean 24-hour percentile distributions of vinyl acetate at monitoring stations across the United States. The minimum mean site-specific values reported were below the level of detection for all years.

Table 5-7. Percentile Distribution of Annual Mean Vinyl Acetate Concentrations (ppbv) Measured in Ambient Air at Locations Across the United States[a,b]

Year	Number of U.S. locations	10th	50th	75th	95th	Maximum
2019	33	0.037	0.176	0.269	0.554	7.7
2020	32	0.059	0.205	0.361	2.50	114
2021	33	0.026	0.393	0.741	1.71	29.4
2022	31	0.023	0.173	0.306	0.750	5.38
2023[c]	17	0.010	0.125	0.223	0.480	1.78

[a]Values were originally reported in parts per billion carbon (ppbC) and converted to ppbv.
[b]24-hour sampling period.
[c]As of October 26, 2023.

Source: EPA Air Quality System (AQS) annual summaries (EPA 2023a)

Vinyl acetate has been detected in the air at NPL sites between 1981 and 2002, with a median value of 45.5 ppbv (ATSDR 2022a). A summary of this data is provided in Table 5-6.

Indoor air samples were collected by the Montana Department of Environmental Quality in March 2012, from 50 nonsmoking residential buildings in urban and rural areas (Montana DEQ 2012). Vinyl acetate was detected in 2% of samples analyzed; an average of 9.3±3.89 µg/m^3 (ranging from 6.7 to 32 µg/m^3; equivalent to 2.6±1.10 and 1.9–9.1 ppbv) was reported. In another study, indoor air samples were collected between 2013 and 2015 in school and office buildings in 18 states (Rago et al. 2021). Vinyl acetate was detected in 6% of samples (n=14,668) at concentrations ranging from 1.3 to 1.83 µg/m^3 (0.37–0.520 ppbv); vinyl acetate was detected in office air samples only.

5.5.2 Water

Surface water and groundwater monitoring data are available from EPA's NWIS, STORET, and STEWARDS systems. No drinking water monitoring data were located for vinyl acetate. Vinyl acetate is not a contaminant that has been monitored for during the first five rounds of the Unregulated Contaminant Monitoring Rule (UCMR), which monitors occurrence data for contaminants in public water systems (PWSs) around the United States that may be present but are not currently subject to EPA drinking water regulations.

Vinyl acetate is not a common contaminant of surface water. Between 2010 and 2019, vinyl acetate was only detected in 3% of samples, at an average of 1.2 µg/L (range 0.5–2 µg/L; n=594) (WQP 2024). Vinyl acetate was not detected in more recent surface water samples, collected between 2020 to early March 2024 (n=197).

Vinyl acetate has been more frequently detected in groundwater: between 2010 and 2019, vinyl acetate was detected in 11% of ambient groundwater samples at an average concentration of 7.6 µg/L (range 0.15–100 µg/L; n=6,410) (WQP 2024). More recently, however, vinyl acetate was not detected in samples collected between 2020 and early March 2024 (n=1,886).

Recent monitoring data for groundwater from Superfund sites are limited. Vinyl acetate was not detected in samples from the Palermo Wellfield superfund site in Tumwater, Washington, collected between 2013 and 2020 (WQP 2024).

5.5.3 Sediment and Soil

Limited recent ambient soil and sediment monitoring data are available. Vinyl acetate was present at levels below the quantification limit in six sediment samples collected from Indiana in 2000 or in two sediment samples collected as part of the EPA Great Lakes National Program in 2007 (WQP 2024). Reported quantitation limits ranged from 14 to 82 µg/kg in Indiana and from 3,900 to 5,300 µg/kg in the Great Lakes Program. In soil, vinyl acetate was not detected in 11 samples collected from Washington state in 2004 or in 273 samples collected from New Mexico in 2009 (WQP 2024).

Vinyl acetate has typically not been detected in soil or sediment samples collected from several Superfund sites since 2000 (WQP 2024). The single exception is 10 µg/kg vinyl acetate reported in one

soil sample from the Ogden Railyard site in Ogden, Utah collected in 2000; vinyl acetate was not detected in any other soil or sediment samples from the Ogden Railyard site between 2000 and 2001. Similarly, vinyl acetate was not detected in sediment samples from the Portland Harbor site in Portland, Oregon from 2002, 2004, 2006, and 2007; sediment samples from the Lower Duwamish Waterway site in Seattle, Washington from 2003 and 2006; soil samples from the Intermountain Waste Oil Refinery site in Bountiful, Utah from 2004; or sediment samples from the Palermo Wellfield site in Tumwater, Washington from 2021 (WQP 2024).

Vinyl acetate has been detected in the soil at NPL sites between 1981 and 2002, with a median value of 580 µg/kg (ATSDR 2022a). A summary of NPL data is provided in Table 5-6.

5.5.4 Other Media

Vinyl acetate was present, but below the quantification limits, in 160 biota samples collected between 1984 to 1992 in Indiana (WQP 2024). Reported limits of detection ranged from 10 to 25 µg/kg. The most frequent sampling occurred in three species of fish (*Cyprinous carpio*, *Ictalurus punctatus*, and *Micropterus salmoides*). More recent fish biomonitoring data are not available (WQP 2024).

Vinyl acetate was detected in the volatile organic carbon (VOC) emissions of one carpet type representative of those used in residence, school, and office buildings. The measured emission rates were 853±41.5 µg/m^2/hour over 24 hours and 103±20.2 µg/m^2/hour over 168 hours (1 week) (Hodgson et al. 1993).

Available monitoring data for other media are limited to reports of vinyl acetate as a constituent of the vapor phase of cigarette smoke at concentrations of 0.4 µg/cigarette (Guerin 1980) and 0.5 µg/puff (Battista 1976). A more recent analysis of reference and commercial Chinese cigarettes reported 0.096–1.014 µg/vinyl acetate per cigarette (Xu et al. 2017).

Since vinyl acetate has a few approved uses as a food additive, it may be present in certain foods. However, no food monitoring data are available.

5.6 GENERAL POPULATION EXPOSURE

Quantitative exposure estimates for the general population are not available; however, vinyl acetate has been detected in outdoor air, surface water, groundwater, and soil. Concentrations have typically been low, and vinyl acetate has been infrequently detected in soil and water. The ambient environment may not be a significant exposure route due to the relatively short residence times of vinyl acetate. Therefore, exposure to the general population is expected to be low. The most likely sources of general population exposure to very small amounts of vinyl acetate include: (1) inhalation of contaminated ambient air and cigarette smoke; (2) inhalation, dermal contact, or ingestion of residual monomers in consumer products containing the compound (e.g., paints, adhesives); (3) ingestion of food items containing vinyl acetate; and (4) dermal and inhalation exposure during domestic water use activities (e.g., showering) if water contains vinyl acetate. Vapor intrusion of vinyl acetate into buildings and residences from contaminated groundwater may result in indoor air inhalation exposure. Since vinyl acetate has been detected at NPL sites (see Section 5.1), populations living near hazardous waste sites may be exposed.

Vapor intrusion may be a potential source of vinyl acetate exposure, though indoor and ambient sources may also contribute to indoor air levels. The EPA (2016) includes vinyl acetate in its Vapor Intrusion Screening Levels (VISL) Calculator, indicating that it is sufficiently volatile and sufficiently toxic to be considered a concern for vapor intrusion from soil and ground water. A review of vapor intrusion data from ATSDR public health assessments identified five sites with vinyl acetate in soil or outdoor air; vinyl acetate was detected in indoor air at three of the sites ranging from 0.21 $\mu g/m^3$ (0.06 ppb) to 17.6 $\mu g/m^3$ (5 ppb) (ATSDR 2005a, 2005b, 2005c, 2007, 2009). Accordingly, ATSDR (2016) recommends that health assessors should evaluate potential health implications of vapor intrusion for vinyl acetate during site risk assessments.

Vinyl acetate in water is expected to rapidly volatilize; thus, there is potential for inhalation exposure during domestic water use activities, primarily showering and bathing. ATSDR's three-compartment Shower and Household-Use Exposure (SHOWER) model predicts air concentrations in the shower stall, bathroom, and main house throughout the day by estimating the contribution from showering or bathing and the contribution from other water sources in the house, such as the dishwasher, clothes washer, and faucets (ATSDR 2022b). This information, along with human activity patterns, is used to calculate a daily time-weighted average (TWA) exposure concentration via inhalation exposure and from dermal uptake from skin contact. ATSDR's SHOWER model is available by sending a request to showermodel@cdc.gov. Reasonable Maximum Exposure (RME) levels for vinyl acetate were calculated

based on concentrations in water and outdoor air; RME levels for different exposure groups are presented in Table 5-8. Since treated water levels were not available, the average value of detections in groundwater and surface water (discussed in Section 5.5.2) was used as a surrogate value, in addition to a representative outdoor air level reported by EPA's HAP monitoring sites (discussed in Section 5.5.1).

Table 5-8. RME Daily Inhalation Dose and Administered Dermal Dose of Vinyl Acetate for the Target Person[a]

Exposure group	Inhalation (μg/m^3)	Dermal (μg/kg/day)
Birth–<1 year	1.1	0.0017
1–<2 years	1.1	0.0015
2–<6 years	1.1	0.0013
6–<11 years	1.1	0.0011
11–<16 years	1.1	0.00089
16–<21 years	1.1	0.00081
Adult	1.1	0.00079
Pregnant and breastfeeding women	1.1	0.00080

[a]Based on 2.1 μg/L in water and 0.125 ppb in air.

Source: ATSDR 2022b

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Workers involved in the production, processing, storage, transport, or use of vinyl acetate are potentially exposed to high concentrations of the compound (European Chemicals Bureau 2008; IARC 1995; NIOSH 1978, 1983, 1990). Workplace air concentration levels reviewed by NIOSH (1978, 1983) were generally within the recommended 15-minute ceiling limit of 4 ppmv. In a corn starch processing plant, where vinyl acetate was one of the chemicals used to modify starch, air levels ranged from 0.94 ppmv on a tank to 20 ppmv on a starch drying press (NIOSH 1990). Personal air samples ranged measured for a period of 165 minutes ranged from below detectible to 5.7 ppmv (NIOSH 1990). In another survey of vinyl acetate production facilities in Texas, the following workplace airborne concentrations were reported: average time-weighted average concentrations of 5.2–8.2 ppmv; average breathing zone concentrations of 8.6 ppmv; intermittent exposure concentrations of about 50 ppmv; and potential short-term exposures of up to 300 ppmv (Deese and Joyner 1969). More recent occupational exposure data are not available.

Occupational exposures for European Union workers were estimated for three scenarios: production of vinyl acetate and polymerization in the chemical industry; manufacturing of formulations and products;

and use of formulations and products containing residual vinyl acetate monomer (European Chemicals Bureau 2008). The results suggested that handling the monomer substance in the areas of production and polymerization, the formulation of adhesives, as well as the use of formulations, especially of adhesives, are the main sources for occupational exposure.

Members of the general population living in the vicinity of industrial point emission sources, and individuals living near waste sites that are contaminated with vinyl acetate may also be exposed to potentially high concentrations of the compound. The sizes of these populations and the concentrations of vinyl acetate in the contaminated media to which these people may be exposed have not been adequately characterized.

Based on measured vapor concentrations from cigarettes, smokers have potentially increased exposure to vinyl acetate. In comparison, second-hand smoke exposure may not be as high; in an exposure chamber study of room air levels after 4-hour use of cartridge- or tank-based e-vapor products and cigarettes, vinyl acetate was not detected in the air (limit of detection of 6.11 $\mu g/m^3$, or 1.74 ppbv) after pre-specified (80 puffs per volunteer) or *ad libitum* use (Liu et al. 2017).

CHAPTER 6. 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 NTP, is required to assure the initiation of a program of research designed to determine the adverse health effects (and techniques for developing methods to determine such health effects) of vinyl acetate.

Data needs are defined as substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

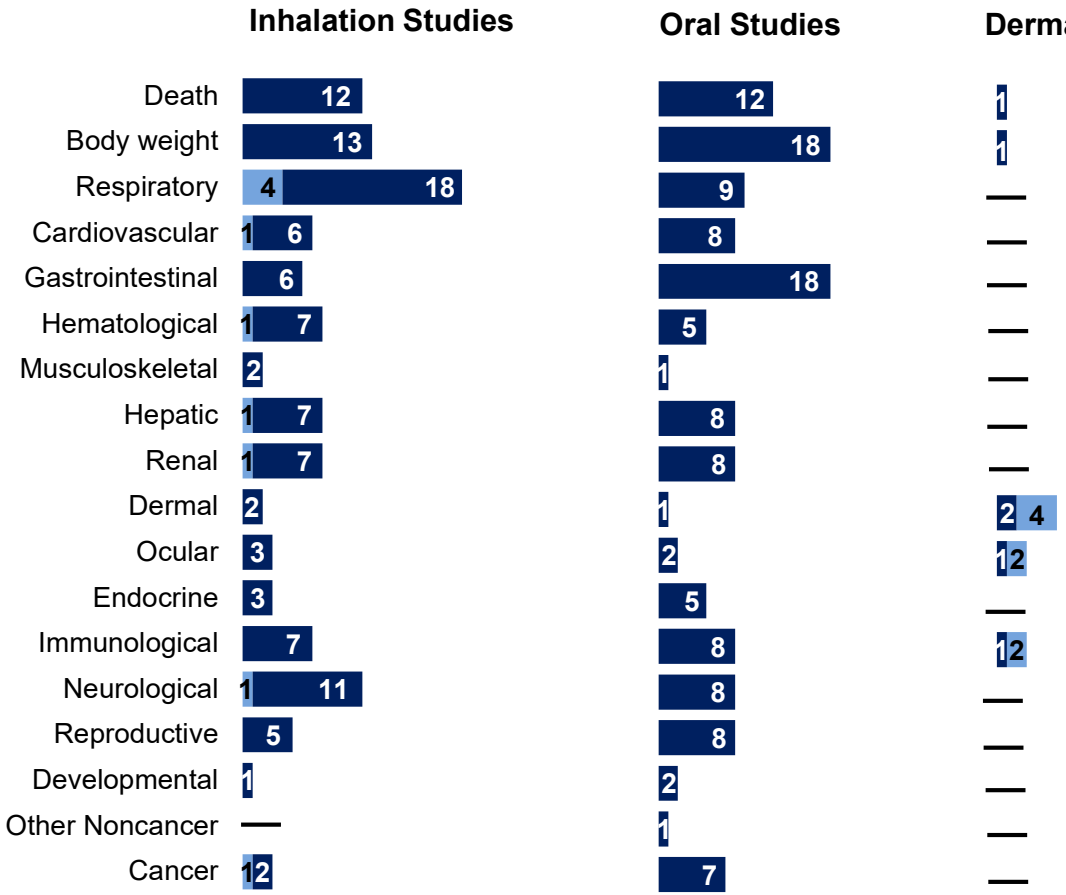
6.1 INFORMATION ON HEALTH EFFECTS

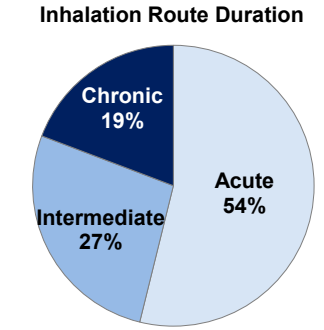
Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to vinyl acetate that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of vinyl acetate. The number of human and animal studies examining each endpoint is indicated regardless of whether an effect was found and the quality of the study or studies.

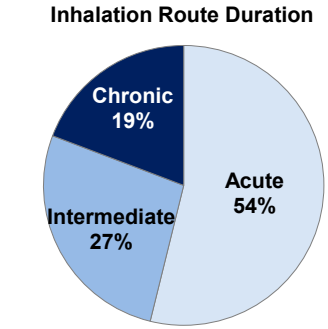
As illustrated in Figure 6-1, most of the data on the toxicity of vinyl acetate come from inhalation and oral studies in laboratory animals. The most examined endpoints in these studies were death, body weight, respiratory, and gastrointestinal effects. The dermal animal database is limited to six acute-duration studies and one intermediate-duration study, evaluating limited endpoints. The available human studies were limited to a few controlled exposure and occupational studies. These were predominantly focused on evaluation of respiratory, dermal, and ocular effects.

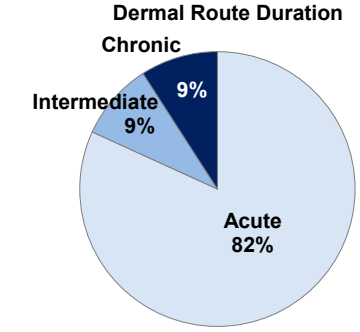
Figure 6-1. Summary of Existing Health Effects Studies on Vinyl Acetate by Route and Endpoint*

Potential for death, body weight, respiratory, and gastrointestinal effects were the most studied endpoints
The majority of the studies examined inhalation or oral exposure in **animals** (versus **humans**)









*Includes studies discussed in Chapter 2. The number of studies include those finding no effect; most studies examined multiple endpoints.

6.2 IDENTIFICATION OF DATA NEEDS

Missing information in Figure 6-1 should not be interpreted as a "data need." A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Acute-Duration MRLs. The inhalation database is adequate to derive an acute-duration inhalation MRL, and a relevant PBPK model is available for human dose extrapolation. Additional studies evaluating the concentrations between the lowest identified LOAEL of 598.5 ppm for nasal lesions, and its associated NOAEL of 199.6 ppm (Bogdanffy et al. 1997), would be useful. Nasal lesion data between 199.6 ppm (0% incidence) and 598.5 ppm (100% incidence) could better inform the dose-response curve for this effect following acute-duration exposure, decreasing uncertainty in the acute-duration inhalation MRL. The oral database is inadequate to derive an acute-duration oral MRL; no adverse effects were identified below the lowest reported acute oral LD_{50} value of 1,613 mg/kg (Goeva 1966). Since inhalation is the most likely route of exposure to vinyl acetate, and no clear oral toxicity targets have been identified, additional studies on the acute effects of vinyl acetate following oral exposure may not be necessary.

Intermediate-Duration MRLs. The inhalation database is adequate to derive an intermediate-duration inhalation MRL, and a relevant PBPK model is available for human dose extrapolation. Additional studies evaluating the concentrations between the lowest identified LOAEL of 598.5 ppm for nasal lesions, and its associated NOAEL of 199.6 ppm (Bogdanffy et al. 1997), would be useful. Nasal lesion data between 199.6 ppm (0% incidence) and 598.5 ppm (100% incidence) could better inform the dose-response curve for this effect following intermediate-duration exposure, decreasing uncertainty in the intermediate-duration inhalation MRL. The oral database is inadequate to derive an intermediate-duration oral MRL. The only adverse effects identified (decreased body weights in adults and offspring) may be due, at least in part, to observed decreases in water intake associated with palatability issues. Since inhalation is the most likely route of exposure to vinyl acetate, and no clear oral toxicity targets have been identified, additional studies on the effects of vinyl acetate following intermediate-duration oral exposure may not be necessary.

Chronic-Duration MRLs. The inhalation database is adequate to derive a chronic-duration inhalation MRL, and a relevant PBPK model is available for human dose extrapolation. Additional studies evaluating the concentrations between the lowest identified LOAEL of 200.5 ppm for nasal lesions, and its associated NOAEL of 49.4 ppm (Bogdanffy et al. 1994a; Hazleton 1988), would be useful. Nasal lesions data between 49.4 ppm (<10% incidence) and 200.5 ppm (>88%% incidence) could better inform the dose-response curve for this effect following chronic-duration exposure, decreasing uncertainty in the chronic-duration inhalation MRL. The oral database is inadequate to derive a chronic-duration oral MRL. The only adverse effects identified (decreased body weights) may be due, at least in part, to observed decreases in water intake associated with palatability issues and/or decreased food consumption. No other non-neoplastic effects were identified below chronic-duration doses associated with cancer and/or death. Therefore, the chronic-duration oral exposure database was deemed inadequate to derive an MRL. Since inhalation is the most likely route of exposure to vinyl acetate, and no clear oral toxicity targets have been identified, additional studies on the chronic effects of vinyl acetate following oral exposure may not be necessary.

Health Effects. Identification of data needs for health effects is limited to targets included in the systematic review and endpoints with major data gaps.

Respiratory. The upper respiratory tract has been identified as a sensitive target following acute-, intermediate-, and chronic-duration inhalation exposure in animals. However, the available studies have wide dose-spacing between the NOAEL and LOAEL concentrations, resulting in low-to-no lesions at the NOAEL, and ~90–100% lesions at the LOAEL. Additional studies designed to define the shape of the dose-response curve between the NOAEL and LOAEL values for upper respiratory lesions could be useful.

Reproductive. No information is available in humans to indicate that vinyl acetate affects reproductive function. Reproductive function has not been assessed in animals following inhalation exposure; however, there is no evidence of damage to reproductive organs following intermediate- or chronic-duration exposure. No significant reproductive effects were noted in a 2-generation drinking water study in rats. 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 by the inhalation route is warranted to clarify whether this chemical has the potential to affect reproduction in humans.

Developmental. 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 during gestation (Hurtt et al. 1995), and decreased body weight was observed in F1 pups at weaning following exposure of rats to vinyl acetate in drinking water in a 2-generation study (Mebus et al. 1995). These effects were observed at levels causing decreased body weight gain in dams. Additionally, water intake was significantly decreased in dams in the 2-generation study, which may have caused decreased milk production. No adverse developmental effects have been observed in animals following oral exposure to vinyl acetate during gestation only (Hurtt et al. 1995). 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 (no 2-generation study) and it is the most relevant route for humans.

Epidemiology and Human Dosimetry Studies. Human studies are limited to three acute-duration inhalation exposure studies focused on respiratory and/or ocular irritation (Deese and Joyner 1969; Hinderliter et al. 2005; Union Carbide 1973), three occupational studies/reports evaluating dermal effects (Gruvberger et al. 1998; Tanaka and Lucas 1984; Union Carbide 1958), one occupational hygiene study (Deese and Joyner 1969), and one occupational cross-sectional study (Khoshakhlagh et al. 2023). These studies provide evidence of respiratory, ocular, and dermal irritation following exposure to vinyl acetate. All studies are limited by small sample size and limited endpoint evaluation. The most likely identifiable subpopulation exposed to vinyl acetate is chemical workers involved in its production and use. Well-designed epidemiological studies of exposed workers that specifically examine the effects of vinyl acetate on respiratory, reproductive, and developmental systems would be useful to further characterize the extent of possible injury to these systems in humans.

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 CO_2 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 or its metabolites as biomarkers of exposure to this chemical (Hazleton 1979a; Simon et al. 1985a). Additional investigation of the utility of biomarkers of exposure in characterizing human exposure to vinyl acetate would be useful.

Exposure to vinyl acetate *in vitro* has been shown to result in various positive genotoxic endpoints 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). However, these results are from *in vitro* tests and many other chemicals can also induce such abnormalities; therefore, these should not be considered specific biomarkers of vinyl acetate effects. While vinyl acetate does not form adducts with DNA, its metabolite acetaldehyde forms protein or hemoglobin adducts, suggesting these types of adducts could potentially be used as markers 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 also been shown to be formed following chronic alcohol ingestion, though, so acetaldehyde adducts are also not useful as specific biomarkers of effect for vinyl acetate. 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. The metabolism of vinyl acetate has been characterized in humans. Additionally, the toxicokinetics of vinyl acetate in rats and mice are relatively well characterized following oral and inhalation exposure. Since the dermal route is a relevant exposure route for human, quantitative absorption data may be useful.

Comparative Toxicokinetics. The toxicokinetics of inhaled vinyl acetate in humans are similar to those that have been observed in rats and mice, although some differences may occur due to differences in carboxylesterase distribution and/or activity. PBPK models for vinyl acetate have been developed to simulate characteristics of the anatomy and physiology of the rat and human that are thought to contribute to interspecies differences in dose-response relationships for nasal lesions. A PBPK model evaluating interspecies differences between the mouse and human may be useful. While no oral toxicokinetic data are available in humans, data in laboratory animals indicate that toxicokinetics are similar between routes and species. Oral tissue carboxylesterase activities were similar between rats and mice.

Children's Susceptibility. No human data are available regarding children's susceptibility; epidemiological data for children would be useful to address this data gap. Available data from inhalation and oral developmental studies do not indicate that developing animals are uniquely susceptible to toxicity following exposure to vinyl acetate. However, the inhalation database is limited to a single gestation-only exposure study, and the oral database is limited due to palatability issues with drinking

water exposure. Additional inhalation studies (e.g., a 2-generation study) and oral studies below doses associated with palatability issues would be useful to address these data gaps.

Physical and Chemical Properties. The physical/chemical properties of vinyl acetate are sufficiently well defined to enable assessment of the environmental fate of this compound (Tables 4-1 and 4-2).

Production, Import/Export, Use, Release, and Disposal. Vinyl acetate is used primarily as a chemical intermediate in the production of polymeric materials and is contained in polymeric consumer products only as residual monomer. Data pertaining to production, import, and export of vinyl acetate are available through 2019 (EPA 2022a). Vinyl acetate is released to the environment as a result of its commercial production, use, storage, transport, and disposal. Releases of the compound from industrial processes are mainly to the atmosphere. Underground injection is also an important source of release for certain facilities. It is uncertain whether the United States is incinerating or using landfill disposal for vinyl acetate, as identified regulations for vinyl acetate are outdated (EPA 1981, 1991). Additional information on disposal methods and pertinent regulations would be useful in evaluating the potential for release of and exposure to vinyl acetate.

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

Bioavailability from Environmental Media. No information was found regarding human absorption of vinyl acetate following inhalation, oral, or dermal exposures from environmental media. Limited data from laboratory animals suggest that absorption may occur following exposure by all of these routes (Hazleton 1979a, 1980a; Smyth and Carpenter 1948). Additional information is needed on the uptake of

vinyl acetate following inhalation of workplace and ambient air, dermal contact with or ingestion of contaminated soils, and ingestion of contaminated drinking water. This information would be useful in determining the bioavailability of the compound from environmental media.

Food Chain Bioaccumulation. No studies were identified that were designed to evaluate bioconcentration of vinyl acetate by plants, aquatic organisms, or animals, or the biomagnification of the compound in terrestrial or aquatic food chains. On the basis of the reactivity, volatility, and water solubility of the compound, bioconcentration and biomagnification are not expected to be important environmental fate processes (Fujisawa and Masuhara 1981; Hansch and Leo 1979). Additional information is needed to confirm this predicted behavior. This information would be useful in establishing the importance of food chain bioaccumulation as a source of human exposure to vinyl acetate.

Exposure Levels in Environmental Media. Vinyl acetate has been detected infrequently and at low levels in ambient air, surface water, groundwater, sediment, and soil. Limited monitoring data at Superfund sites are available. No biomonitoring data for drinking water or food were located. This information would be useful in estimating human exposure to vinyl acetate.

Exposure Levels in Humans. Biomonitoring data in humans are not available due to a lack of a reliable biomarker. Vinyl acetate metabolism is rapid; *in vivo* tests with laboratory animals indicate that most of the compound is eliminated within 24 hours after exposure (Hazleton 1979a, 1980a). Therefore, it would be difficult to measure the presence of vinyl acetate or acetaldehyde after reasonable periods following exposure to vinyl acetate. Acetaldehyde and acetate may also not be useful as indicators of vinyl acetate exposure. Because these compounds are incorporated into normal metabolic pathways, it would be difficult to determine which metabolites were due to vinyl acetate exposure and which were endogenous in biological tissues and fluids. Investigations into the utility of biomarkers of exposure in characterizing human exposure to vinyl acetate would be useful.

Exposures of Children. Exposure pathways for children will be similar to those for adults. As with adults, biomonitoring data for children are not available due to a lack of a reliable biomarker. If a reliable biomarker is identified, biological monitoring studies for children of workers employed in industries that produce, transport, or store this product, or for children who reside in close proximity to facilities that produce vinyl acetate would be useful.

6.3 ONGOING STUDIES

No ongoing studies were identified in the National Institute of Health (NIH) RePORTER (2024) database.

CHAPTER 7. REGULATIONS AND GUIDELINES

Pertinent international and national regulations, advisories, and guidelines regarding vinyl acetate in air, water, and other media are summarized in Table 7-1. This table is not an exhaustive list, and current regulations should be verified by the appropriate regulatory agency.

ATSDR develops MRLs, which are substance-specific guidelines intended to serve as screening levels by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites. See Section 1.3 and Appendix A for detailed information on the MRLs for vinyl acetate.

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

Agency	Description	Information	Reference
	Air		
EPA	RfC	0.2 mg/m^3 (0.06 ppm)	IRIS 1990
WHO	Air quality guidelines	No data	WHO 2010
	Water & Food		
EPA	Drinking water standards and health advisories	Not listed	EPA 2018a
	National primary drinking water regulations	Not listed	EPA 2023b
	RfD	Not assessed	IRIS 1990
WHO	Drinking water quality guidelines	No data	WHO 2022
FDA	Substances added to food[a]	Allowed for specific uses under food additives regulations (masticatory substance, solvent, or vehicle)	FDA 2024
	Cancer		
HHS	Carcinogenicity classification	Not evaluated	NTP 2021
EPA	Carcinogenicity classification	Not evaluated	IRIS 1990
IARC	Carcinogenicity classification	Group 2B[b]	IARC 1995
	Occupational		
OSHA	PEL (8-hour TWA) for general industry, construction, and shipyards	Not listed	OSHA 2023a, 2023b, 2023c
NIOSH	Ceiling REL (15-minute)	4 ppm (15 mg/m^3)	NIOSH 2019

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

Agency	Description	Information	Reference
	Emergency Criteria		
EPA	AEGLs-air		EPA 2018b
	AEGL 1[c]		
	10-minute	6.7 ppm	
	30-minute	6.7 ppm	
	60-minute	6.7 ppm	
	4-hour	6.7 ppm	
	8-hour	6.7 ppm	
	AEGL 2[c]		
	10-minute	46 ppm	
	30-minute	46 ppm	
	60-minute	36 ppm	
	4-hour	23 ppm	
	8-hour	15 ppm	
	AEGL 3[c]		
	10-minute	230 ppm	
	30-minute	230 ppm	
	60-minute	180 ppm	
	4-hour	110 ppm	
	8-hour	75 ppm	
	Level of distinct odor awareness	0.25 ppm	
DOE	PACs-air		DOE 2024a
	PAC-1[d]	6.7 ppm	
	PAC-2[d]	36 ppm	
	PAC-3[d]	180 ppm	

[a]The Substances Added to Food inventory replaces EAFUS and contains the following types of ingredients: food and color additives listed in FDA regulations, flavoring substances evaluated by FEMA or JECFA, GRAS substances listed in FDA regulations, substances approved for specific uses in food prior to September 6, 1958, substances that are listed in FDA regulations as prohibited from use in food, delisted color additives, and some substances "no longer FEMA GRAS."
[b]Group 2B: possibly carcinogenic to humans.
[c]Definitions of AEGL terminology are available from U.S. Environmental Protection Agency (EPA 2018c).
[d]Definitions of PAC terminology are available from U.S. Department of Energy (DOE 2024b).

AEGL = acute exposure guideline levels; DOE = U.S. Department of Energy; EAFUS = Everything Added to Food in the United States; EPA = U.S. Environmental Protection Agency; FAO = Food and Agriculture Organization of the United Nations; FDA = Food and Drug Administration; FEMA = Flavor and Extract Manufacturers Association of the United States; GRAS = generally recognized as safe; HHS = Department of Health and Human Services; IARC = International Agency for Research on Cancer; JECFA = Joint FAO/WHO Expert Committee on Food Additives; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; PAC = protective action criteria; PEL = permissible exposure limit; ppm = parts per million; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TWA = time-weighted average; WHO = World Health Organization

CHAPTER 8. REFERENCES

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APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

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

MRLs are derived for hazardous substances using the NOAEL/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (≥365 days) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive substance-induced endpoint considered to be of relevance to humans. LOAELs for serious health effects (such as irreparable damage to the liver or kidneys, or serious birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

APPENDIX A

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Office of Innovation and Analytics, Toxicology Section, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published MRLs. For additional information regarding MRLs, please contact the Office of Innovation and Analytics, Toxicology Section, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop S106-5, Atlanta, Georgia 30329-4027.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Vinyl acetate
CAS Numbers: 108-05-4
Date: January 2025
Profile Status: Final
Route: Inhalation
Duration: Acute
MRL 1 ppm (3.5 mg/m^3)
Critical Effect: Nasal lesions
Reference: Bogdanffy et al. 1997
Point of Departure: NOAEL of 199.6 ppm ($NOAEL_{HEC}$ of 29.1 ppm)
Uncertainty Factor: 30
LSE Graph Key: 2
Species: Rat

MRL Summary: An acute-duration inhalation MRL of 1 ppm was derived for vinyl acetate based on nasal lesions in male rats exposed to concentrations ≥598.5 ppm for 6 hours/day for 5 days; a NOAEL of 199.6 ppm was identified (Bogdanffy et al. 1997). The MRL is based on a $NOAEL_{HEC}$ of 29.1 ppm derived using the PBPK model by Bogdanffy et al. (1999). The $NOAEL_{HEC}$ was divided by a total uncertainty factor of 30 (3 for extrapolation from animals to humans after dosimetric adjustment and 10 for human variability).

Selection of the Critical Effect: Available acute-duration inhalation studies report vinyl acetate-related effects at LOAELs in the range of 598.5–1,007.3 ppm, including respiratory effects in rats and mice and body weight and developmental effects in rats (Table A-1). The lowest identified LOAEL is for damage to the upper respiratory tract in rats, with 100% incidence of nasal lesions in rats exposed to ≥598.5 ppm for 6 hours/day for 1 or 5 days (Bogdanffy et al. 1997). While this study did not look at a comprehensive set of endpoints, data from intermediate- and chronic-duration studies, as well as mechanistic data, support that the nasal cavity is the most sensitive target following inhalation exposure (see ***Other Additional Studies of Pertinent Information that Lend Support to this MRL*** below). Based on these data, the nasal cavity lesions are selected as the critical effect.

Selection of the Principal Study: Bogdanffy et al. (1997) was selected as the principal study because it provided the lowest point of departure (POD) for the critical effect (nasal cavity lesions). The 5-day study was selected over the 1-day study since observed severity of nasal lesions increased over the 5-day exposure period.

Table A-1. Select NOAEL and LOAEL Values in Animals Following Acute-Duration Inhalation Exposure to Vinyl Acetate

Species	Duration	NOAEL/LOAEL (ppm) NOAEL	LOAEL	Effect	Reference
Respiratory					
Rat (SD)	6 hours (WB)	199.6	598.5	Minimal-to-moderate nasal cavity lesions, cell proliferation in nasal epithelium	Bogdanffy et al. 1997
Rat (SD)	5 days 6 hours/day (WB)	199.6	598.5	Mild-to-severe nasal cavity lesions[a]	Bogdanffy et al. 1997
Rat (SD)	6 hours (WB)	201.6	604.8	Slight-to-marked degeneration/ necrosis of nasal tissue (primarily proximal olfactory epithelium)	Krieger et al. 2020
Rat (SD)	5 days 6 hours/day (WB)	201.6	604.8	Slight-to-moderate atrophy and necrosis of nasal tissue	Krieger et al. 2020
Mouse (NS)	4 hours (WB)	410	820	Labored breathing	Union Carbide 1973
Body weight					
Rat (SD)	10 days GDs 6–15 6 hours/day (WB)	197.5	1,005	9–12% decrease in maternal body weight on GDs 10–20	Hurtt et al. 1995; Hazleton 1980d
Rat (SD)	5 days 6 hours/day (WB)	598.5	1,007.3	14% decrease in body weight	Bogdanffy et al. 1997
Developmental					
Rat (SD)	10 days GDs 6–15 6 hours/day (WB)	197.5	1,005	28% decrease in fetal weight; 12% decrease in crown-to-rump-length, delayed ossification; associated with maternal body weight decreases	Hurtt et al. 1995; Hazleton 1980d

[a]Selected study/endpoint for derivation of acute-duration inhalation MRL.

GD = gestation day; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; NS = not specified; SD = Sprague-Dawley; (WB) = whole-body exposure

Summary of the Principal Study:

Bogdanffy MS, Gladnick NL, Kegelman T, et al. 1997. Four-week inhalation cell proliferation study of the effects of vinyl acetate on rat nasal epithelium. Inhal Toxicol 9(4):331-350. http://doi.org/10.1080/089583797198178.

Groups of male Sprague-Dawley (Crl:CD BR) rats (5/group) were exposed to 0, 50, 200, 600, or 1,000 ppm for 5 consecutive days (6 hours/day); analytical concentrations (± standard error [SE]) were 0±0, 50.8±0.7, 199.6±5.3, 598.5±6.4, and 1,007.3±11.0 ppm, respectively. Rats were observed for

clinical signs and weighed 3 times/week. Sixteen hours after exposure, rats were injected with bromodeoxyuridine (BrdU) to assess cell proliferation and sacrificed 2 hours later. Respiratory tract tissues were examined for gross alterations, and nasal cavities were dissected and cut into five cross sections for histopathological analysis. Immunocytochemistry was performed for BrdU analysis of Level 2, the region with the most observed damage.

Body weights were statistically significantly decreased by 14% on day 5. No gross lesions were observed. Olfactory epithelium regenerative hyperplasia was observed in Levels 2, 3, and 5 in all rats at 598.5 and 1,007.3 ppm and 4/5 and 5/5 rats in Level 4. The most severe lesions were observed in the second and third levels (mild to severe). Increased incidence of minimal degeneration/necrosis of the olfactory epithelium were also observed in Levels 4 and 5. Incidence and severity of respiratory epithelium lesions were low across all groups. No significant changes in cell proliferation were observed.

Selection of the Point of Departure for the MRL: Bogdanffy et al. (1997) identified a NOAEL of 199.6 ppm for nasal lesions in rats following exposure to vinyl acetate for 5 days (6 hours/day). The available data in Bogdanffy et al. (1997) are not amenable to benchmark dose (BMD) modeling because incidences go from 0% at the NOAEL to 100% at the LOAEL for the most sensitive nasal lesions. Therefore, the NOAEL of 199.6 ppm is selected as the POD.

Adjustment for Intermittent Exposure: Exposure over time is accounted for in the PBPK model (HEC simulations are for continuous exposure, see details below); therefore, no additional duration adjustment is needed.

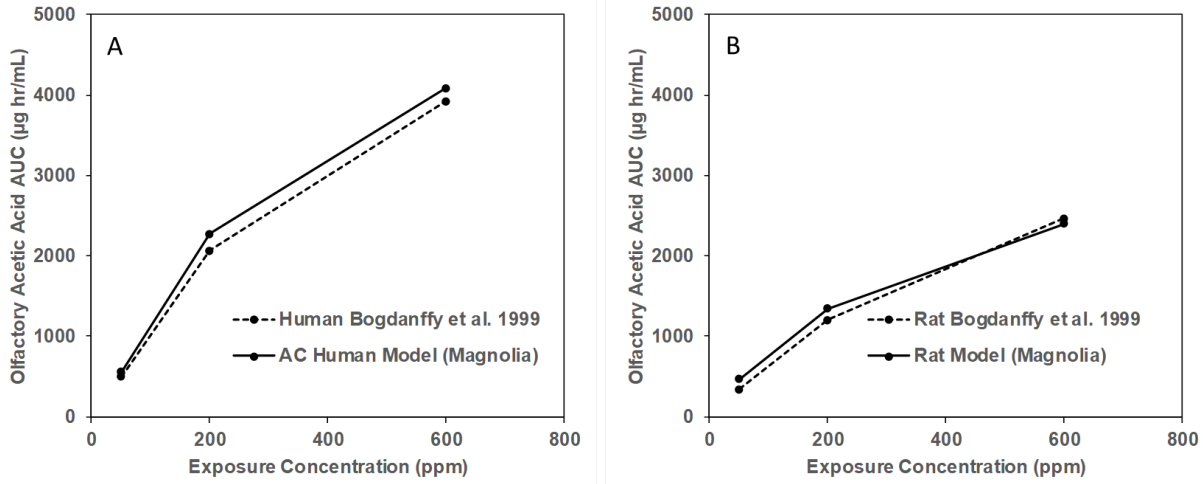
Conversion to Human Equivalent Concentration: A PBPK model (Bogdanffy et al. 1999; Hinderliter et al. 2005) was used for rat-to-human dosimetry extrapolation in deriving the acute-duration inhalation MRL for vinyl acetate. A description of the model can be found in Section 3.1.5 of the profile. This model was selected for dosimetry extrapolation because it has been shown to reliably simulate the kinetics of vinyl acetate uptake and metabolism in the nasal cavity of rats and humans (Bogdanffy et al. 1999; Hinderliter et al. 2005). Important features of vinyl acetate-induced nasal lesions and vinyl acetate kinetics that are relevant to interspecies dosimetry extrapolation include: (1) regional gradients of nasal lesions to the olfactory epithelium, with more severe lesions occurring in the anterior regions (Bogdanffy et al. 1994a, 1997); (2) nearly 100% first-pass extraction of vinyl acetate from inspired air at low concentrations which saturates at higher concentrations (Plowchalk et al. 1997); and (3) intracellular acidification resulting from metabolism of vinyl acetate to acetic acid (Bogdanffy 2002). In the derivation of inhalation MRLs, the PBPK model was used to simulate the acetic acid dose to the surficial layers of the olfactory epithelium in the anterior region of the rat and human nasal cavities. The dose metric used for interspecies dosimetry extrapolation was the area under the curve (AUC) for the acetic acid concentration. The AUC was selected based on evidence that the nature and severity of the nasal lesions in rats change with increasing duration of exposure to vinyl acetate (Bogdanffy et al. 1997; see further discussion of the selection of the dose metric below).

Implementation of the Bogdanffy et al. (1999; Hinderliter et al. 2005) Model

Source and verification of model code. Code for implementing the human vinyl acetate model in Advance Continuous Simulation Language (ASCL) was reported in Hinderliter et al. (2005). For simulations run to support derivation of MRLs, the ACSL code was migrated to Magnolia (v1.3.9 beta). Performance of the Magnolia code was confirmed by comparing predictions with those from the ACSL code reported in Table 2 of Bogdanffy et al. (1999). Examples of these comparisons are presented in Figure A-1, Panel A. The code for the rat model described in Bogdanffy et al. (1999) has not been published; however, the human model was revised to recreate the rat model via addition of a second (posterior) olfactory compartment that is present in rats, but not in humans. Parameter values for the rat

model were based on those reported in Bogdanffy et al. (1999) and Plowchalk et al. (1997). Performance of the Magnolia code for the rat model was confirmed by comparing predictions with those from the ACSL model reported in Table 2 of Bogdanffy et al. (1999). Examples of these comparisons are presented in Figure A-1, Panel B. Figure A-1 shows the non-linear relationship between the vinyl acetate exposure concentration and the AUC for the acetic acid concentration in olfactory tissue that results from capacity limited metabolism of vinyl acetate (see Section 3.1.3 of the profile).

Figure A-1. Area Under the Curve for Acetic Acid Concentration in Human (A) and Rat (B) Olfactory Epithelium Predicted by the Physiologically Based Pharmacokinetic (PBPK) Model*



*Shown are predictions from the ACSL model reported in Table 2 of Bogdanffy et al. (1999) and from the Magnolia version of the model. The simulations are of a continuous 60-hour exposure to vinyl acetate and an inspiratory flow of 197 mg/minute for rats and 7.5 L/minute for humans.

Revisions to the rat model. In addition to including the second olfactory compartment in the rat model, parameters were introduced into the rat model to simulate body weight-dependence of the nasal cavity air flow (model variable *qin*). The Bogdanffy et al. (1999) model parameter value for nasal air flow was the air inspiration rate for a 0.25 kg body weight male rat (197 mL/minute; 11,820 mL/hour). However, in deriving MRLs, simulations were needed for rats having different body weights. The inspiration rate (mL/hour) in rats is dependent on body weight. Therefore, body weight dependence of nasal cavity air flow was simulated in the Magnolia code using an allometric relationship derived for inspiration rate in the male Fischer rat (EPA 1988):

$$qin = 0.80 \cdot bw^{0.8206}$$

where *qin* is the modal parameter for nasal air flow (m^3/day) and *bw* is body weight (kg). The conversion to mL/hour for use in the model is 1,000,000/24. This yields a value for *qin* of 0.271 m^3/day and 11,279 mL/hour for a 0.25-kg rat, which is 4.5% lower than the value used in Bogdanffy et al. (1999).

Uncertainties regarding relationship between body weight and size of nasal tissue compartments. In simulations run to support derivation of inhalation MRLs, dimensions of nasal cavity tissue compartments (surface area, depth) in the rat were assumed to be independent of body weight over the range of body weights simulated in derivation of MRLs (0.2–0.6 kg). This assumption precluded having to develop a model for nasal cavity tissue growth. The assumption appears to be reasonable for simulating rats having body weights >0.25 kg. Viscerocranial growth (nose length) in *hooded* laboratory rats was shown to be

complete by age 80 days postconception (~58 days postpartum), with relatively little growth beyond age 50 days (see Figure 3 of Hughes et al. 1978). At age 50 days (postpartum), the average body weight of male and female Sprague-Dawley is approximately 0.26 kg (Timchalk et al. 2007), which is close to the value assumed in the Bogdanffy et al. (1997) model (0.25 kg). The Hughes et al. (1978) observations are for viscerocranial length, and do not necessarily reflect growth of the nasal cavity tissues; it is possible that surface area or depth of nasal cavity tissues could change independently of viscerocranial length. The assumption of independence of nasal cavity dimensions and body weight introduces some uncertainty into predictions of nasal olfactory tissue doses, particularly in simulations of rats having body weights <0.25 kg (e.g., rat body weights during the first two weeks of exposure in the Bogdanffy et al. 1997 inhalation toxicity studies).

Simulation of olfactory tissue dosimetry in derivation of MRLs. The dose metric used in dosimetry extrapolation was the AUC for the acetic acid concentration in the surficial layers of the anterior olfactory epithelium. This dose metric was selected for the following reasons:

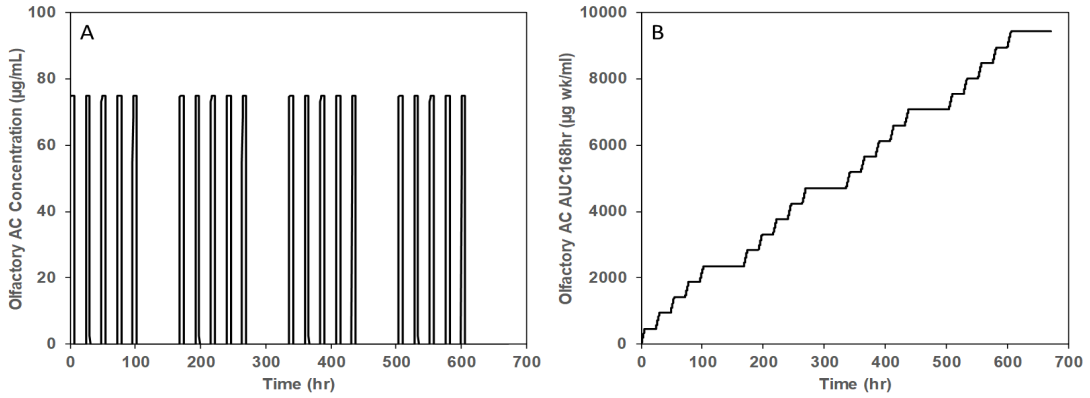
1. Acetic acid was selected because it is considered to be crucial in the mode of action of vinyl acetate. The mode of action is thought to be intracellular acidification resulting from metabolism of vinyl acetate to acetic acid (Bogdanffy 2002).
2. The AUC for acetic acid concentration was selected based on evidence that the severity of lesions in the olfactory epithelium of rats exposed to vinyl acetate is affected by exposure concentration and duration (Bogdanffy et al. 1994a, 1997). Therefore, a cumulative dose metric was considered to be a more appropriate internal dose metric for olfactory tissue than a mean or peak tissue concentration. The PBPK model predicts a steady state acetic acid concentration in olfactory tissue after 1 hour of exposure. As a result, the predicted olfactory concentration is independent of exposure duration for exposures >1 hour, while the AUC increases with increasing exposure duration.
3. The anterior olfactory tissue compartment was selected because it is predicted to receive the highest acetic acid doses during inhalation as a result of anterior-to-posterior air flow and clearance of vinyl acetate and metabolites along the air pathway. This pattern of internal dose is consistent with observations of regional gradients of lesions to the olfactory epithelium, with more severe lesions occurring in the anterior regions (Bogdanffy et al. 1994a, 1997).
4. The surficial region of the rat olfactory epithelium was selected because it is predicted to receive the highest tissue dose as a result of diffusive clearance and metabolism of acetic acid in the surficial layer which limits the concentration experienced by irrepressibly deeper layers (Bogdanffy et al. 1999).

Due to the complexity of the PBPK model to estimate the HEC value, it is impractical to list all the equations and parameters used in the simulations. ATSDR can provide the Magnolia source code and parameter values (based on Bogdanffy et al. 1999 and Plowchalk et al. 1997) upon request. An example of a simulation of the acetic acid concentration in the surficial layer of olfactory epithelium in rats exposed to vinyl acetate, 6 hours/day, 5 days/week for 4 weeks (Bogdanffy et al. 1997) is presented in Figure A-2 (Panel A). The model predicts two patterns of periodicity in the olfactory tissue concentration during this toxicity study. The first pattern appears daily with the attainment of steady state and complete clearance following cessation of each daily exposure. This daily pattern is repeated during each week of exposure (168 hours, inclusive of exposed plus unexposed hours during each weekly interval). The AUC for the acetic acid concentration shows a corresponding pattern of step increases in the AUC during each week of exposure (Figure A-2, Panel B). Because of the complete clearance of acetic acid between exposures, there is no accumulation of acetic acid with increasing exposure duration. As a result, the AUC for durations of more than 1 week ($AUC_{x\ wks}$) at the same exposure frequency (6 hours/day, 5 day/week) is predicted by the AUC for the first week (AUC_{168hr}) times the number of weeks:

$$AUC_{x\ wks} = AUC_{168\ hr} \cdot x$$

This equation indicates that, for exposures that have durations of multiple weeks, the number of weeks included in the calculation of the AUC will transform the dose axis of the dose-response relationship without changing its shape on the response axis. Therefore, the AUC_{168hr} can be used as the dose-response metric in continuous-exposure dosimetry extrapolation for studies of any duration in which the exposure frequency was 6 hours/day, 5 days/week, including a single-week (5-day) study (Bogdanffy et al. 1994a, 1997).

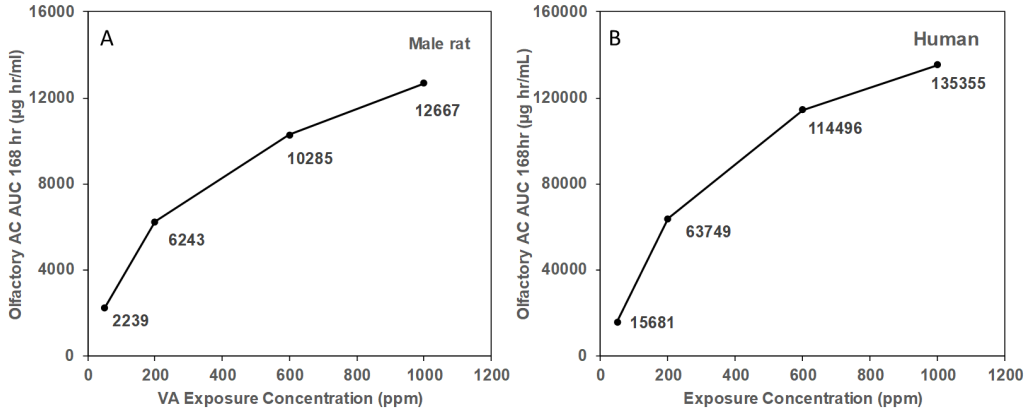
Figure A-2. Concentration (A) and AUC_{168hr} (B) for Acetic Acid (AC) in Olfactory Epithelium for Rats Predicted by the Physiologically Based Pharmacokinetic Model*



*The simulations are of 4 weeks of exposure to 50 ppm vinyl acetate for 6 hours/day, 5 days/week (Bogdanffy et al. 1997).

Figure A-3 (Panel A) shows the AUC_{168hr} predicted for rats exposed 6 hours/day, 5 days/week in the Bogdanffy et al. (1997) 4-week toxicity study. Figure A-3 (Panel B) shows the corresponding AUC_{168hr} predicted for humans exposed continuously to the same concentrations of vinyl acetate based on the PBPK model developed by Bogdanffy et al. (1999; Hinderliter et al. 2005). Using this model, the human is predicted to experience a 10-fold higher AUC for acetic acid concentration in olfactory tissue than the rat. This prediction applies only to exposures that occur when ventilation is restricted to nasal breathing and reflects the higher ratio of the nasal passage surface area to ventilation volume in the rat compared to the adult human. The Bogdanffy et al. (1997) model cannot be used to predict dosimetry in infants or children without reevaluating all parameters and assigning values (e.g., ventilation rate) that represent specific pre-adult life stages. It is also noted that this model does not account for situations in which nasal exposure would be lower when ventilation in the human occurs from a mix of nasal and oral breathing (e.g., during moderate to heavy exercise or in people who habitually breathe through their mouth) (ICRP 1994). This introduces some uncertainty in animal-to-human extrapolations since rodents are obligate nasal breathers (EPA 1994).

Figure A-3. AUC_{168hr} for Acetic Acid (AC) in Olfactory Epithelium for Rats (A) and Humans (B) Predicted by the Physiologically Based Pharmacokinetic Model*



*The simulations are of 4 weeks of exposure for 6 hours/day, 5 days/week in rats (Bogdanffy et al. 1997) and continuous exposure in humans.

HECs that are pharmacokinetically equivalent to PODs (e.g., AUC_{168hr} POD) were computed by reverse dosimetry simulations using the human PBPK model. In these simulations, the human model was run over a range of vinyl acetate exposure concentrations to determine the exposure concentration that corresponded to the AUC_{168hr} POD. The study-specific parameters utilized in the PBPK model to calculate a $NOAEL_{HEC}$ of 29.1 ppm for the selected POD are shown in Table A-2. As previously indicated, all model parameters were based on values reported by Bogdanffy et al. (1999) and Plowchalk et al. (1997), with the exception of body weights, which were based on TWA body weights calculated for the principal study.

Table A-2. HECs Corresponding to the Rat POD Selected for Acute-Duration Inhalation MRL for Vinyl Acetate

Study	Exposure (ppm)	Duration and frequency	POD basis	POD metric	POD (hour µg/mL)	HEC[a] (ppm)
Bogdanffy et al. (1997)	0, 50.8, 199.6, 598.5, 1,007.3	5 days 6 hours/day	NOAEL (199.6 ppm)	$AUC_{168\ hr}$	6,175	29.1

[a]Calculated for continuous human exposure.

AUC = area under the curve for acetic acid concentration in olfactory epithelium; HEC = human equivalent exposure concentration; MRL = Minimal Risk Level; NOAEL = no-observed adverse effect level; POD = dose-response point of departure

Uncertainty Factor: The $NOAEL_{HEC}$ was then by divided by a total uncertainty factor of 30:

- 3 for extrapolation from animals to humans with dosimetric adjustments
- 10 for human variability

$$MRL = \frac{NOAEL_{HEC}}{UFs} = \frac{29.1\ ppm}{30} = 1\ ppm$$

Other Additional Studies of Pertinent Information that Lend Support to this MRL: Limited evidence from humans has shown that the respiratory tract is a sensitive target of acute-duration vinyl acetate exposure, with irritation of throat mucous membranes from acute-duration exposure levels as low as 4 ppm and persistent irritation at 74 ppm (Deese and Joyner 1969; Union Carbide 1973). The intermediate- and chronic-duration databases confirm that the respiratory system, particularly the extrathoracic region, is the most sensitive target of toxicity following inhalation exposure to vinyl acetate. Nasal lesions are observed in rats following intermediate-duration exposure to ≥598.5 ppm (Bogdanffy et al. 1997; Krieger et al. 2020) and in rats and mice following chronic-duration exposure to ≥200.5 ppm (Bogdanffy et al. 1994a; Hazleton 1988). Lower respiratory tract lesions are also seen in rats and mice following intermediate-duration exposure to 998.9 ppm (Hazleton 1980b, 1980c) and mice following chronic-duration exposure to ≥200.5 ppm (Bogdanffy et al. 1994a; Hazleton 1988). In acute-duration inhalation lethality studies, deaths were attributed to lung damage in rats, mice, guinea pigs, and rabbits (Union Carbide 1973). Mechanistic data predict portal-of-entry effects (i.e., respiratory tract lesions) based on rapid hydrolysis of vinyl acetate into acetaldehyde and acetic acid following contact with mucosal surfaces, resulting in irritation due to tissue acidification (Bogdanffy et al. 1999, 2001, 2004; Slikker et al. 2004).

Agency Contacts (Chemical Managers): Rae T. Benedict

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Vinyl acetate
CAS Numbers: 108-05-4
Date: January 2025
Profile Status: Final
Route: Inhalation
Duration: Intermediate
MRL 0.7 ppm (2.5 mg/m^3)
Critical Effect: Nasal lesions
Reference: Bogdanffy et al. 1997
Point of Departure: NOAEL of 199.6 ppm ($NOAEL_{HEC}$ of 21.6 ppm)
Uncertainty Factor: 30
LSE Graph Key: 11
Species: Rat

MRL Summary: An intermediate-duration inhalation MRL of 0.7 ppm was derived for vinyl acetate based on nasal lesions in male rats exposed to concentrations ≥598.5 ppm for 4 weeks (6 hours/day, 5 days/week); a NOAEL of 199.6 ppm was identified (Bogdanffy et al. 1997). The MRL is based on a $NOAEL_{HEC}$ of 21.6 ppm derived using the PBPK model by Bogdanffy et al. (1999). The $NOAEL_{HEC}$ was divided by a total uncertainty factor of 30 (3 for extrapolation from animals to humans after dosimetric adjustment and 10 for human variability).

Selection of the Critical Effect: Available intermediate-duration inhalation studies for vinyl acetate consistently report exposure-related respiratory and body weight effects in rats and mice at LOAELs in the range of 497.6–998.9 and 998.9 –1,007.3 ppm, respectively (Table A-3). One study in rats reported neurological effects (degeneration/atrophy of olfactory nerve bundles) at 598.8 ppm; however, this effect was not noted in other studies in rats and mice (Table A-3). Respiratory effects are considered the most sensitive effect, with clinical signs (intermittent respiratory distress) at ≥497.6 ppm, nasal lesions at ≥598.5 ppm, and lower respiratory tract lesions at 998.9 ppm. While intermittent respiratory distress is reported at a slightly lower administered concentration, compared to nasal lesions, confidence in this endpoint is low due to intermittent nature (decreasing over the course of treatment), lack of incidence data, lack of concurrent histopathological evaluation, and lack of observation in chronic-duration studies. In contrast, the upper respiratory system (nasal cavity) is a clear target of vinyl acetate toxicity following acute-, intermediate-, and chronic-duration inhalation exposure. Therefore, nasal cavity lesions were selected as the critical effect for derivation of the intermediate-duration inhalation MRL.

Selection of the Principal Study: The 4-week rat study (Bogdanffy et al. 1997) was selected as the principal study because it provides the lowest LOAEL for the critical effect (nasal lesions) following intermediate-duration inhalation exposure. While the NOAEL for nasal lesions is similar in rats and mice, the rat is more sensitive to nasal toxicity, showing higher incidence (100%) and more severe effects (atrophy, hyperplasia) at the LOAEL of 598.5 ppm compared to mice (70% incidence of rhinitis at the LOAEL of 998.9 ppm). Additionally, a PBPK model estimating olfactory epithelium exposure metrics in rats and humans is available (Bogdanffy et al. 1999; Hinderliter et al. 2005). Use of a PBPK model will result in a higher confidence in the HEC calculation in rats, compared to use of a default HEC concentration for mice based on the regional gas dose ratio (RGDR) recommended by the EPA (1994).

Table A-3. Select NOAEL and LOAEL Values in Animals Following Intermediate-Duration Inhalation Exposure to Vinyl Acetate

Species	Duration	NOAEL/LOAEL (ppm) NOAEL	LOAEL	Effect	Reference
Respiratory					
Rat (SD)	4 weeks 5 days/week 6 hours/day (WB)	150.5	497.6	Intermittent respiratory distress (histology not evaluated)	Hazleton 1979c
Mouse (CD-1)	4 weeks 5 days/week 6 hours/day (WB)	150.5	497.6	Intermittent respiratory distress (histology not evaluated)	Hazleton 1979b
Rat (SD)	4 weeks 5 days/week 6 hours/day (WB)	199.6	598.5	Nasal lesions[a]	Bogdanffy et al. 1997
Rat (SD)	4 weeks 5 days/week 6 hours/day (WB)	201.6	604.8	Slight-to-marked atrophy of the olfactory epithelium; minimal-to-mild transitional hyperplasia and slight respiratory metaplasia of nasal tissue	Krieger et al. 2020
Rat (SD)	13 weeks 5 days/week 6 hours/day (WB)	201.6	604.8	Slight-to-marked atrophy and necrosis/degeneration of the olfactory epithelium; slight respiratory metaplasia of nasal tissue	Krieger et al. 2020
Rat (SD)	3 months 5 days/week 6 hours/day (WB)	199.9	998.9	Intermittent respiratory distress, focal histiocytic alveolitis	Hazleton 1980c
Mouse (CD-1)	3 months 5 days/week 6 hours/day (WB)	199.8	998.9	Intermittent respiratory distress, focal and diffuse rhinitis, mild multifocal bronchitis, hyperplasia, and metaplasia of the trachea.	Hazleton 1980b
Body weight					
Rat (SD)	3 months 5 days/week 6 hours/day (WB)	199.9	998.9	18–22% decrease in body weight	Hazleton 1980c
Mouse (CD-1)	3 months 5 days/week 6 hours/day (WB)	199.8	998.9	20–24% decrease in body weight	Hazleton 1980b
Mouse (CD-1)	4 weeks 5 days/week 6 hours/day (WB)	497.6	1,000.2	16% decrease in body weight in males	Hazleton 1979b

Table A-3. Select NOAEL and LOAEL Values in Animals Following Intermediate-Duration Inhalation Exposure to Vinyl Acetate

Species	Duration	NOAEL/LOAEL (ppm) NOAEL	LOAEL	Effect	Reference
Rat (SD)	4 weeks 5 days/week 6 hours/day (WB)	598.5	1,007.3	>10% decrease in body weight	Bogdanffy et al. 1997
Neurological effects					
Rat (SD)	4 weeks 5 days/week 6 hours/day (WB)	199.6	598.5	Degeneration/atrophy of olfactory nerve bundle	Bogdanffy et al. 1997
Rat (SD)	3 months 5 days/week 6 hours/day (WB)	998.9	ND	No adverse effects	Hazleton 1980c
Mouse (CD-1)	3 months 5 days/week 6 hours/day (WB)	998.9	ND	No adverse effects	Hazleton 1980b

[a]Selected study/endpoint for derivation of intermediate-duration inhalation MRL.

LOAEL = lowest-observed-adverse-effect level; ND = not determined; NOAEL = no-observed-adverse-effect level; SD = Sprague-Dawley; (WB) = whole-body exposure

Summary of the Principal Study:

Bogdanffy MS, Gladnick NL, Kegelman T, et al. 1997. Four-week inhalation cell proliferation study of the effects of vinyl acetate on rat nasal epithelium. Inhal Toxicol 9(4):331-350. http://doi.org/10.1080/089583797198178.

Groups of male rats (5/group) were exposed to 0, 50, 200, 600, or 1,000 ppm for 4 weeks (5 days/week, 6 hours/day); analytical concentrations (±SE) were 0±0, 50.8±0.7, 199.6±5.3, 598.5±6.4, and 1,007.3±11.0 ppm, respectively. Rats were observed for clinical signs, and for the 5-day study, weighed 3 times/week. Sixteen hours after exposure rats were injected with BrdU to assess cell proliferation and sacrificed 2 hours later. Respiratory tract tissues were examined for gross alterations and nasal cavities were dissected and cut into five cross sections for histopathological analysis. Immunocytochemistry was performed for BrdU analysis of Level 2, the region with the most observed damage.

Body weights were statistically decreased >10% at 1,007.3 ppm from day 3 through 26 (maximal reduction of 15% on day 5). No gross lesions were observed. Microscopic lesions were observed in several nasal cavity levels in all rats at ≥598.5 ppm, including olfactory epithelium regenerative hyperplasia and degeneration/necrosis and nerve bundle degeneration/atrophy. The most severe lesions were observed in the second and third levels (mild to severe). Incidence and severity of respiratory epithelium lesions were low across all groups. Increased cell proliferation was observed in the olfactory epithelium at ≥598.5 ppm, but not the respiratory epithelium.

Selection of the Point of Departure for the MRL: Bogdanffy et al. (1997) identified a NOAEL of 199.6 ppm for nasal lesions in rats following exposure to vinyl acetate for 4 weeks (6 hours/day; 5 days/week). The available data in Bogdanffy et al. (1997) are not amenable to BMD modeling because incidences go from 0% at the NOAEL to 100% at (and above) the LOAEL for the most sensitive nasal lesions. Therefore, the NOAEL of 199.6 ppm is selected as the POD.

Adjustment for Intermittent Exposure: Exposure over time is accounted for in the PBPK model (HEC simulations are for continuous exposure, see details below); therefore, no additional duration adjustment is needed.

Conversion to Human Equivalent Concentration: The PBPK model (Bogdanffy et al. 1999; Hinderliter et al. 2005) was used for rat-to-human dosimetry extrapolation in deriving inhalation MRLs for vinyl acetate as described in the acute-duration inhalation MRL worksheet. The study-specific parameters utilized in the PBPK model to calculate a $NOAEL_{HEC}$ of 21.6 ppm for the selected POD are shown in Table A-4. As previously indicated, model parameters were based on values reported by Bogdanffy et al. (1999) and Plowchalk et al. (1997), with the exception of body weights, which were based on TWA body weights calculated for the principal study. The difference in the acute- and intermediate-duration $NOAEL_{HEC}$ values (based on identical administered concentrations) is due to different TWA body weight values.

Table A-4. HECs Corresponding to the Rat POD Selected for Intermediate-Duration Inhalation MRL for Vinyl Acetate

Study	Exposure (ppm)	Duration and frequency	POD basis	POD metric	POD (hour µg/mL)	HEC[a] (ppm)
Bogdanffy et al. (1997)	0, 50.8, 199.6, 598.5, 1,007.3	4 weeks 5 days/week 6 hours/day	NOAEL (199.6 ppm)	$AUC_{168\ hr}$	6,243	21.6

[a]Calculated for continuous human exposure.

AUC = area under the curve for acetic acid concentration in olfactory epithelium; HEC = human equivalent exposure concentration; MRL = Minimal Risk Level; NOAEL = no-observed adverse effect level; POD = dose-response point of departure

Uncertainty Factor: The $NOAEL_{HEC}$ was then by divided by a total uncertainty factor of 30:

- 3 for extrapolation from animals to humans with dosimetric adjustment
- 10 for human variability

$$MRL = \frac{NOAEL_{HEC}}{UFs} = \frac{21.6\ ppm}{30} = 0.7\ ppm$$

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Limited evidence from humans has shown that the respiratory tract is a sensitive target of acute-duration vinyl acetate exposure, with irritation of throat mucous membranes from acute-duration exposure levels as low as 4 ppm and persistent irritation at 74 ppm (Deese and Joyner 1969; Union Carbide 1973). The acute-, intermediate-, and chronic-duration databases confirm that the respiratory system, particularly the extrathoracic region, is the most sensitive target of toxicity following inhalation exposure to vinyl acetate. Nasal lesions are observed in rats following acute- or intermediate-duration exposure to ≥598.5 ppm (Bogdanffy et al. 1997; Krieger et al. 2020) and in rats and mice following chronic-duration exposure to

≥200.5 ppm (Bogdanffy et al. 1994a; Hazleton 1988). Lower respiratory tract lesions are also seen in rats and mice following intermediate-duration exposure to 998.9 ppm (Hazleton 1980b, 1980c) and mice following chronic-duration exposure to ≥200.5 ppm (Bogdanffy et al. 1994a; Hazleton 1988). In acute-duration inhalation lethality studies, deaths were attributed to lung damage in rats, mice, guinea pigs, and rabbits (Union Carbide 1973). Mechanistic data predict portal-of-entry effects (i.e., respiratory tract lesions) based on rapid hydrolysis of vinyl acetate into acetaldehyde and acetic acid following contact with mucosal surfaces, resulting in irritation due to tissue acidification (Bogdanffy et al. 1999, 2001, 2004; Slikker et al. 2004).

Agency Contacts (Chemical Managers): Rae T. Benedict

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Vinyl acetate
CAS Numbers: 108-05-4
Date: January 2025
Profile Status: Final
Route: Inhalation
Duration: Chronic
MRL 0.3 ppm (1.1 mg/m^3)
Critical Effect: Nasal lesions
References: Bogdanffy et al. 1994a; Hazleton 1988
Point of Departure: NOAEL of 49.4 ppm ($NOAEL_{HEC}$ of 8.52 ppm)
Uncertainty Factor: 30
LSE Graph Key: 19
Species: Rat

MRL Summary: A chronic-duration inhalation MRL of 0.3 ppm was derived for vinyl acetate based on nasal lesions in male rats exposed to concentrations ≥200.5 ppm for 104 weeks (6 hours/day, 5 days/week); a NOAEL of 49.4 ppm was identified (Bogdanffy et al. 1994a; Hazleton 1988). The MRL is based on a $NOAEL_{HEC}$ of 8.52 ppm derived using the PBPK model by Bogdanffy et al. (1999). The $NOAEL_{HEC}$ was divided by a total uncertainty factor of 30 (3 for extrapolation from animals to humans after dosimetric adjustment and 10 for human variability).

Selection of the Critical Effect: Available chronic-duration inhalation studies for vinyl acetate report exposure-related respiratory and body weight effects in rats and mice at LOAELs of 200.5 and 594.7 ppm, respectively (Table A-5). Respiratory effects are considered the most sensitive effect, with nasal lesions in rats and mice and pulmonary lesions in mice at ≥200.5 ppm. Therefore, respiratory lesions were selected as the critical effect for derivation of the chronic-duration inhalation MRL.

Selection of the Principal Study: While both rats and mice are similarly sensitive to the development of respiratory lesions, the chronic-duration rat study (Bogdanffy et al. 1994a; Hazleton 1988) was selected as the principal study due to the availability of a PBPK model estimating olfactory epithelium exposure metrics in rats and humans (Bogdanffy et al. 1999). Use of a PBPK model will result in higher confidence in the HEC calculation, compared to use of a default HEC concentration based on the RGDR recommended by EPA (1994).

Table A-5. Select NOAEL and LOAEL Values in Animals Following Chronic-Duration Inhalation Exposure to Vinyl Acetate

		NOAEL/LOAEL (ppm)			
Species	Duration	NOAEL	LOAEL	Effect	Reference
Respiratory					
Rat (SD)	104 weeks 5 days/week 6 hours/day (WB)	49.4	200.5	Nasal lesions[a]	Bogdanffy et al. 1994a; Hazleton 1988
Mouse (CD-1)	104 weeks 5 days/week 6 hours/day (WB)	49.4	200.5	Nasal lesions	Bogdanffy et al. 1994a; Hazleton 1988

Table A-5. Select NOAEL and LOAEL Values in Animals Following Chronic-Duration Inhalation Exposure to Vinyl Acetate

Species	Duration	NOAEL/LOAEL (ppm) NOAEL	LOAEL	Effect	Reference
Body weight					
Rat (SD)	104 weeks 5 days/week 6 hours/day (WB)	200.5	594.7	14% decrease in terminal body weight in females	Bogdanffy et al. 1994a; Hazleton 1988
Mouse (CD-1)	104 weeks 5 days/week 6 hours/day (WB)	200.5	594.7	11–15% decrease in terminal body weight	Bogdanffy et al. 1994a; Hazleton 1988

[a]Selected study for derivation of chronic-duration inhalation MRL.

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; SD = Sprague-Dawley; (WB) = whole-body exposure

Summary of the Principal Study:

Bogdanffy MS, Dreef-van der Meulen HC, Beems RB, et al. 1994a. Chronic toxicity and oncogenicity inhalation study with vinyl acetate in the rat and mouse. Fundam Appl Toxicol 23(2):215-229. http://doi.org/10.1006/faat.1994.1100.

Hazleton. 1988. Vinyl acetate: 104 week inhalation combined chronic toxicity and carcinogenicity study in the rat and mouse (Vol. I, II, IV & Vol. I of Amendment to final report, with cover letter 01/31/89). The Society of the Plastics Industry Inc. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8e. OTS0510582. 890000088. 8EHQ01890642.

Groups of Crl:CD(SD)BR Sprague-Dawley rats (60/sex/group) were exposed whole-body to vinyl acetate at concentrations of 0, 50, 200, or 600 ppm for 6 hours/day, 5 days/week for 104 weeks. Analytical concentrations for the exposure groups were 49.4±2.4, 200.5±9.7, and 594.7±16.8 ppm, respectively. Body weights were recorded at weekly intervals to Week 28 and every 4 weeks thereafter. All animals were observed briefly for clinical abnormalities before each exposure, received a detailed examination 1 time/week, and were examined twice daily for morbidity and mortality. Blood was collected from 10/sex/group in Week 104 for clinical chemistry and hematology. Urine samples were collected overnight. All animals underwent gross necropsy at sacrifice. The adrenals, gonads, kidneys, lungs, spleen, brain, heart, liver, pituitary, and thyroids were weighed. Histopathology was conducted on a complete set of tissues in control and high-exposure group. The respiratory tract tissues, including the nasal cavity, were examined in all animals. The respiratory tract histology was conducted in two independent labs, while one lab evaluated the nasal cavity in four cross sections.

Additional animals were used in satellite groups. One satellite group (10/sex/group) was used for clinical laboratory evaluation at Week 51 and interim sacrifice at Weeks 52–53. A second satellite group (10/sex/group) was used for clinical laboratory evaluation at Week 81 and interim sacrifice at Weeks 85–86. A third satellite group (10/sex/group) was used to evaluate recovery after 70 weeks of exposure followed by 15–16 weeks exposure-free.

No adverse treatment-related effects or mortality were observed. The study authors mentioned treatment-related clinical signs of rough haircoat and hunched posture at all concentrations; however, these findings were not uncommon in the control group and no exposure-related findings were observed when weekly incidence data were reviewed. Body weight gain was significantly decreased at 594.7 ppm during the study and absolute body weight in the high exposure group was decreased ~10%. No clear exposure-related hematological changes were observed. Blood glucose was decreased in 594.7-ppm females and urine volume was significantly reduced at 594.7 ppm in males at Week 51 and both sexes at Weeks 81 and 104. These findings were attributed by the study author to reductions in food and water intake (although these parameters were not specifically measured). Relative lung weight was significantly increased in all exposure groups at terminal sacrifice by 12–17% in females; this effect was reversed in the satellite recovery group. Elevated relative lung weight in males was only observed at the 53-week interim sacrifice at 594.7 ppm (20–30%). The biological relevance of reversible elevated relative lung weight in the absence of histopathological changes is unclear, especially considering body weight effects. The unpublished study (Hazleton 1988) also reported decreased relative spleen weight; this is not mentioned in the published report (Bogdanffy et al. 1994a), nor is it accompanied by histopathological changes.

Treatment-related nonneoplastic nasal lesions were observed in animals exposed to 200.5 or 594.7 ppm (olfactory epithelial atrophy, olfactory epithelial squamous metaplasia, olfactory epithelial regeneration, olfactory epithelial inflammatory cell infiltrate, epithelial nest-like infolds, olfactory epithelial leukocytic exudate, basal cell hyperplasia, turbinate leukocytic exudate, submucosal inflammatory cell infiltrate). Nonneoplastic lesions in the lungs were observed at 594.7 ppm (bronchial exfoliation, intraluminal fibrous projections, pigmented macrophages, peribronchiolar/ perivascular lymphoid aggregates). The total incidence of neoplastic nasal tumors (combined) was significantly elevated in male rats at 594.7 ppm (7/59) compared with controls (0/59) and nonsignificantly elevated in females (4/59 compared with 0/59 controls). Only squamous cell carcinoma was observed in females at 594.7 ppm. Nasal tumors observed in 594.7-ppm males included inverted papilloma, two squamous cell carcinomas, carcinoma *in situ* (4/59 total incidence of benign tumors and 3/59 total incidence of malignant tumors). One 200-ppm male had a nasal papilloma. No exposure-related lung tumors were observed in either sex. One squamous cell carcinoma of the larynx was observed in a 594.7-ppm female. The study author attributed the observed olfactory atrophy and tumors in the nasal cavity and lung lesions to chronic irritation.

Selection of the Point of Departure for the MRL: In order to identify the POD, BMD modeling was attempted for nasal lesions (atrophy, basal cell hyperplasia) in male and female rats reported by Bogdanffy et al. (1994a). Male and female rat nasal lesion data modeled are shown in Tables A-6 and A-7, respectively. Prior to modeling, the PBPK model described in the acute-duration inhalation MRL section was utilized to convert administered concentrations to acetic acid concentration overtime (AUC) in rat nasal olfactory epithelial tissue. Conversion to tissue dosimetry was performed prior to BMD modeling due to nonlinear relationship observed between external concentration and tissue concentration (attributed to metabolic saturation). The data were fit to all available dichotomous models in EPA's Benchmark Dose Software (BMDS) (version 3.2) using a benchmark response (BMR) of 10% extra risk. Adequate model fit was judged by four criteria: goodness-of-fit statistics (p-value >0.1), visual inspection of the dose-response curve, BMCL (95% lower confidence limit on the benchmark concentration [BMC]) that is not 10 times lower than the lowest non-zero dose, and scaled residual within ±2 units at the data point (except the control) closest to the predefined BMR. Among all of the models providing adequate fit to the data, the lowest BMCL was selected as the POD when the difference between the BMCLs estimated from these models was ≥3 fold; otherwise, the BMCL from the model with the lowest Akaike Information Criterion (AIC) was chosen.

Table A-6. Incidence of Select Nasal Lesions in the Olfactory Epithelium of Male Sprague-Dawley Rats Following Inhalation Exposure to Vinyl Acetate for 104 Weeks (5 Days/Week, 6 Hours/Day)

	Analytical concentration in ppm (AC AUC in week µg/mL[a])			
	0 (0)	49.4 (2,295)	200.5 (5,975)	594.7 (9,715)
Atrophy	0/59 (0%)	0/60 (0%)	53/60[b] (88%)	50/60[b] (83%)
Basal cell hyperplasia	2/59 (3%)	5/60 (8%)	54/60[b] (92%)	46/60[b] (78%)

[a]Calculated using the PBPK model by Bogdanffy et al. (1999), described in the acute-duration inhalation MRL worksheet.
[b]Statistically significant ($p<0.05$) based on Fisher's Exact Probability test conducted for this review.

AC = acetic acid; AUC = area under the curve; PBPK = physiologically based pharmacokinetic

Source: Bogdanffy et al. 1994a

Table A-7. Incidence of Select Nasal Lesions in the Olfactory Epithelium of Female Sprague-Dawley Rats Following Inhalation Exposure to Vinyl Acetate for 104 Weeks (5 Days/Week, 6 Hours/Day)

	Analytical concentration in ppm (AC AUC in week µg/mL[a])			
	0 (0)	49.4 (2,267)	200.5 (6,224)	594.7 (10,140)
Atrophy	0/60 (0%)	1/60 (2%)	27/60[b] (45%)	51/59[b] (86%)
Basal cell hyperplasia	0/60 (0%)	0/60 (0%)	34/60[b] (57%)	51/59[b] (86%)

[a]Calculated using the PBPK model by Bogdanffy et al. (1999), described in the acute-duration inhalation MRL worksheet.
[b]Statistically significant ($p<0.05$) based on Fisher's Exact Probability test conducted for this review.

AC = acetic acid; AUC = area under the curve; PBPK = physiologically based pharmacokinetic

Source: Bogdanffy et al. 1994a

Details of the modeling results for atrophy in male rats are provided in Table A-8. The only model that provided an adequate statistical fit was the Dichotomous Hill model. However, this model was considered unstable due to overparameterization for this dataset (only four exposure groups) and a mid-range p-value ($p=0.41$). Additionally, graphing the cumulative distribution function plot did not result in the characteristic sigmoidal shape expected for a viable model (Figure A-4). None of the models tested adequately fit the data for basal cell hyperplasia in male rats.

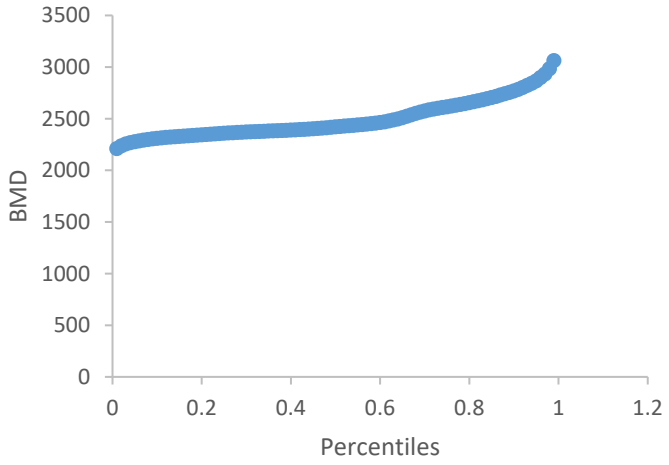
Table A-8. BMD Model Predictions for Olfactory Epithelium Atrophy in Male Sprague-Dawley Rats Following Inhalation to Vinyl Acetate for 104 Weeks (5 Days/Week, 6 Hours/Day) (Bogdanffy et al. 1994a)

Model	BMC_{10}[a] (week µg/mL)	$BMCL_{10}$[a] (week µg/mL)	p-value[b]	AIC	Scaled residuals[c]	
					Dose below BMC	Dose above BMC
Dichotomous Hill	2,419.085	2275.090	0.407	119.708	-0.0001	-0.001
Gamma[d]			<0.0001	143.918	-1.637	-0.001
Log-Logistic[e]			<0.0001	136.008	-1.249	-0.001
Multistage Degree 3[f]			<0.0001	147.915	-2.117	-0.001
Multistage Degree 2[f]			<0.0001	145.915	-2.117	-0.001
Multistage Degree 1[f]			<0.0001	163.073	-0.001	-0.001
Weibull[d]			<0.0001	149.646	-2.416	-0.001
Logistic			<0.0001	155.779	-1.792	-1.284
Log-Probit			<0.0001	138.181	-1.282	-0.001
Probit			<0.0001	159.273	-1.889	-1.186

[a]BMC and BMCLs values for models that do not provide adequate fit are not included in this table.
[b]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMC.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Betas restricted to ≥0.

AIC = Akaike Information Criterion; BMC = benchmark concentration (maximum likelihood estimate of the concentration associated with the selected benchmark response); $BMCL_{10}$ = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., 10 = dose associated with 10% extra risk)

Figure A-4. Cumulative Distribution Function of Dichotomous Hill Model for Olfactory Epithelium Atrophy in Male Sprague-Dawley Rats Following Inhalation Exposure to Vinyl Acetate for 104 Weeks (Bogdanffy et al. 1994a)



Details of the modeling results for olfactory epithelium atrophy in female rats are in Table A-9. All models except the Multistage (1-Degree) provided adequate fit to the incidence data. The Gamma model was recommended by BMDS; however, the *p*-value of approximately 1 and scaled residuals of 0.0 suggest that the Gamma model is overfit, so it was not considered further. In accordance with the selection criteria mentioned above, the models with the next lowest AIC value were reviewed (Dichotomous Hill and Log-Logistic). From these, the model with the slightly lower BMCL was selected (frequentist, restricted Log-Logistic model) for olfactory epithelium atrophy in female rats.

Table A-9. BMD Model Predictions for Olfactory Epithelium Atrophy in Female Sprague-Dawley Rats Following Inhalation to Vinyl Acetate for 104 Weeks (6 Hours/Day) (Bogdanffy et al. 1994a)

					Scaled residuals[c]	
Model	BMC_{10}[a] (week µg/mL)	$BMCL_{10}$[a] (week µg/mL)	p-Value[b]	AIC	Dose below BMC	Dose above BMC
Dichotomous Hill	3,768.407	3,036.528	0.805	145.640	0.174	-0.001
Gamma[d]	3,607.948	2,909.137	0.995	145.581	0.004	-0.001
Log-Logistic[e,f]	**3,768.406**	**3,036.527**	**0.805**	**145.640**	**0.174**	**-0.001**
Multistage Degree 3[g]	3,573.788	2,713.506	0.303	146.685	-0.569	-0.001
Multistage Degree 2[g]	2,527.031	2,197.032	0.224	147.522	-1.832	-0.001
Multistage Degree 1[g]			<0.0001	175.866	-0.001	-0.001
Weibull[d]	3,480.679	2,746.145	0.365	146.482	-0.649	-0.015
Logistic	3,843.494	3,187.257	0.184	147.591	-0.900	-0.718
Log-Probit	3,572.231	2,930.895	0.481	146.060	0.411	-0.001
Probit	3,725.311	3,047.144	0.328	146.067	-0.716	-0.442

[a]BMC and BMCLs values for models that do not provide adequate fit are not included in this table.
[b]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMC.
[d]Power restricted to ≥1.
[e]Selected model. All models except the Multistage (1-degree) provided adequate statistical fit to the data. The Gamma model was overfit to the data and was not considered further. BMCLs for the remaining models differed by <3-fold; therefore, the models with the next lowest AIC were reviewed (Dichotomous Hill, Log-Logistic). Since these models have identical AIC values, the model with the (slightly) lower BMCL (Log-Logistic) was selected.
[f]Slope restricted to ≥1.
[g]Betas restricted to ≥0.

AIC = Akaike Information Criterion; BMC = benchmark concentration (maximum likelihood estimate of the concentration associated with the selected benchmark response); $BMCL_{10}$ = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., 10 = dose associated with 10% extra risk)

Details of the modeling results for basal cell hyperplasia in female rats in female rats are in Table A-10. The Dichotomous Hill, Log-Logistic, and Log-Probit models provided adequate fit to the incidence data for atrophy. The Dichotomous Hill model was recommended by BMDS; however, the p-value of approximately 1 and scaled residuals of 0.0 suggest that the Dichotomous Hill model is overfit, so it was not considered further. In accordance with the selection criteria mentioned above, the next lowest AIC was selected (frequentist, restricted Log-Probit model) for basal cell hyperplasia in female rats.

Table A-10. BMD Constant Variance Model Predictions for Olfactory Epithelium Basal Cell Hyperplasia in Female Sprague-Dawley Rats Following Inhalation to Vinyl Acetate for 104 Weeks (6 Hours/Day) (Bogdanffy et al. 1994a)

					Scaled residuals[c]	
Model	BMC_{10}[a] (week µg/mL)	$BMCL_{10}$[a] (week µg/mL)	p-Value[b]	AIC	Dose below BMC	Dose above BMC
Dichotomous Hill	4,943.384	3,326.149	0.977	134.942	0.0005	-0.001
Gamma[d]			0.079	138.960	-1.014	-0.003
Log-Logistic[e]	3,631.587	2,933.453	0.154	137.815	-0.952	-0.001
Multistage Degree 3[f]			0.007	144.070	-1.481	-0.001
Multistage Degree 2[f]			0.081	143.161	-2.460	-0.001
Multistage Degree 1[f]			<0.0001	174.279	-0.001	-0.001
Weibull[d]			0.016	143.239	-1.630	-0.001
Logistic			0.005	146.229	-1.717	-0.769
Log-Probit[g]	**3,576.574**	**2,929.227**	**0.232**	**136.868**	**-0.724**	**-0.001**
Probit			0.009	144.601	-1.585	-0.488

[a]BMC and BMCLs values for models that do not provide adequate fit are not included in this table.
[b]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the BMC.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Betas restricted to ≥0.
[g]Selected model. Only the Dichotomous Hill, Log-Logistic, and Log-Probit models provided adequate statistical fit. However, the Dichotomous Hill model was considered unstable due to low number of dose groups and a p-value near unity; it was not considered further. BMCLs for the remaining two models providing adequate fit differed by <3-fold; therefore, the model with the lowest AIC of these models was selected (Log-Probit).

AIC = Akaike Information Criterion; BMC = benchmark concentration (maximum likelihood estimate of the concentration associated with the selected benchmark response); $BMCL_{10}$ = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., 10 = dose associated with 10% extra risk)

To select the POD for the chronic-duration inhalation MRL, the POD values for olfactory epithelial lesions in male and female rats were compared (Table A-11). The increased incidence for olfactory epithelial lesions in male rats was selected because it is the most sensitive POD for the critical effect (nasal lesions). Incidence data also support that the male rat is more sensitive to nasal toxicity associated with vinyl acetate exposure, compared to the female rat. The apparent (slight) decrease in the incidence of atrophy and basal cell hypertrophy in male rats at the highest exposure concentration is likely attributable to progression to lesions of increased severity (e.g., metaplasia) that are only observed at the highest exposure level.

Table A-11. Summary of Candidate Effects and POD Values Considered for Derivation of a Chronic-Duration Inhalation MRL for Vinyl Acetate

Species	Duration	Effect	Candidate POD (week µg/mL)	POD type	Reference
Sprague-Dawley rat (male)	104 weeks	Olfactory epithelial atrophy and basal cell hypertrophy	2,295[a]	NOAEL	Bogdanffy et al. 1994a; Hazleton 1988
Sprague-Dawley rat (female)	104 weeks	Olfactory epithelial atrophy	3,037	$BMCL_{10}$	Bogdanffy et al. 1994a; Hazleton 1988
Sprague-Dawley rat (female)	104 weeks	Olfactory epithelial basal cell hypertrophy	2,929	$BMCL_{10}$	Bogdanffy et al. 1994a; Hazleton 1988

[a]Selected POD for derivation of chronic-duration inhalation MRL.

BMC = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; $BMCL_{10}$ = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., 10 = dose associated with 10% extra risk); MRL = Minimal Risk Level; NOAEL = no-observed-adverse-effect level; POD = point of departure

Adjustment for Intermittent Exposure: Exposure over time is accounted for in the PBPK model (HEC simulations are for continuous exposure, see details below); therefore, no additional duration adjustment is needed.

Conversion to Human Equivalent Concentration: The PBPK model (Bogdanffy et al. 1999; Hinderliter et al. 2005) was used for rat-to-human dosimetry extrapolation in deriving the chronic-duration inhalation MRL for vinyl acetate as described in the acute-duration inhalation MRL section. The study-specific parameters utilized in the PBPK model to calculate a $NOAEL_{HEC}$ of 8.52 ppm for the selected POD are shown in Table A-12. As previously indicated, all model parameters were based on values reported by Bogdanffy et al. (1999) and Plowchalk et al. (1997), with the exception of body weights, which were based on TWA body weights calculated for the principal study.

Table A-12. HECs Corresponding to Rat POD Selected for Chronic-Duration Inhalation MRL for Vinyl Acetate

Study	Exposure (ppm)	Duration and frequency	POD basis	POD metric	POD (hour µg/mL)	HEC[a] (ppm)
Bogdanffy et al. (1994a)	0, 49.4, 200.5, 594.7	4 weeks 5 days/week 6 hours/day	NOAEL (49.4 ppm)	$AUC_{168\ hr}$	2,295	8.52

[a]Calculated for continuous human exposure.

AUC = area under the curve for acetic acid concentration in olfactory epithelium; HEC = human equivalent exposure concentration; MRL = Minimal Risk Level; NOAEL = no-observed adverse effect level; POD = dose-response point of departure

Uncertainty Factor: The $NOAEL_{HEC}$ was then by divided by a total uncertainty factor of 30:

- 3 for extrapolation from animals to humans with dosimetric adjustment
- 10 for human variability

$$MRL = \frac{NOAEL_{HEC}}{UFs} = \frac{8.52\ ppm}{30} = 0.3\ ppm$$

Other Additional Studies of Pertinent Information that Lend Support to this MRL: Limited evidence from humans has shown that the respiratory tract is a sensitive target of acute-duration vinyl acetate exposure, with irritation of throat mucous membranes from acute-duration exposure levels as low as 4 ppm and persistent irritation at 74 ppm (Deese and Joyner 1969; Union Carbide 1973). One cross-sectional study reported subjective respiratory complaints and mild reductions in pulmonary function at an average vinyl acetate concentration of 3.61 ppm (range of 0.02–11.71 ppm) in carpet manufacturers (Khoshakhlagh et al. 2023). However, another occupational study suggests that repeated occupational exposure to vinyl acetate is generally without adverse respiratory effect at levels <10 ppm (Deese and Joyner 1969).

In rodents, the acute-, intermediate- and chronic-duration databases confirm that the respiratory system, particularly the extrathoracic region, is the most sensitive target of toxicity following inhalation exposure to vinyl acetate. Nasal lesions are observed in rats following acute- or intermediate-duration exposure to ≥598.5 ppm (Bogdanffy et al. 1997; Krieger et al. 2020) and in rats and mice following chronic-duration exposure to ≥200.5 ppm (Bogdanffy et al. 1994a; Hazleton 1988). Lower respiratory tract lesions are also seen in rats and mice following intermediate-duration exposure to 998.9 ppm (Hazleton 1980b, 1980c) and mice following chronic-duration exposure to ≥200.5 ppm (Bogdanffy et al. 1994a; Hazleton 1988). In acute-duration inhalation lethality studies, deaths were attributed to lung damage in rats, mice, guinea pigs, and rabbits (Union Carbide 1973). Mechanistic data predict portal-of-entry effects (i.e., respiratory tract lesions) based on rapid hydrolysis of vinyl acetate into acetaldehyde and acetic acid following contact with mucosal surfaces, resulting in irritation due to tissue acidification (reviewed by Bogdanffy et al. 1999, 2001, 2004; Slikker et al. 2004).

Agency Contacts (Chemical Managers): Rae T. Benedict

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Vinyl acetate
CAS Numbers: 108-05-4
Date: January 2025
Profile Status: Final
Route: Oral
Duration: Acute

MRL Summary: There are insufficient data for derivation of an acute-duration oral MRL.

Rationale for Not Deriving an MRL: The acute oral database is limited to acute-duration lethality studies (Goeva 1966; Smyth and Carpenter 1948), a developmental exposure study that does not identify adverse effects at maternal doses up to 477 mg/kg/day (Hurtt et al. 1995), and a study reporting a lack of gastrointestinal lesions in rats and mice exposed to doses up to 1,400 mg/kg/day and 5,300 mg/kg/day, respectively, for 1–8 days (no other organ systems were evaluated) (Valentine et al. 2002).

Agency Contacts (Chemical Managers): Rae T. Benedict

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Vinyl acetate
CAS Numbers: 108-05-4
Date: January 2025
Profile Status: Final
Route: Oral
Duration: Intermediate

MRL Summary: There are insufficient data for derivation of an intermediate-duration oral MRL.

Rationale for Not Deriving an MRL: No intermediate-duration oral MRL was derived for vinyl acetate because effects potentially associated with intermediate-duration oral exposure to vinyl acetate are of questionable biological significance and/or human relevance:

1. Body weight effects noted in drinking water studies at ≥165 mg/kg/day in F1 rats and 697 mg/kg/day in F0 rats in a 2-generation study and at 1,040 mg/kg/day in mice exposed for 4 weeks were associated with decreased water consumption during some or all of the exposure period (attributed to palatability issues) (Hazleton 1979d; Mebus et al. 1995). Since decreased water consumption can result in body weight loss even in the absence of clinical dehydration (Vasilev et al. 2021), it is difficult to distinguish compound-related effects on body weight from direct effects of decreased water consumption.
2. The developmental serious LOAEL of 697 mg/kg/day based on decreased F1 weanling body weight in a 2-generation study in rats (Mebus et al. 1995) is thought to be secondary to a significant decrease in maternal water intake, attributed to unpalatability of drinking water (which could impair milk supply); F0 dams also showed significant decreases in body weight gain during lactation at 669 mg/kg/day. Therefore, these effects are of questionable biological significance and therefore, not an appropriate basis for the MRL.
3. All of the remaining available intermediate-duration oral NOAELs are "free-standing" and are thus not an appropriate basis for the calculation of an MRL (Hazleton 1979d, 1980e, 1980f; Valentine et al. 2002).

Agency Contacts (Chemical Managers): Rae T. Benedict

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Vinyl acetate
CAS Numbers: 108-05-4
Date: January 2025
Profile Status: Final
Route: Oral
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration oral MRL.

Rationale for Not Deriving an MRL: No chronic-duration oral MRL was derived for vinyl acetate. Only one reliable, comprehensive chronic-duration study was identified (Bogdanffy et al. 1994b). In this study, the only potentially adverse effect reported was decreased body weight at ≥202 mg/kg/day in rats. However, as observed in intermediate-duration drinking water studies, findings were associated with decreased water consumption (attributed to palatability issues). Since decreased water consumption can result in body weight loss even in the absence of clinical dehydration (Vasilev et al. 2021), it is difficult to distinguish compound-related effects on body weight from direct effects of decreased water consumption. Additionally, male rats also showed decreased food intake, further confounding body weight findings. The remaining reliable chronic-duration studies focused on neoplastic changes. Exposure-related effects in these studies were limited to serious LOAELs, including death and cancer (Belpoggi et al. 2002; Maltoni et al. 1997; Minardi et al. 2002).

A second comprehensive chronic-duration study reported pre-neoplastic and neoplastic lesions in the upper gastrointestinal tract of rats and mice (Umeda et al. 2004). However, this study is not listed in the LSE tables as there are quality issues with this study precluding accurate dose estimation. The drinking-water solution was only mixed twice weekly (instead of daily, as found in other drinking water studies for vinyl acetate). The study authors reported that the test solution stabilities at 4 days were 72–80% in the rat study and 86–96% in the mouse study. The lost concentration was attributed mainly to evaporation. Acetic acid concentration after 4 days was 9.2, 4.7, and 263 ppm at 400, 2,000, or 10,000 ppm, respectively. It is unclear if acetic acid in the drinking water and/or decreased pH contributed to the observed effects. Therefore, while discussed in the profile, this study was not considered as the basis for the MRL.

Agency Contacts (Chemical Managers): Rae T. Benedict

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR VINYL ACETATE

The objective of the toxicological profile is to evaluate the potential for human exposure and the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to vinyl acetate.

B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen were conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, chemical interactions, physical and chemical properties, production, use, environmental fate, environmental releases, and environmental and biological monitoring data for vinyl acetate. ATSDR primarily focused on peer-reviewed articles without language restrictions. Foreign language studies are reviewed based on available English-language abstracts and/or tables (or summaries in regulatory assessments, such as IARC documents). If the study appears critical for hazard identification or MRL derivation, translation into English is requested. Non-peer-reviewed studies that were considered relevant to the assessment of the health effects of vinyl acetate have undergone peer review by at least three ATSDR-selected experts who have been screened for conflict of interest. The inclusion criteria used to identify relevant studies examining the health effects of vinyl acetate are presented in Table B-1.

Table B-1. Inclusion Criteria for the Literature Search and Screen[a]

Health Effects
Species
Human
Laboratory mammals
Route of exposure
Inhalation
Oral
Dermal (or ocular)
Parenteral (these studies will be considered supporting data)
Health outcome
Death
Systemic effects
Body weight effects
Respiratory effects
Cardiovascular effects
Gastrointestinal effects
Hematological effects
Musculoskeletal effects
Hepatic effects
Renal effects
Dermal effects
Ocular effects
Endocrine effects
Immunological effects
Neurological effects
Reproductive effects

Table B-1. Inclusion Criteria for the Literature Search and Screen[a]

Developmental effects
Other noncancer effects
Cancer
Toxicokinetics
Absorption
Distribution
Metabolism
Excretion
PBPK models
Biomarkers
Biomarkers of exposure
Biomarkers of effect
Interactions with other chemicals
Potential for human exposure
Releases to the environment
Air
Water
Soil
Environmental fate
Transport and partitioning
Transformation and degradation
Environmental monitoring
Air
Water
Sediment and soil
Other media
Biomonitoring
General populations
Occupation populations

[a]Physical-chemical properties are not generally obtained from literature searches, but rather from curated governmental databases such as PubChem.

B.1.1 Literature Search

The literature search was conducted to update the Toxicological Profile for Vinyl Acetate released in 1992. All literature cited in the previous (1992) toxicological profile were considered for inclusion in the updated profile. The initial literature search, which was performed in April 2017 and October 2021, was restricted to studies added to databases since January 1990. An updated literature search was performed after the Toxicological Profile for Vinyl Acetate Draft for Public Comment was released in August 2023 to identify any additional studies added to databases between September 2021 and December 2023.

The following main databases were searched in April 2017, October 2021, and December 2023:

- PubMed
- National Technical Reports Library (NTRL)
- Scientific and Technical Information Network's TOXCENTER
- National Library of Medicine's TOXLINE (April 2017 only)

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, Medical Subject Headings (MeSH) headings, and keywords for vinyl acetate. The query strings used for the literature search are presented in Table B-2.

The search was augmented by searching the Toxic Substances Control Act Test Submissions (TSCATS), NTP website, and National Institute of Health Research Portfolio Online Reporting Tools Expenditures and Results (NIH RePORTER) databases using the queries presented in Table B-3. Additional databases were searched in the creation of various tables and figures, such as the TRI Explorer, the Substance Priority List (SPL) resource page, and other items as needed. Regulations applicable to vinyl acetate were identified by searching international and U.S. agency websites and documents.

Review articles were identified and used for the purpose of providing background information and identifying additional references. ATSDR also identified reports from the grey literature, which included unpublished research reports, technical reports from government agencies, conference proceedings and abstracts, and theses and dissertations.

Table B-2. Database Query Strings

Database search date	Query string
PubMed	
12/2023	((108-05-4[rn] OR "vinyl acetate"[supplementary concept]) AND (2021/09/01:3000[mhda])) OR ((("1-Acetoxyethylene"[tw] OR "Acetate de vinyle"[tw] OR "Acetic acid vinyl ester"[tw] OR "Acetic acid, ethenyl ester"[tw] OR "Acetic acid, ethylene ether"[tw] OR "Acetoxyethene"[tw] OR "Ethanoic acid, ethenyl ester"[tw] OR "Ethenyl acetate"[tw] OR "Ethenyl ethanoate"[tw] OR "Octan winylu"[tw] OR "Vinile (acetato di)"[tw] OR "Vinyl A monomer"[tw] OR "Vinyl acetate"[tw] OR "Vinyl acetate H.Q."[tw] OR "Vinyl acetate monomer"[tw] OR "Vinyl ethanoate"[tw] OR "Vinylacetaat"[tw] OR "Vinylacetat"[tw] OR "Vinylacetate"[tw] OR "Vinyle (acetate de)"[tw] OR "Vinylester kyseliny octove"[tw] OR "Zeset T"[tw]) AND (2021/09/01:3000[edat] OR 2021/09/01:3000[crdat])) NOT medline[sb])
10/2021	((108-05-4[rn] OR L9MK238N77[rn] OR "vinyl acetate"[supplementary concept] OR "vinyl acetate"[nm]) AND (1990/01/01 : 3000[dp] OR 1990/01/01 : 3000[mhda])) OR ((("1-Acetoxyethylene"[tw] OR "Acetate de vinyle"[tw] OR "Acetic acid vinyl ester"[tw] OR "Acetic acid, ethenyl ester"[tw] OR "Acetic acid, ethylene ether"[tw] OR "Acetoxyethene"[tw] OR "Ethanoic acid, ethenyl ester"[tw] OR "Ethenyl acetate"[tw] OR "Ethenyl ethanoate"[tw] OR "Octan winylu"[tw] OR "Vinile (acetato di)"[tw] OR "Vinyl A monomer"[tw] OR "Vinyl acetate"[tw] OR "Vinyl acetate H.Q."[tw] OR "Vinyl acetate monomer"[tw] OR "Vinyl ethanoate"[tw] OR "Vinylacetaat"[tw] OR "Vinylacetat"[tw] OR "Vinylacetate"[tw] OR "Vinyle (acetate de)"[tw] OR "Vinylester kyseliny octove"[tw] OR "Zeset T"[tw]) AND (1990/01/01 : 3000[dp] OR 1990/01/01 : 3000[crdat] OR 1990/01/01 : 3000[edat])) NOT medline[sb])

Table B-2. Database Query Strings

Database search date	Query string
NTRL	
12/2023	Limited to date published 2020 to 2023 Searched in title or keyword "1-Acetoxyethylene" OR "Acetate de vinyle" OR "Acetic acid vinyl ester" OR "Acetic acid, ethenyl ester" OR "Acetic acid, ethylene ether" OR "Acetoxyethene" OR "Ethanoic acid, ethenyl ester" OR "Ethenyl acetate" OR "Ethenyl ethanoate" OR "Octan winylu" OR "Vinile (acetato di)" OR "Vinyl A monomer" OR "Vinyl acetate" OR "Vinyl acetate H.Q." OR "Vinyl acetate monomer" OR "Vinyl ethanoate" OR "Vinylacetaat" OR "Vinylacetat" OR "Vinylacetate" OR "Vinyle (acetate de)" OR "Vinylester kyseliny octove" OR "Zeset T"
10/2021	"1-Acetoxyethylene" OR "Acetate de vinyle" OR "Acetic acid vinyl ester" OR "Acetic acid, ethenyl ester" OR "Acetic acid, ethylene ether" OR "Acetoxyethene" OR "Ethanoic acid, ethenyl ester" OR "Ethenyl acetate" OR "Ethenyl ethanoate" OR "Octan winylu" OR "Vinile (acetato di)" OR "Vinyl A monomer" OR "Vinyl acetate" OR "Vinyl acetate H.Q." OR "Vinyl acetate monomer" OR "Vinyl ethanoate" OR "Vinylacetaat" OR "Vinylacetat" OR "Vinylacetate" OR "Vinyle (acetate de)" OR "Vinylester kyseliny octove" OR "Zeset T"
Toxcenter	
12/2023	FILE 'TOXCENTER' ENTERED AT 16:48:25 ON 11 DEC 2023 CHARGED TO COST=ET027.02.08.LB.01 L1 4404 SEA FILE=TOXCENTER 108-05-4 L2 1957 SEA FILE=TOXCENTER L1 NOT PATENT/DT L3 205 SEA FILE=TOXCENTER L2 AND ED>=20210901 L38 200 DUP REM L3 (5 DUPLICATES REMOVED)
10/2021	FILE 'TOXCENTER' ENTERED AT 11:35:18 ON 01 OCT 2021 CHARGED TO COST=EH038.10.01.04 L1 3988 SEA 108-05-4 L2 3903 SEA L1 NOT TSCATS/FS L3 1652 SEA L2 NOT PATENT/DT L4 284 SEA L3 AND ED>=20170401 ACT TOXQUERY/Q --------- L5 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L6 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L7 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L8 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L9 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L10 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) L11 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?) L12 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) L13 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?) L14 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?)

Table B-2. Database Query Strings

Database search date	Query string
	L15 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?)
	L16 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?)
	L17 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?)
	L18 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
	L19 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
	L20 QUE (ENDOCRIN? AND DISRUPT?)
	L21 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L22 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L23 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L24 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?)
	L25 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L26 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L27 QUE (NEPHROTOX? OR HEPATOTOX?)
	L28 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L29 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L30 QUE L5 OR L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29
	L31 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?)
	L32 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)
	L33 QUE L30 OR L31 OR L32
	L34 QUE (NONHUMAN MAMMALS)/ORGN
	L35 QUE L33 OR L34
	L36 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?)
	L37 QUE L35 OR L36

	L38 128 SEA L4 AND L37
	L39 11 SEA L38 AND MEDLINE/FS
	L40 2 SEA L38 AND BIOSIS/FS
	L41 115 SEA L38 AND CAPLUS/FS
	L42 0 SEA L38 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS)

Table B-2. Database Query Strings

Database search date	Query string
	L43 127 DUP REM L39 L40 L41 (1 DUPLICATE REMOVED) L*** DEL 11 S L38 AND MEDLINE/FS L*** DEL 11 S L38 AND MEDLINE/FS L44 11 SEA L43 L*** DEL 2 S L38 AND BIOSIS/FS L*** DEL 2 S L38 AND BIOSIS/FS L45 2 SEA L43 L*** DEL 115 S L38 AND CAPLUS/FS L*** DEL 115 S L38 AND CAPLUS/FS L46 114 SEA L43 L47 116 SEA (L44 OR L45 OR L46) NOT MEDLINE/FS SAVE TEMP L47 VINYLACETATE/A D SCAN L47 FILE HOME FILE TOXCENTER
04/2017	(FILE 'HOME' ENTERED AT 12:26:28 ON 07 APR 2017) FILE 'TOXCENTER' ENTERED AT 12:26:47 ON 07 APR 2017 CHARGED TO COST=EH011.13.01.01 L1 2765 SEA 108-05-4 L2 2680 SEA L1 NOT TSCATS/FS L3 1221 SEA L2 NOT PATENT/DT L4 2125 SEA L1 AND PY>=1990 L5 795 SEA L3 AND PY>=1990 ACTIVATE TOXQUERY/Q --------- L6 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L7 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L8 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L9 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L10 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L11 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) L12 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?) L13 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) L14 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?) L15 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?) L16 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?) L17 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?) L18 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?)

Table B-2. Database Query Strings

Database search date	Query string
	L19 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
	L20 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
	L21 QUE (ENDOCRIN? AND DISRUPT?)
	L22 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L23 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L24 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L25 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?)
	L26 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L27 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L28 QUE (NEPHROTOX? OR HEPATOTOX?)
	L29 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L30 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L31 QUE L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29 OR L30
	L32 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?)
	L33 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)
	L34 QUE L31 OR L32 OR L33
	L35 QUE (NONHUMAN MAMMALS)/ORGN
	L36 QUE L34 OR L35
	L37 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?)
	L38 QUE L36 OR L37

	L39 382 SEA L5 AND L38
	L40 43 SEA L39 AND MEDLINE/FS
	L41 48 SEA L39 AND BIOSIS/FS
	L42 274 SEA L39 AND CAPLUS/FS
	L43 17 SEA L39 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS)
	L44 323 DUP REM L40 L41 L43 L42 (59 DUPLICATES REMOVED)
	L*** DEL 43 S L39 AND MEDLINE/FS
	L*** DEL 43 S L39 AND MEDLINE/FS
	L45 43 SEA L44
	L*** DEL 48 S L39 AND BIOSIS/FS
	L*** DEL 48 S L39 AND BIOSIS/FS

Table B-2. Database Query Strings

Database search date	Query string
	L46 30 SEA L44 L*** DEL 274 S L39 AND CAPLUS/FS L*** DEL 274 S L39 AND CAPLUS/FS L47 235 SEA L44 L*** DEL 17 S L39 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) L*** DEL 17 S L39 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) L48 15 SEA L44 L49 280 SEA (L45 OR L46 OR L47 OR L48) NOT MEDLINE/FS
Toxline	
04/2017	("1-acetoxyethylene" OR "acetate de vinyle" OR "acetic acid vinyl ester" OR "acetic acid ethenyl ester" OR "acetic acid ethylene ether" OR "acetoxyethene" OR "ethanoic acid ethenyl ester" OR "ethenyl acetate" OR "ethenyl ethanoate" OR "octan winylu" OR "vinile (acetato di) " OR "vinyl a monomer" OR "vinyl acetate" OR "vinyl acetate h q " OR "vinyl acetate monomer" OR "vinyl ethanoate" OR "vinylacetaat" OR "vinylacetat" OR "vinylacetate" OR "vinyle (acetate de) " OR "vinylester kyseliny octove" OR "zeset t" OR 108-05-4 [rn]) AND 1990:2017 [yr] AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org]

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via ChemView	
12/2023; 10/2021	Compounds searched: 108-05-4
NTP	
12/2023	Limited 2020-present 108-05-4 "Vinyl acetate" "Vinylacetate" "Acetic acid, ethenyl ester" "1-Acetoxyethylene" "Acetic acid vinyl ester" "Acetic acid, ethylene ether" "Acetoxyethene" "Ethanoic acid, ethenyl ester" "Ethenyl acetate" "Vinyl A monomer" "Vinyl ethanoate"
10/2021	"108-05-4" "Vinyl acetate" "Vinylacetate" "Acetic acid, ethenyl ester" "1-Acetoxyethylene" "Acetic acid vinyl ester" "Acetic acid, ethylene ether" "Acetoxyethene" "Ethanoic acid, ethenyl ester" "Ethenyl acetate" "Vinyl A monomer" "Vinyl ethanoate"
Regulations.gov	
12/2023	"108-05-4" "Vinyl acetate" "Vinylacetate" No date limit; Docket and EPA notices

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
NIH RePORTER	
09/11/2024	Fiscal Year: Active Projects Text Search: "1-Acetoxyethylene" OR "Acetate de vinyle" OR "Acetic acid vinyl ester" OR "Acetic acid, ethenyl ester" OR "Acetic acid, ethylene ether" OR "Acetoxyethene" OR "Ethanoic acid, ethenyl ester" OR "Ethenyl acetate" OR "Ethenyl ethanoate" OR "Octan winylu" OR "Vinile (acetato di)" OR "Vinyl A monomer" OR "Vinyl acetate" OR "Vinyl acetate H.Q." OR "Vinyl acetate monomer" OR "Vinyl ethanoate" OR "Vinylacetaat" OR "Vinylacetat" OR "Vinylacetate" OR "Vinyle (acetate de)" OR "Vinylester kyseliny octove" OR "Zeset T" (advanced) Limit to: Project Title, Project Terms, Project Abstracts
06/2022	Text Search: "1-Acetoxyethylene" OR "Acetate de vinyle" OR "Acetic acid vinyl ester" OR "Acetic acid, ethenyl ester" OR "Acetic acid, ethylene ether" OR "Acetoxyethene" OR "Ethanoic acid, ethenyl ester" OR "Ethenyl acetate" OR "Ethenyl ethanoate" OR "Octan winylu" OR "Vinile (acetato di)" OR "Vinyl A monomer" OR "Vinyl acetate" OR "Vinyl acetate H.Q." OR "Vinyl acetate monomer" OR "Vinyl ethanoate" OR "Vinylacetaat" OR "Vinylacetat" OR "Vinylacetate" OR "Vinyle (acetate de)" OR "Vinylester kyseliny octove" OR "Zeset T" (advanced) Limit to: Project Title, Project Terms, Project Abstracts
Other	Includes additional reference identified throughout the assessment process, which may include studies found by tree searching; recommended by intraagency, interagency, peer, or public reviewers; or published more recently than the date of literature search(es). Additional references include those for specific regulations or guidelines and publications found by targeted searches for specific information (e.g., searches for reviews of general [not chemical-specific] mechanisms of toxicity).

The 2021 pre-public comment search results were:

- Number of records identified from PubMed, NTRL, TOXCENTER, and Toxline (after duplicate removal): 1,491
- Number of records identified from other strategies: 76
- Total number of records to undergo literature screening: 1,567

The 2023 post-public comment search results were:

- Number of records identified from PubMed, NTRL, and TOXCENTER (after duplicate removal): 456
- Number of records identified from other strategies: 36
- Total number of records to undergo literature screening: 492

B.1.2 Literature Screening

A two-step process was used to screen the literature search to identify relevant studies on vinyl acetate during the pre- and post-public comment drafts:

- Title and abstract screen
- Full text screen

Pre-Public Comment Title and Abstract Screen. Within the reference library, titles and abstracts were screened manually for relevance. Studies that were considered (see Table B-1 for inclusion criteria) were

moved to the second step of the literature screening process. Studies were excluded when the title and abstract clearly indicated that the study was not relevant to the toxicological profile.

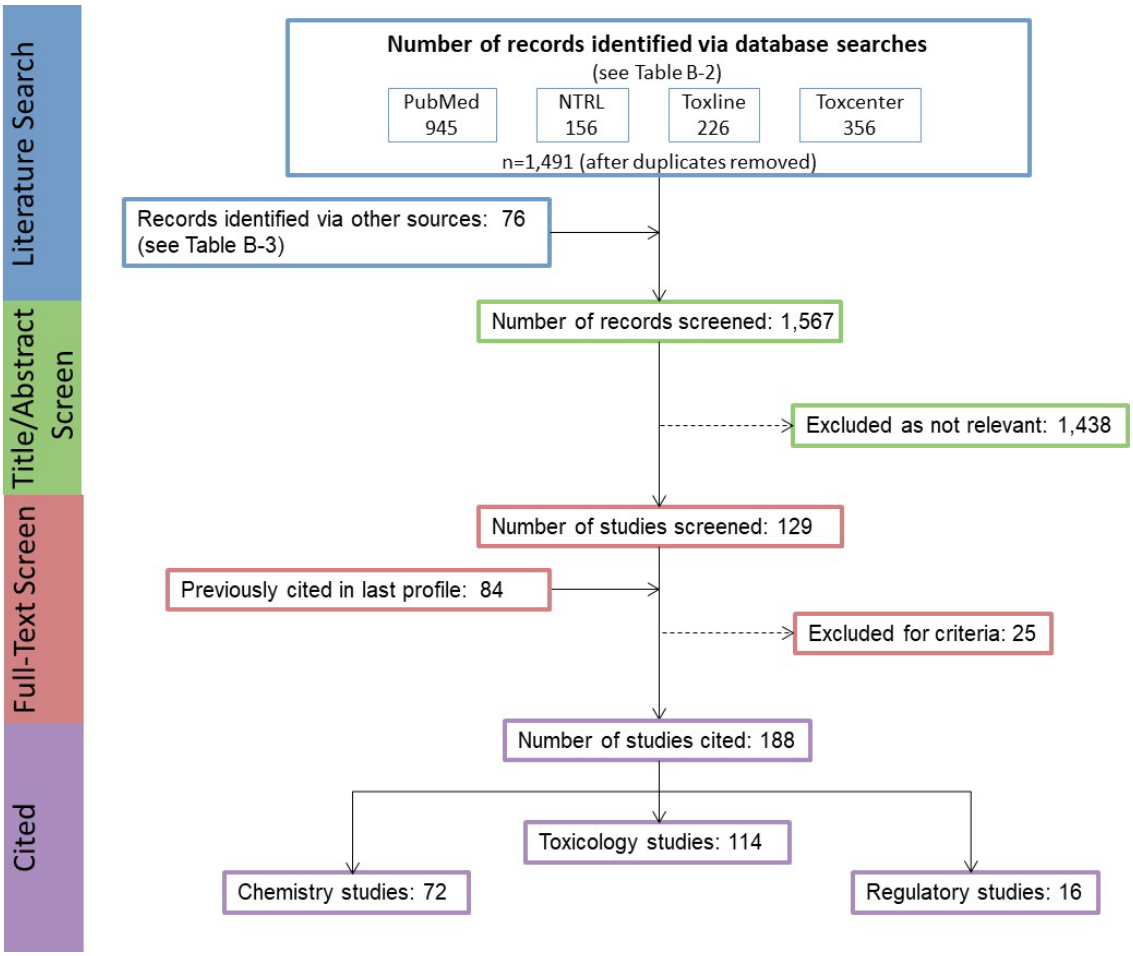
- Number of titles and abstracts screened: 1,567
- Number of studies considered relevant and moved to the next step: 129

Pre-Public Comment Full Text Screen. The second step in the literature screening process was a full text review of individual studies considered relevant in the title and abstract screen step. Each study was reviewed to determine whether it was relevant for inclusion in the toxicological profile.

- Number of studies undergoing full text review: 129
- Number of studies cited in the previous toxicological profile: 84
- Total number of studies cited in the profile: 188

A summary of the results of the pre-public literature search and screening is presented in Figure B-1.

Figure B-1. October 2021 Literature Search Results and Screen for Vinyl Acetate



*The chemistry studies category includes studies pertaining to the potential for human exposure (Table B-1). The toxicology studies category includes human and animal studies of health effects as well as studies of toxicokinetics, biomarkers, and interactions with other chemicals (Table B-1). The regulatory studies category includes those studies cited in Chapter 7.

Post-Public Comment Title and Abstract Screen. Within the reference library, titles and abstracts were screened manually for relevance. Studies that were considered relevant (see Table B-1 for inclusion criteria) were moved to the second step of the literature screening process. Studies were excluded when the title and abstract clearly indicated that the study was not relevant to the toxicological profile.

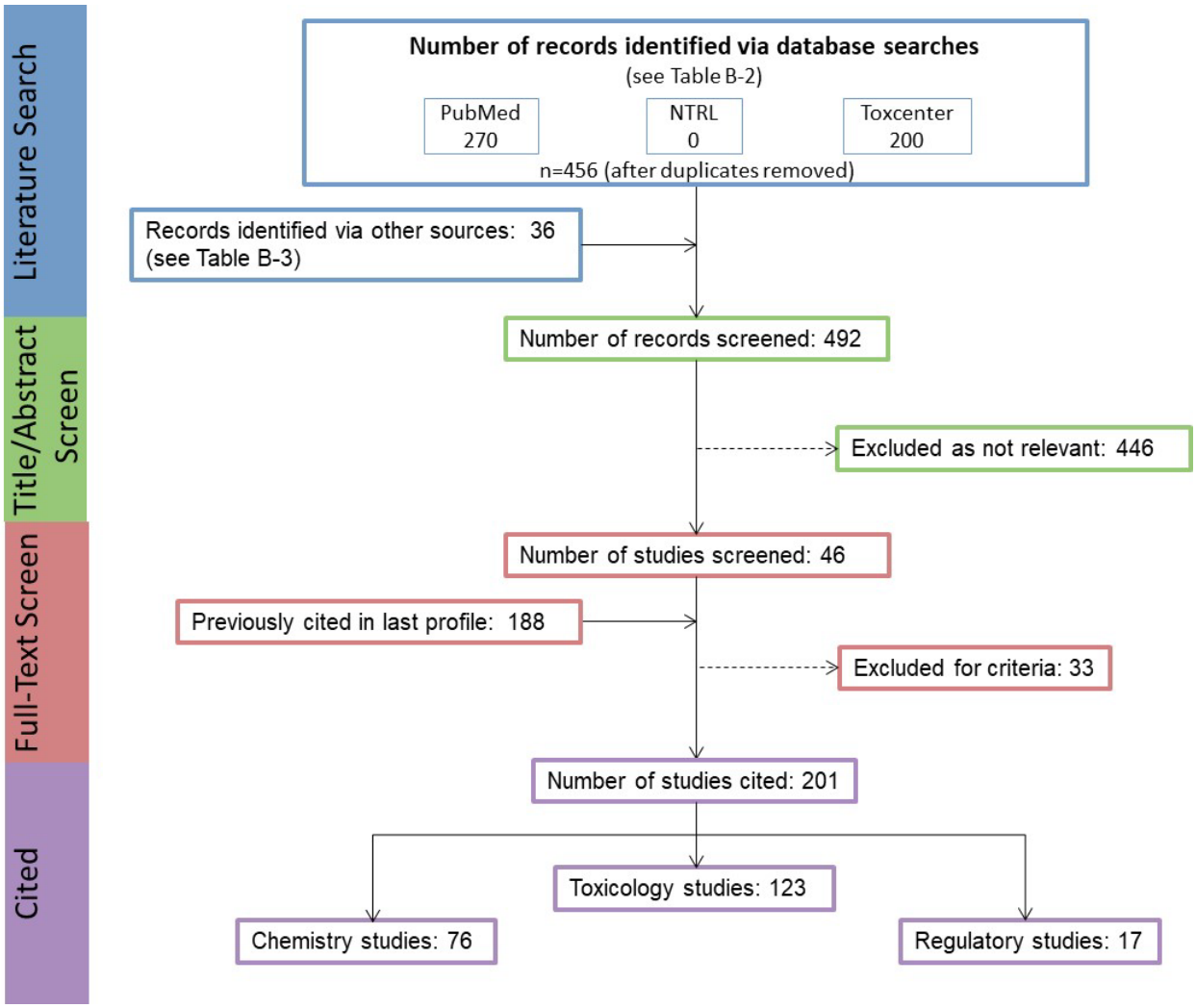
- Number of titles and abstracts screened: 492
- Number of studies considered relevant and moved to the next step: 46

Post-Public Comment Full Text Screen. The second step in the literature screening process was a full text review of individual studies considered relevant in the title and abstract screen step. Each study was reviewed to determine whether it was relevant for inclusion in the toxicological profile.

- Number of studies undergoing full text review: 46
- Number of studies cited in the pre-public draft of the toxicological profile: 188
- Total number of studies cited in the profile: 201

A summary of the results of the post-public comment literature search and screening is presented in Figure B-2.

Figure B-2. December 2023 Post-Public Comment Literature Search Results and Screen for Vinyl Acetate*



*The chemistry studies category includes studies pertaining to the potential for human exposure (Table B-1). The toxicology studies category includes human and animal studies of health effects as well as studies of toxicokinetics, biomarkers, and interactions with other chemicals (Table B-1). The regulatory studies category includes those studies cited in Chapter 7.

APPENDIX C. FRAMEWORK FOR ATSDR'S SYSTEMATIC REVIEW OF HEALTH EFFECTS DATA FOR VINYL ACETATE

To increase the transparency of ATSDR's process of identifying, evaluating, synthesizing, and interpreting the scientific evidence on the health effects associated with exposure to vinyl acetate, ATSDR utilized a slight modification of NTP's Office of Health Assessment and Translation (OHAT) systematic review methodology (NTP 2013, 2015; Rooney et al. 2014). ATSDR's framework is an eight-step process for systematic review with the goal of identifying the potential health hazards of exposure to vinyl acetate:

- Step 1. Problem Formulation
- Step 2. Literature Search and Screen for Health Effects Studies
- Step 3. Extract Data from Health Effects Studies
- Step 4. Identify Potential Health Effect Outcomes of Concern
- Step 5. Assess the Risk of Bias for Individual Studies
- Step 6. Rate the Confidence in the Body of Evidence for Each Relevant Outcome
- Step 7. Translate Confidence Rating into Level of Evidence of Health Effects
- Step 8. Integrate Evidence to Develop Hazard Identification Conclusions

C.1 PROBLEM FORMULATION

The objective of the toxicological profile and this systematic review was to identify the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to vinyl acetate. The inclusion criteria used to identify relevant studies examining the health effects of vinyl acetate are presented in Table C-1.

Data from human and laboratory animal studies were considered relevant for addressing this objective. Human studies were divided into two broad categories: observational epidemiology studies and controlled exposure studies. The observational epidemiology studies were further divided: cohort studies (retrospective and prospective studies), population studies (with individual data or aggregate data), and case-control studies.

Table C-1. Inclusion Criteria for Identifying Health Effects Studies

Species
Human
Laboratory mammals
Route of exposure
Inhalation
Oral
Dermal (or ocular)
Parenteral (these studies will be considered supporting data)
Health outcome
Death
Systemic effects
Body weight effects
Respiratory effects
Cardiovascular effects

Table C-1. Inclusion Criteria for Identifying Health Effects Studies

Gastrointestinal effects
Hematological effects
Musculoskeletal effects
Hepatic effects
Renal effects
Dermal effects
Ocular effects
Endocrine effects
Immunological effects
Neurological effects
Reproductive effects
Developmental effects
Other noncancer effects
Cancer

C.2 LITERATURE SEARCH AND SCREEN FOR HEALTH EFFECTS STUDIES

A literature search and screen were conducted to identify studies examining the health effects of vinyl acetate. The literature search framework for the toxicological profile is discussed in detail in Appendix B.

C.2.1 Literature Search

As noted in Appendix B, the literature searches were intended to update the Toxicological Profile for Vinyl Acetate. See Appendix B for the databases searched and the search strategy.

A total of 1,567 and 492 records relevant to all sections of the toxicological profile were identified in the initial and update literature search, respectively.

C.2.2 Literature Screening

As described in Appendix B, a two-step process was used to screen the literature search to identify relevant studies examining the health effects of vinyl acetate.

Title and Abstract Screen. In the Title and Abstract Screen step, 35 documents (inclusive of both literature searches) were considered to meet the health effects inclusion criteria in Table C-1 and were moved to the next step in the process.

Full Text Screen. In the second step in the literature screening process for the systematic review, a full text review of 35 health effect documents (documents identified in the update literature search and documents cited in older versions of the profile) was performed. From those 35 documents (61 studies), 16 documents (26 studies) were included in the qualitative review.

C.3 EXTRACT DATA FROM HEALTH EFFECTS STUDIES

Relevant data extracted from the individual studies selected for inclusion in the systematic review were collected in customized data forms. A summary of the type of data extracted from each study is presented in Table C-2. For references that included more than one experiment or species, data extraction records were created for each experiment or species.

Table C-2. Data Extracted from Individual Studies

Citation
Chemical form
Route of exposure (e.g., inhalation, oral, dermal)
Specific route (e.g., gavage in oil, drinking water)
Species
Strain
Exposure duration category (e.g., acute, intermediate, chronic)
Exposure duration
Frequency of exposure (e.g., 6 hours/day, 5 days/week)
Exposure length
Number of animals or subjects per sex per group
Dose/exposure levels
Parameters monitored
Description of the study design and method
Summary of calculations used to estimate doses (if applicable)
Summary of the study results
Reviewer's comments on the study
Outcome summary (one entry for each examined outcome)
No-observed-adverse-effect level (NOAEL) value
Lowest-observed-adverse-effect level (LOAEL) value
Effect observed at the LOAEL value

A summary of the extracted data for each study is presented in the Supplemental Document for vinyl acetate and overviews of the results of the inhalation, oral, and dermal exposure studies are presented in presented in Sections 2.2–2.19 of the profile and in the Levels Significant Exposures tables in Section 2.1 of the profile (Tables 2-2, 2-3, and 2-4, respectively).

C.4 IDENTIFY POTENTIAL HEALTH EFFECT OUTCOMES OF CONCERN

Overviews of the potential health effect outcomes for vinyl acetate identified in human and animal studies are presented in Tables C-3 and C-4, respectively. Human data include a limited number of human controlled inhalation exposure and occupational studies with potential for exposure via multiple routes. These limited human studies indicate that the respiratory system may be susceptible to vinyl acetate toxicity. Animal studies examined a comprehensive set of endpoints following inhalation or oral exposure, but dermal studies were limited to acute lethality, skin and eye irritation, and skin sensitization. Respiratory effects were considered sensitive outcomes following inhalation exposure and developmental effects were considered sensitive outcomes following inhalation and oral exposure (i.e., effects were observed at low concentrations or doses). Decreased body weight effects were also noted in some

drinking water studies; however, assessment of compound-related effects on body weight is difficult due to concomitant decreases in water and/or food intake. No additional nonneoplastic effects were noted at concentrations or doses below high levels associated with increased mortality. Studies examining identified sensitive outcomes (respiratory effects following inhalation exposure; developmental effects following inhalation or oral exposure) were carried through to Steps 4–8 of the systematic review. There were 26 studies (published in 16 documents) examining these potential outcomes carried through to Steps 4–8 of the systematic review.

APPENDIX C

Table C-3. Overview of the Health Outcomes for Vinyl Acetate Evaluated in Human Studies

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological	Neurological	Reproductive	Developmental	Other Noncancer	Caner
Inhalation studies																	
Cohort		2 2	1 0		1 0		1 0	1 0					1 0				
Case control		1 1															1 0
Cross-sectional		1 1															
Case series																	
Oral studies																	
Cohort																	
Case control																	
Cross-sectional																	
Case series																	
Dermal studies																	
Cohort									3 1	2 1		2 0					
Case control										1 1							
Cross-sectional																	
Case series									1 0								

Number of studies examining endpoint	0	1	2	3	4	5–9	≥10
Number of studies reporting outcome	0	1	2	3	4	5–9	≥10

Table C-4. Overview of the Health Outcomes for Vinyl Acetate Evaluated in Experimental Animal Studies

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological[a]	Neurological[a]	Reproductive[a]	Developmental	Other Noncancer	Caner
Inhalation studies																	
Acute-duration	4	8											4	1	1		
	2	8											4	0	1		
Intermediate-duration	7	8	4	4	5		5	5		1	1	5	5	2			
	4	8	0	0	0		0	0		0	0	0	1	0			
Chronic-duration	2	2	2	2	2	2	2	2	2	2	2	2	2	2			2
	2	2	0	0	0	0	0	0	0	0	0	0	0	0			1
Oral studies																	
Acute-duration	5			4										1	1		
	0			0										0	0		
Intermediate-duration	9	5	4	8	4		4	4		1	1	4	4	3	1	1	
	3	0	0	0	0		0	0		0	0	0	0	0	1	1	
Chronic-duration	4	4	4	6	1	1	4	4	1	1	4	4	4	4			7
	1	0	0	0	0	0	0	0	0	0	0	0	0	0			6
Dermal studies																	
Acute-duration	1								2			1					
	0								2			1					
Intermediate-duration										1							
										1							
Chronic-duration																	

Number of studies examining endpoint	0	1	2	3	4	5–9	≥10	
Number of studies reporting outcome	0	1	2	3	4	5–9	≥10	

[a]Number of studies examining endpoint includes studies evaluating histopathology, but not evaluating function.

C.5 ASSESS THE RISK OF BIAS FOR INDIVIDUAL STUDIES

C.5.1 Risk of Bias Assessment

The risk of bias of individual studies was assessed using OHAT's Risk of Bias Tool (NTP 2015). The risk of bias questions for observational epidemiology studies, human-controlled exposure studies, and animal experimental studies are presented in Tables C-5, C-6, and C-7, respectively. Each risk of bias question was answered on a four-point scale:

- **Definitely low risk of bias (++)**
- **Probably low risk of bias (+)**
- **Probably high risk of bias (-)**
- **Definitely high risk of bias (– –)**

In general, "definitely low risk of bias" or "definitely high risk of bias" were used if the question could be answered with information explicitly stated in the study report. If the response to the question could be inferred, then "probably low risk of bias" or "probably high risk of bias" responses were typically used.

Table C-5. Risk of Bias Questionnaire for Observational Epidemiology Studies

Selection bias
Were the comparison groups appropriate?
Confounding bias
Did the study design or analysis account for important confounding and modifying variables?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

Table C-6. Risk of Bias Questionnaire for Human-Controlled Exposure Studies

Selection bias
Was administered dose or exposure level adequately randomized?
Was the allocation to study groups adequately concealed?
Performance bias
Were the research personnel and human subjects blinded to the study group during the study?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

Table C-7. Risk of Bias Questionnaire for Experimental Animal Studies

Selection bias
Was administered dose or exposure level adequately randomized?
Was the allocation to study groups adequately concealed?
Performance bias
Were experimental conditions identical across study groups?
Were the research personnel blinded to the study group during the study?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

After the risk of bias questionnaires were completed for the health effects studies, the studies were assigned to one of three risk of bias tiers based on the responses to the key questions listed below and the responses to the remaining questions.

- Is there confidence in the exposure characterization? (only relevant for observational studies)
- Is there confidence in the outcome assessment?
- Does the study design or analysis account for important confounding and modifying variables? (only relevant for observational studies)

First Tier. Studies placed in the first tier received ratings of "definitely low" or "probably low" risk of bias on the key questions **AND** received a rating of "definitely low" or "probably low" risk of bias on the responses to at least 50% of the other applicable questions.

Second Tier. A study was placed in the second tier if it did not meet the criteria for the first or third tiers.

Third Tier. Studies placed in the third tier received ratings of "definitely high" or "probably high" risk of bias for the key questions **AND** received a rating of "definitely high" or "probably high" risk of bias on the response to at least 50% of the other applicable questions.

The results of the risk of bias assessment for human controlled exposure studies, human observational studies, and animal experimental studies are presented in Tables C-8, C-9, and C-10, respectively.

Table C-8. Summary of Risk of Bias Assessment for Vinyl Acetate —Human Controlled Exposure Studies

Reference	Risk of bias criteria and ratings: Selection bias — Was administered dose or exposure level adequately randomized	Performance Bias — Does the study design or analysis account for important confounding and modifying variables?	Attrition / exclusion bias — Were outcome data complete without attrition or exclusion from analysis?	Detection bias — Is there confidence in the exposure characterization?	Detection bias — **Is there confidence in the outcome assessment?***	Selective reporting bias — Are all measured outcomes reported?	Risk of bias tier
Outcome: Respiratory Effects (inhalation only)							
Inhalation acute exposure							
Hinderliter et al. 2005	– –	–	++	++	–	++	Second
Union Carbide 1973	– –	–	++	++	–	++	Second
Outcome: Developmental Effects							
None identified							

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; na = not applicable

*Key question used to assign risk of bias tier

Table C-9. Summary of Risk of Bias Assessment for Vinyl Acetate —Human Observational Studies

Reference	Risk of bias criteria and ratings: Selection bias — Were the comparison groups appropriate?	Selection bias — **Does the study design or analysis account for important confounding and modifying variables?***	Attrition / exclusion bias — Were outcome data complete without attrition or exclusion from analysis?	Detection bias — **Is there confidence in exposure characterization?***	Detection bias — **Is there confidence in the outcome assessment?***	Selective reporting bias — Were all measured outcomes reported?	Risk of bias tier
Outcome: Respiratory Effects (inhalation only)							
Inhalation acute exposure							
Deese and Joyner 1969	– –	–	++	++	–	++	Second
Inhalation chronic exposure							
Deese and Joyner 1969	++	–	++	++	+	++	Second
Khoshakhlagh et al. 2023	++	–	++	++	–	++	Second
Outcome: Developmental Effects							
None identified							

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; na = not applicable

*Key question used to assign risk of bias tier

Table C-10. Summary of Risk of Bias Assessment for Vinyl Acetate —Experimental Animal Studies

Reference	Risk of bias criteria and ratings									
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	**Is there confidence in the outcome assessment?***	Were all measured outcomes reported?	Did the study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Outcome: Respiratory Effects (inhalation only)										
Inhalation acute exposure										
Bogdanffy et al. 1997 (1 day, rat)	++	+	++	+	++	++	**++**	++	NA	First
Bogdanffy et al. 1997 (5 days, rat)	++	+	++	+	++	++	**++**	++	NA	First
Krieger et al. 2020 (1 day, rat)	++	+	++	+	++	++	**++**	++	NA	First
Krieger et al. 2020 (5 days, rat)	++	+	++	+	++	++	**++**	++	NA	First
Union Carbide 1973 (rat)	–	+	+	+	–	–	**–**	–	NA	Third
Union Carbide 1973 (mouse)	–	+	+	+	–	–	**–**	–	NA	Third
Union Carbide 1973 (rabbit)	–	+	+	+	–	–	**–**	–	NA	Third
Union Carbide 1973 (guinea pig)	–	+	+	+	–	–	**–**	–	NA	Third
Inhalation intermediate exposure										
Bogdanffy et al. 1997 (4 weeks, rat)	++	+	++	+	++	++	**++**	++	NA	First
Gage 1970 (15 days, rat)	–	–	–	+	+	–	**–**	+	NA	Third
Hazleton 1979c (4 weeks, rat)	++	+	+	+	++	++	**–**	++	NA	Second
Hazleton 1979b (4 weeks, mouse)	++	+	+	+	++	++	**–**	++	NA	Second
Hazleton 1980c (3 months, rat)	++	+	++	+	++	++	**++**	++	NA	First
Hazleton 1980b (3 months, mouse)	++	+	++	+	++	++	**++**	++	NA	First

Table C-10. Summary of Risk of Bias Assessment for Vinyl Acetate —Experimental Animal Studies

Reference	Risk of bias criteria and ratings									
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	**Is there confidence in the outcome assessment?***	Were all measured outcomes reported?	Did the study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Krieger et al. 2020 (20 days, rat)	++	+	++	+	++	++	++	++	NA	First
Krieger et al. 2020 (65 days, rat)	++	+	++	+	++	++	++	++	NA	First
Inhalation chronic exposure										
Bogdanffy et al. 1994a; Hazleton 1988 (rat)	++	+	++	+	++	++	++	++	NA	First
Bogdanffy et al. 1994a; Hazleton 1988 (mouse)	++	+	++	+	++	++	++	++	NA	First
Outcome: Developmental Effects										
Inhalation acute exposure										
Hurtt et al. 1995; Hazleton 1980d	++	+	++	+	++	++	+	++	NA	First
Oral acute exposure										
Hurtt et al. 1995	++	+	++	+	++	++	++	++	NA	First

Table C-10. Summary of Risk of Bias Assessment for Vinyl Acetate —Experimental Animal Studies

Reference	Risk of bias criteria and ratings										Risk of bias tier
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other bias		
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	**Is there confidence in the outcome assessment?***	Were all measured outcomes reported?	Did the study design or analysis account for important confounding and modifying variables?		
Oral intermediate exposure											
Mebus et al. 1995	++	+	+	+	++	++	–	++	NA		Second

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; na = not applicable

*Key question used to assign risk of bias tier

C.6 RATE THE CONFIDENCE IN THE BODY OF EVIDENCE FOR EACH RELEVANT OUTCOME

Confidences in the bodies of human and animal evidence were evaluated independently for each potential outcome. ATSDR did not evaluate the confidence in the body of evidence for carcinogenicity; rather, the Agency defaulted to the cancer weight-of-evidence assessment of other agencies including HHS, EPA, and IARC. The confidence in the body of evidence for an association or no association between exposure to vinyl acetate and a particular outcome was based on the strengths and weaknesses of individual studies. Four descriptors were used to describe the confidence in the body of evidence for effects or when no effect was found:

- **High confidence:** the true effect is highly likely to be reflected in the apparent relationship
- **Moderate confidence:** the true effect may be reflected in the apparent relationship
- **Low confidence:** the true effect may be different from the apparent relationship
- **Very low confidence:** the true effect is highly likely to be different from the apparent relationship

Confidence in the body of evidence for a particular outcome was rated for each type of study: case-control, case series, cohort, population, human-controlled exposure, and experimental animal. In the absence of data to the contrary, data for a particular outcome were collapsed across animal species, routes of exposure, and exposure durations. If species (or strain), route, or exposure duration differences were noted, then the data were treated as separate outcomes.

C.6.1 Initial Confidence Rating

In ATSDR's modification to the OHAT approach, the body of evidence for an association (or no association) between exposure to vinyl acetate and a particular outcome was given an initial confidence rating based on the key features of the individual studies examining that outcome. The presence of these key features of study design was determined for individual studies using four "yes or no" questions, which were customized for epidemiology, human controlled exposure, or experimental animal study designs. Separate questionnaires were completed for each outcome assessed in a study. The key features for observational epidemiology (cohort, population, and case-control) studies, human controlled exposure, and experimental animal studies are presented in Tables C-11, C-12, and C-13, respectively. The initial confidence in the study was determined based on the number of key features present in the study design:

- **High Initial Confidence:** Studies in which the responses to the four questions were "yes".

- **Moderate Initial Confidence:** Studies in which the responses to only three of the questions were "yes".

- **Low Initial Confidence:** Studies in which the responses to only two of the questions were "yes".

- **Very Low Initial Confidence:** Studies in which the response to one or none of the questions was "yes".

Table C-11. Key Features of Study Design for Observational Epidemiology Studies

Exposure was experimentally controlled
Exposure occurred prior to the outcome
Outcome was assessed on individual level rather than at the population level
A comparison group was used

Table C-12. Key Features of Study Design for Human-Controlled Exposure Studies

A comparison group was used or the subjects served as their own control
A sufficient number of subjects were tested
Appropriate methods were used to measure outcomes (i.e., clinically-confirmed outcome versus self-reported)
Appropriate statistical analyses were performed and reported or the data were reported in such a way to allow independent statistical analysis

Table C-13. Key Features of Study Design for Experimental Animal Studies

A concurrent control group was used
A sufficient number of animals per group were tested
Appropriate parameters were used to assess a potential adverse effect
Appropriate statistical analyses were performed and reported or the data were reported in such a way to allow independent statistical analysis

The presence or absence of the key features and the initial confidence levels for studies examining respiratory (inhalation only) and developmental effects in human controlled exposure studies, human observational studies, and animal experimental studies are presented in Tables C-14, C-15 and C-16, respectively.

A summary of the initial confidence ratings for each outcome is presented in Table C-17. If individual studies for a particular outcome and study type had different study quality ratings, then the highest confidence rating for the group of studies was used to determine the initial confidence rating for the body of evidence; any exceptions were noted in Table C-17.

Table C-14. Presence of Key Features of Study Design for Vinyl Acetate—Human-Controlled Exposure Studies

Reference	Key features				Initial study confidence
	Comparison group	Sufficient number subjects	Appropriate methods to assessed outcomes	Appropriate Statistical analysis	
Outcome: Respiratory Effects (inhalation only)					
Inhalation acute exposure					
Hinderliter et al. 2005	Yes	No	Yes	No	Low
Union Carbide 1973	No	Yes	No	No	Very Low
Outcome: Developmental					
None identified					

Table C-15. Presence of Key Features of Study Design for Vinyl Acetate—Observational Epidemiology Studies

Reference	Key features				Initial study confidence
	Controlled exposure	Exposure prior to outcome	Outcomes assessed on an individual level	Comparison group	
Outcome: Respiratory Effects (inhalation only)					
Inhalation acute exposure					
Deese and Joyner 1969	No	Yes	Yes	No	Low
Inhalation chronic exposure					
Deese and Joyner 1969	No	Yes	Yes	Yes	Moderate
Khoshakhlagh et al. 2023	No	No	Yes	Yes	Low
Outcome: Developmental					
None identified					

Table C-16. Presence of Key Features of Study Design for Vinyl Acetate — Experimental Animal Studies

Reference	Key feature: Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	Initial study confidence
Outcome: Respiratory Effects (inhalation only)					
Inhalation acute exposure					
Bogdanffy et al. 1997 (rat, 1 day)	Yes	Yes	Yes	Yes	High
Bogdanffy et al. 1997 (rat, 5 days)	Yes	Yes	Yes	Yes	High
Krieger et al. 2020 (1 day, rat)	Yes	Yes	Yes	Yes	High
Krieger et al. 2020 (5 days, rat)	Yes	Yes	Yes	Yes	High
Union Carbide 1973 (rat)	No	Yes	No	No	Very Low
Union Carbide 1973 (mouse)	No	Yes	No	No	Very Low
Union Carbide 1973 (rabbit)	No	Yes	No	No	Very Low
Union Carbide 1973 (guinea pig)	No	Yes	No	No	Very Low
Inhalation intermediate exposure					
Bogdanffy et al. 1997 (4 weeks)	Yes	Yes	Yes	Yes	High
Gage 1970 (rat, 15 days)	No	Yes	Yes	No	Low
Hazleton 1979c (rat, 4 weeks)	Yes	Yes	No	Yes	Moderate
Hazleton 1979b (mouse, 4 weeks)	Yes	Yes	No	Yes	Moderate
Hazleton 1980c (rat, 3 months)	Yes	Yes	Yes	Yes	High
Hazleton 1980b (mouse, 3 months)	Yes	Yes	Yes	Yes	High
Krieger et al. 2020 (20 days, rat)	Yes	Yes	Yes	Yes	High
Krieger et al. 2020 (65 days, rat)	Yes	Yes	Yes	Yes	High
Inhalation chronic exposure					
Bogdanffy et al. 1994a; Hazleton 1988 (rat)	Yes	Yes	Yes	Yes	High
Bogdanffy et al. 1994a; Hazleton 1988 (mouse)	Yes	Yes	Yes	Yes	High
Outcome: Developmental					
Inhalation acute exposure					
Hurtt et al. 1995; Hazleton 1980d	Yes	Yes	Yes	Yes	High
Oral acute exposure					
Hurtt et al. 1995	Yes	Yes	Yes	Yes	High
Oral intermediate exposure					
Mebus et al. 1995	Yes	Yes	Yes	Yes	High

Table C-17. Initial Confidence Rating for Vinyl Acetate Health Effects Studies

	Initial study confidence	Initial confidence rating
Outcome: Respiratory Effects (inhalation only)		
Inhalation acute exposure		
Human studies		
Deese and Joyner 1969	Low	Low
Hinderliter et al. 2005	Low	
Union Carbide 1973	Very Low	
Animal studies		
Bogdanffy et al. 1997 (rat, 1 day)	High	High
Bogdanffy et al. 1997 (rat, 5 days)	High	
Krieger et al. 2020 (1 day, rat)	High	
Krieger et al. 2020 (5 days, rat)	High	
Union Carbide 1973 (rat)	Very Low	
Union Carbide 1973 (mouse)	Very Low	
Union Carbide 1973 (rabbit)	Very Low	
Union Carbide 1973 (guinea pig)	Very Low	
Inhalation intermediate exposure		
Animal studies		
Bogdanffy et al. 1997 (4 weeks)	High	High
Gage 1970 (rat, 15 days)	Low	
Hazleton 1979c (rat, 4 weeks)	Moderate	
Hazleton 1979b (mouse, 4 weeks)	Moderate	
Hazleton 1980c (rat, 3 months)	High	
Hazleton 1980b (mouse, 3 months)	High	
Krieger et al. 2020 (20 days, rat)	High	
Krieger et al. 2020 (65 days, rat)	High	
Inhalation chronic exposure		
Human studies		
Deese and Joyner 1969	Moderate	Moderate
Khoshakhlagh et al. 2023	Low	
Animal studies		
Bogdanffy et al. 1994a; Hazleton 1988 (rat)	High	High
Bogdanffy et al. 1994a; Hazleton 1988 (mouse)	High	
Outcome: Developmental effects		
Inhalation acute exposure		
Animal studies		
Hurtt et al. 1995; Hazleton 1980d	High	High
Oral acute exposure		
Animal studies		
Hurtt et al. 1995	High	High

Table C-17. Initial Confidence Rating for Vinyl Acetate Health Effects Studies

	Initial study confidence	Initial confidence rating
Oral intermediate exposure		
Animal studies		
Mebus et al. 1995	High	High

C.6.2 Adjustment of the Confidence Rating

The initial confidence rating was then downgraded or upgraded depending on whether there were substantial issues that would decrease or increase confidence in the body of evidence. The nine properties of the body of evidence that were considered are listed below. The summaries of the assessment of the confidence in the body of evidence for respiratory effects are presented in Table C-18. If the confidence ratings for a particular outcome were based on more than one type of human study, then the highest confidence rating was used for subsequent analyses. An overview of the confidence in the body of evidence for all health effects associated with vinyl acetate exposure is presented in Table C-19.

Table C-18. Adjustments to the Initial Confidence in the Body of Evidence

	Initial confidence	Adjustments to the initial confidence rating	Final confidence
Outcome: Respiratory effects (inhalation only)			
Human studies	Moderate	-1 for risk of bias, -1 for imprecision, -1 for unexplained inconsistency	Very low
Animal studies	High	+1 consistency in findings, +1 dose-response	High
Outcome: Developmental effects			
Animal studies	High	-1 for unexplained inconsistency, -1 for indirectness	Low

Table C-19. Confidence in the Body of Evidence for Vinyl Acetate

	Confidence in body of evidence	
Outcome	Human studies	Animal studies
Respiratory effects (inhalation only)	Very low	High
Developmental effects	No data	Low

Five properties of the body of evidence were considered to determine whether the confidence rating should be downgraded:

- **Risk of bias.** Evaluation of whether there is substantial risk of bias across most of the studies examining the outcome. This evaluation used the risk of bias tier groupings for individual studies examining a particular outcome (Tables C-8, C-9 and C-10, respectively). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for risk of bias:
    - No downgrade if most studies are in the risk of bias first tier
    - Downgrade one confidence level if most studies are in the risk of bias second tier
    - Downgrade two confidence levels if most studies are in the risk of bias third tier

- **Unexplained inconsistency.** Evaluation of whether there is inconsistency or large variability in the magnitude or direction of estimates of effect across studies that cannot be explained. Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for unexplained inconsistency:
    - No downgrade if there is little inconsistency across studies or if only one study evaluated the outcome
    - Downgrade one confidence level if there is variability across studies in the magnitude or direction of the effect
    - Downgrade two confidence levels if there is substantial variability across studies in the magnitude or direct of the effect

- **Indirectness.** Evaluation of four factors that can affect the applicability, generalizability, and relevance of the studies:
    - Relevance of the animal model to human health—unless otherwise indicated, studies in rats, mice, and other mammalian species are considered relevant to humans
    - Directness of the endpoints to the primary health outcome—examples of secondary outcomes or nonspecific outcomes include organ weight in the absence of histopathology or clinical chemistry findings in the absence of target tissue effects
    - Nature of the exposure in human studies and route of administration in animal studies—inhalation, oral, and dermal exposure routes are considered relevant unless there are compelling data to the contrary
    - Duration of treatment in animal studies and length of time between exposure and outcome assessment in animal and prospective human studies—this should be considered on an outcome-specific basis

  Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for indirectness:
    - No downgrade if none of the factors are considered indirect
    - Downgrade one confidence level if one of the factors is considered indirect
    - Downgrade two confidence levels if two or more of the factors are considered indirect

- **Imprecision.** Evaluation of the narrowness of the effect size estimates and whether the studies have adequate statistical power. Data are considered imprecise when the ratio of the upper to lower 95% CIs for most studies is ≥10 for tests of ratio measures (e.g., odds ratios) and ≥100 for absolute measures (e.g., percent control response). Adequate statistical power is determined if the study can detect a potentially biologically meaningful difference between groups (20% change from control response for categorical data or risk ratio of 1.5 for continuous data). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for imprecision:
    - No downgrade if there are no serious imprecisions
    - Downgrade one confidence level for serious imprecisions
    - Downgrade two confidence levels for very serious imprecisions

- **Publication bias.** Evaluation of the concern that studies with statistically significant results are more likely to be published than studies without statistically significant results.
    - Downgrade one level of confidence for cases where there is serious concern with publication bias

Four properties of the body of evidence were considered to determine whether the confidence rating should be upgraded:

- **Large magnitude of effect.** Evaluation of whether the magnitude of effect is sufficiently large so that it is unlikely to have occurred as a result of bias from potential confounding factors.
    - Upgrade one confidence level if there is evidence of a large magnitude of effect in a few studies, provided that the studies have an overall low risk of bias and there is no serious unexplained inconsistency among the studies of similar dose or exposure levels; confidence can also be upgraded if there is one study examining the outcome, provided that the study has an overall low risk of bias

- **Dose response.** Evaluation of the dose-response relationships measured within a study and across studies. Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
    - Upgrade one confidence level for evidence of a monotonic dose-response gradient
    - Upgrade one confidence level for evidence of a non-monotonic dose-response gradient where there is prior knowledge that supports a non-monotonic dose-response and a non-monotonic dose-response gradient is observed across studies

- **Plausible confounding or other residual biases.** This factor primarily applies to human studies and is an evaluation of unmeasured determinants of an outcome such as residual bias towards the null (e.g., "healthy worker" effect) or residual bias suggesting a spurious effect (e.g., recall bias). Below is the criterion used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
    - Upgrade one confidence level for evidence that residual confounding or bias would underestimate an apparent association or treatment effect (i.e., bias toward the null) or suggest a spurious effect when results suggest no effect

- **Consistency in the body of evidence.** Evaluation of consistency across animal models and species, consistency across independent studies of different human populations and exposure scenarios, and consistency across human study types. Below is the criterion used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
    - Upgrade one confidence level if there is a high degree of consistency in the database

C.7 TRANSLATE CONFIDENCE RATING INTO LEVEL OF EVIDENCE OF HEALTH EFFECTS

In the seventh step of the systematic review of the health effects data for vinyl acetate, the confidence in the body of evidence for specific outcomes was translated to a level of evidence rating. The level of evidence rating reflected the confidence in the body of evidence and the direction of the effect (i.e., toxicity or no toxicity); route-specific differences were noted. The level of evidence for health effects was rated on a five-point scale:

- **High level of evidence:** High confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Moderate level of evidence:** Moderate confidence in the body of evidence for an association between exposure to the substance and the health outcome

- **Low level of evidence:** Low confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Evidence of no health effect:** High confidence in the body of evidence that exposure to the substance is not associated with the health outcome
- **Inadequate evidence:** Low or moderate confidence in the body of evidence that exposure to the substance is not associated with the health outcome OR very low confidence in the body of evidence for an association between exposure to the substance and the health outcome

A summary of the level of evidence of health effects for vinyl acetate is presented in Table C-20.

Table C-20. Level of Evidence of Health Effects for Vinyl Acetate

Outcome	Confidence in body of evidence	Direction of health effect	Level of evidence for health effect
Human studies			
Respiratory effects (inhalation)	Very Low	Health effect	Inadequate
Animal studies			
Respiratory effects (inhalation)	High	Health effect	High
Developmental effects	Low	Health effect	Low

C.8 INTEGRATE EVIDENCE TO DEVELOP HAZARD IDENTIFICATION CONCLUSIONS

The final step involved the integration of the evidence streams for the human studies and animal studies to allow for a determination of hazard identification conclusions. For health effects, there were four hazard identification conclusion categories:

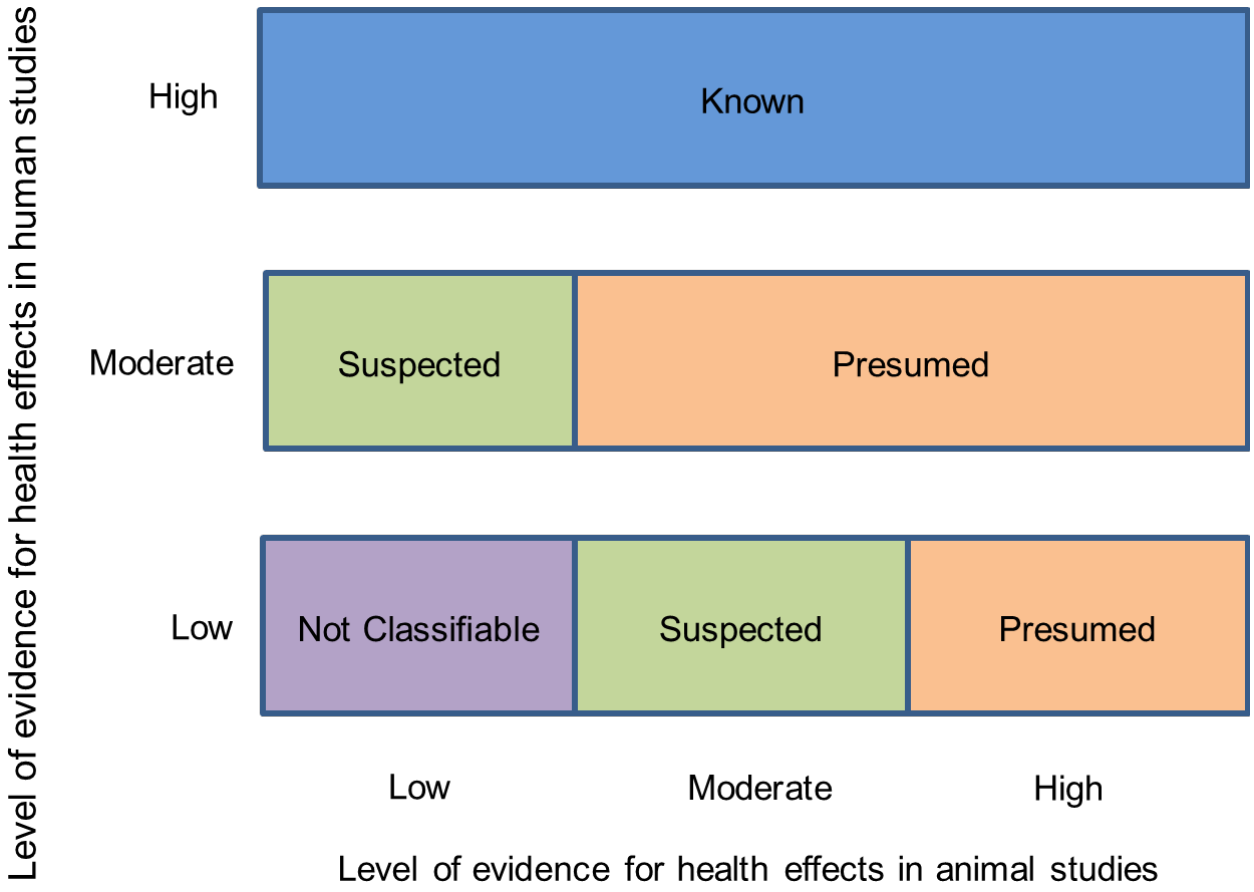
- **Known** to be a hazard to humans
- **Presumed** to be a hazard to humans
- **Suspected** to be a hazard to humans
- **Not classifiable** as to the hazard to humans

The initial hazard identification was based on the highest level of evidence in the human studies and the level of evidence in the animal studies; if there were no data for one evidence stream (human or animal), then the hazard identification was based on the one data stream (equivalent to treating the missing evidence stream as having low level of evidence). The hazard identification scheme is presented in Figure C-1 and described below:

- **Known:** A health effect in this category would have:
  - High level of evidence for health effects in human studies **AND** a high, moderate, or low level of evidence in animal studies.
- **Presumed:** A health effect in this category would have:
  - Moderate level of evidence in human studies **AND** high or moderate level of evidence in animal studies **OR**
  - Low level of evidence in human studies **AND** high level of evidence in animal studies
- **Suspected:** A health effect in this category would have:
  - Moderate level of evidence in human studies **AND** low level of evidence in animal studies **OR**

  - Low level of evidence in human studies **AND** moderate level of evidence in animal studies
- **Not classifiable:** A health effect in this category would have:
  - Low level of evidence in human studies **AND** low level of evidence in animal studies

Figure C-1. Hazard Identification Scheme



Other relevant data such as mechanistic or mode-of-action data were considered to raise or lower the level of the hazard identification conclusion by providing information that supported or opposed biological plausibility.

Two hazard identification conclusion categories were used when the data indicated that there may be no health effect in humans:

- **Not identified** to be a hazard in humans
- **Inadequate** to determine hazard to humans

If the human level of evidence conclusion of no health effect was supported by the animal evidence of no health effect, then the hazard identification conclusion category of "not identified" was used. If the human or animal level of evidence was considered inadequate, then a hazard identification conclusion category of "inadequate" was used. As with the hazard identification for health effects, the impact of other relevant data was also considered for no health effect data.

The hazard identification conclusions for vinyl acetate are listed below and summarized in Table C-21.

Table C-21. Hazard Identification Conclusions for Vinyl Acetate

Outcome	Hazard identification
Respiratory effects (inhalation only)	Presumed health effect
Developmental effects	Not classifiable

Presumed Health Effects

- Respiratory effects (inhalation only)
  - Inadequate evidence of respiratory effects from controlled exposure to vinyl acetate with a very small number of individuals evaluating very limited endpoints (Deese and Joyner 1969; Hinderliter et al. 2005; Union Carbide 1973) and two occupational studies of workers exposed to vinyl acetate (Deese and Joyner 1969; Khoshakhlagh et al. 2023).
  - High level of evidence of respiratory tract damage in rats and mice following acute-, intermediate-, and chronic-duration exposure (Bogdanffy et al. 1997; 1994a; Gage 1970; Hazleton 1980b, 1988; Krieger et al. 2020).

Not Classifiable Effects

- Developmental effects
  - No human data were identified.
  - Low level of evidence for impaired growth and development in rats following developmental exposure to vinyl acetate via inhalation or oral exposure. Decreased fetal weight and length as well as delayed ossification were observed in rat fetuses following maternal inhalation exposure during gestation; these effects may have been secondary to decreased maternal weight (Hazleton 1980d; Hurtt et al. 1995). Decreased F1 weanling weights were also observed in rats in a 2-generation drinking-water study; these effects may have been secondary to decreases in both maternal water intake and body weight gain during lactation (Mebus et al. 1995). However, no effects were noted in F2 pup weights, despite F1 dam body weight effects (Mebus et al. 1995). In an oral gestation-only study, neither maternal nor fetal effects were noted (Hurtt et al. 1995).

APPENDIX D. USER'S GUIDE

Chapter 1. Relevance to Public Health

This chapter provides an overview of U.S. exposures, a summary of health effects based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information, and an overview of the minimal risk levels. This is designed to present interpretive, weight-of-evidence discussions for human health endpoints by addressing the following questions:

1. What effects are known to occur in humans?

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

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

Minimal Risk Levels (MRLs)

Where sufficient toxicologic information is available, ATSDR derives MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a hazardous substance emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Section 1.2, Summary of Health Effects, contains basic information known about the substance. Other sections, such as Section 3.2 Children and Other Populations that are Unusually Susceptible and Section 3.4 Interactions with Other Substances, provide important supplemental information.

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

To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a

substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables that are provided in Chapter 2. Detailed discussions of the MRLs are presented in Appendix A.

Chapter 2. Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species and MRLs to humans for noncancer endpoints. The LSE tables and figures can be used for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE tables and figures follow. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

TABLE LEGEND

See Sample LSE Table (page C-5)

(1) Route of exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically, when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure (i.e., inhalation, oral, and dermal). LSE figures are limited to the inhalation and oral routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures. Profiles with more than one chemical may have more LSE tables and figures.

(2) Exposure period. Three exposure periods—acute (<15 days), intermediate (15–364 days), and chronic (≥365 days)—are presented within each relevant route of exposure. In this example, two oral studies of chronic-duration exposure are reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Figure key. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 51 identified NOAELs and less serious LOAELs (also see the three "51R" data points in sample LSE Figure 2-X).

(4) Species (strain) No./group. The test species (and strain), whether animal or human, are identified in this column. The column also contains information on the number of subjects and sex per group. Chapter 1, Relevance to Public Health, covers the relevance of animal data to human toxicity and Section 3.1, Toxicokinetics, contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(5) Exposure parameters/doses. The duration of the study and exposure regimens are provided in these columns. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 51), rats were orally exposed to “Chemical X” via feed for 2 years. For a

more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Aida et al. 1992).

(6) Parameters monitored. This column lists the parameters used to assess health effects. Parameters monitored could include serum (blood) chemistry (BC), biochemical changes (BI), body weight (BW), clinical signs (CS), developmental toxicity (DX), food intake (FI), gross necropsy (GN), hematology (HE), histopathology (HP), immune function (IX), lethality (LE), neurological function (NX), organ function (OF), ophthalmology (OP), organ weight (OW), reproductive function (RX), urinalysis (UR), and water intake (WI).

(7) Endpoint. This column lists the endpoint examined. The major categories of health endpoints included in LSE tables and figures are death, body weight, respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, dermal, ocular, endocrine, immunological, neurological, reproductive, developmental, other noncancer, and cancer. "Other noncancer" refers to any effect (e.g., alterations in blood glucose levels) not covered in these systems. In the example of key number 51, three endpoints (body weight, hematological, and hepatic) were investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no adverse effects were seen in the organ system studied. The body weight effect reported in key number 51 is a NOAEL at 25.5 mg/kg/day. NOAELs are not reported for cancer and death; with the exception of these two endpoints, this field is left blank if no NOAEL was identified in the study.

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused an adverse health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. Key number 51 reports a less serious LOAEL of 6.1 mg/kg/day for the hepatic system, which was used to derive a chronic exposure, oral MRL of 0.008 mg/kg/day (see footnote "c"). MRLs are not derived from serious LOAELs. A cancer effect level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases. If no LOAEL/CEL values were identified in the study, this field is left blank.

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

(11) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. For example, footnote "c" indicates that the LOAEL of 6.1 mg/kg/day in key number 51 was used to derive an oral MRL of 0.008 mg/kg/day.

FIGURE LEGEND

See Sample LSE Figure (page C-6)

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

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

(13) Endpoint. These are the categories of health effects for which reliable quantitative data exist. The same health effect endpoints appear in the LSE table.

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

(15) LOAEL. In this example, the half-shaded circle that is designated 51R identifies a LOAEL critical endpoint in the rat upon which a chronic oral exposure MRL is based. The key number 51 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 6.1 mg/kg/day (see entry 51 in the sample LSE table) to the MRL of 0.008 mg/kg/day (see footnote "c" in the sample LSE table).

(16) CEL. Key number 59R is one of studies for which CELs were derived. The diamond symbol refers to a CEL for the test species (rat). The number 59 corresponds to the entry in the LSE table.

(17) Key to LSE figure. The key provides the abbreviations and symbols used in the figure.

Table 2-X. Levels of Significant Exposure to [Chemical X] – Oral (1)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effect
CHRONIC EXPOSURE (2)									
51 (3)	Rat (Wistar) 40 M, 40 F	2 years (F)	M: 0, 6.1, 25.5, 138.0 F: 0, 8.0, 31.7, 168.4	CS, WI, BW, OW, HE, BC, HP	Bd wt	25.5	138.0		Decreased body weight gain in males (23–25%) and females (31–39%)
					Hemato	138.0			
					Hepatic		6.1[c]		Increases in absolute and relative weights at ≥6.1/8.0 mg/kg/day after 12 months of exposure; fatty generation at ≥6.1 mg/kg/day in males and at ≥31.7 mg/kg/day in females, and granulomas in females at 31.7 and 168.4 mg/kg/day after 12, 18, or 24 months of exposure and in males at ≥6.1 mg/kg/day only after 24 months of exposure
Aida et al. 1992 (10)									
52	Rat (F344) 78 M	104 weeks (W)	0, 3.9, 20.6, 36.3	CS, BW, FI, BC, OW, HP	Hepatic	36.3			
					Renal	20.6	36.3		Increased incidence of renal tubular cell hyperplasia
					Endocr	36.3			
George et al. 2002									
59	Rat (Wistar) 58M, 58F	Lifetime (W)	M: 0, 90 F: 0, 190	BW, HP	Cancer		190 F		Increased incidence of hepatic neoplastic nodules in females only; no additional description of the tumors was provided
Tumasonis et al. 1985									

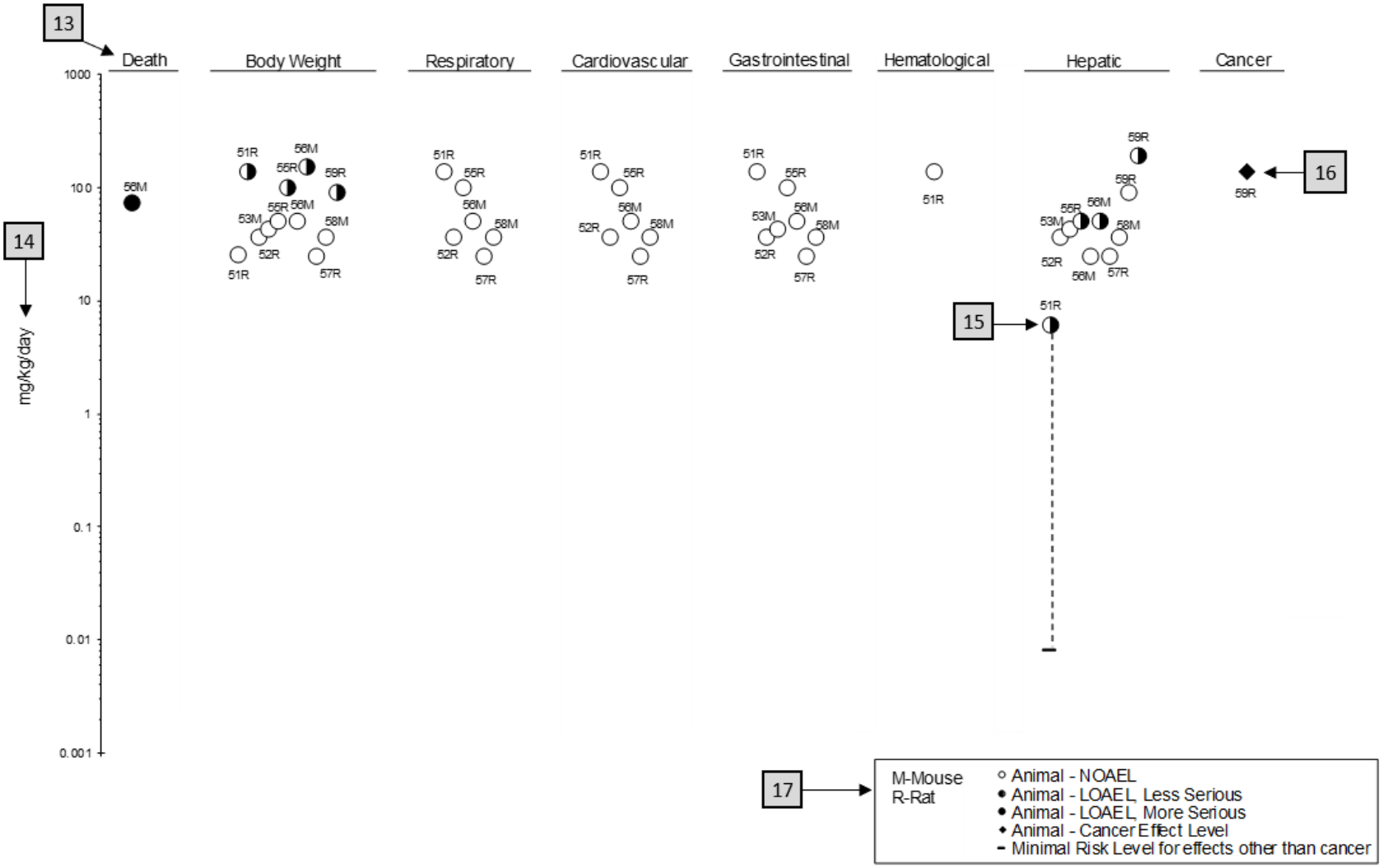
[a]The number corresponds to entries in Figure 2-x.

(11) [b]Used to derive an acute-duration oral minimal risk level (MRL) of 0.1 mg/kg/day based on the $BMDL_{05}$ of 10 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

[c]Used to derive a chronic-duration oral MRL of 0.008 mg/kg/day based on the $BMDL_{10}$ of 0.78 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

APPENDIX D

Figure 2-X. Levels of Significant Exposure to [Chemical X] - Oral



APPENDIX E. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances may find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Relevance to Public Health: The Relevance to Public Health Section provides an overview of exposure and health effects and evaluates, interprets, and assesses the significance of toxicity data to human health. A table listing minimal risk levels (MRLs) is also included in this chapter.

Chapter 2: Health Effects: Specific health effects identified in both human and animal studies are reported by type of health effect (e.g., death, hepatic, renal, immune, reproductive), route of exposure (e.g., inhalation, oral, dermal), and length of exposure (e.g., acute, intermediate, and chronic).
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting.

Pediatrics:

Section 3.2 Children and Other Populations that are Unusually Susceptible
Section 3.3 Biomarkers of Exposure and Effect

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY)
Internet: http://www.atsdr.cdc.gov

ATSDR develops educational and informational materials for health care providers categorized by hazardous substance, clinical condition, and/or by susceptible population. The following additional materials are available online:

Clinician Briefs and Overviews discuss health effects and approaches to patient management in a brief/factsheet style. They are narrated PowerPoint presentations with Continuing Education credit available (see https://www.atsdr.cdc.gov/environmental-medicine/hcp/emhsis/index.html).

Managing Hazardous Materials Incidents is a set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident (see https://www.atsdr.cdc.gov/MHMI/index.html).

Fact Sheets (ToxFAQs™) provide answers to frequently asked questions about toxic substances (see https://wwwn.cdc.gov/TSP/ToxFAQs/ToxFAQsLanding.aspx).

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015 • Web Page: https://www.cdc.gov/nceh/.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 400 7th Street, S.W., Suite 5W, Washington, DC 20024 • Phone: 202-245-0625 or 1-800-CDC-INFO (800-232-4636) • Web Page: https://www.cdc.gov/niosh/.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212 • Web Page: https://www.niehs.nih.gov/.

Clinical Resources (Publicly Available Information)

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266 • Web Page: http://www.acoem.org/.

The American College of Medical Toxicology (ACMT) is a nonprofit association of physicians with recognized expertise in medical toxicology. Contact: ACMT, 10645 North Tatum Boulevard, Suite 200-111, Phoenix AZ 85028 • Phone: 844-226-8333 • FAX: 844-226-8333 • Web Page: http://www.acmt.net.

The Pediatric Environmental Health Specialty Units (PEHSUs) is an interconnected system of specialists who respond to questions from public health professionals, clinicians, policy makers, and the public about the impact of environmental factors on the health of children and reproductive-aged adults. Contact information for regional centers can be found at https://www.pehsu.net/.

The American Association of Poison Control Centers (AAPCC) provide support on the prevention and treatment of poison exposures. Contact: AAPCC, 515 King Street, Suite 510, Alexandria VA 22314 • Phone: 701-894-1858 • Poison Help Line: 1-800-222-1222 • Web Page: http://www.aapcc.org/.

APPENDIX F. GLOSSARY

Absorption—The process by which a substance crosses biological membranes and enters systemic circulation. Absorption can also refer to the taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of ≤14 days, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

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

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

Benchmark Dose (BMD) or Benchmark Concentration (BMC)—is the dose/concentration corresponding to a specific response level estimate using a statistical dose-response model applied to either experimental toxicology or epidemiology data. For example, a BMD_{10} would be the dose corresponding to a 10% benchmark response (BMR). The BMD is determined by modeling the dose-response curve in the region of the dose-response relationship where biologically observable data are feasible. The BMDL or BMCL is the 95% lower confidence limit on the BMD or BMC.

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

Biomarkers—Indicators signaling events in biologic systems or samples, typically classified as markers of exposure, effect, and susceptibility.

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

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-control study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without the outcome.

Case Report—A report that describes a single individual with a particular disease or exposure. These reports may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Reports that describe the experience of a small number of individuals with the same disease or exposure. These reports may suggest potential topics for scientific research, but are not actual research studies.

Ceiling Value—A concentration that must not be exceeded.

Chronic Exposure—Exposure to a chemical for ≥365 days, as specified in the Toxicological Profiles.

Clastogen—A substance that causes breaks in chromosomes resulting in addition, deletion, or rearrangement of parts of the chromosome.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome, and who are disease-free at start of follow-up. Often, at least one exposed group is compared to one unexposed group, while in other cohorts, exposure is a continuous variable and analyses are directed towards analyzing an exposure-response coefficient.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at a specific point in time.

Data Needs—Substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment.

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

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the response or amount of the response.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the effect occurs. Effects include malformations and variations, altered growth, and *in utero* death.

Epidemiology—The investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Excretion—The process by which metabolic waste products are removed from the body.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one-half of a quantity of a chemical from the body or environmental media.

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

Immediately Dangerous to Life or Health (IDLH)—A condition that poses a threat of life or health, or conditions that pose an immediate threat of severe exposure to contaminants that are likely to have adverse cumulative or delayed effects on health.

Immunotoxicity—Adverse effect on the functioning of the immune system that may result from exposure to chemical substances.

Incidence—The ratio of new cases of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

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

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

***In Vivo*—**Occurring within the living organism.

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

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{Lo})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

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

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

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

Metabolism—Process in which chemical substances are biotransformed in the body that could result in less toxic and/or readily excreted compounds or produce a biologically active intermediate.

Minimal LOAEL—Indicates a minimal adverse effect or a reduced capacity of an organ or system to absorb additional toxic stress that does not necessarily lead to the inability of the organ or system to function normally.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—The state of being diseased; the morbidity rate is the incidence or prevalence of a disease in a specific population.

Mortality—Death; the mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations, which are changes in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a hazardous substance.

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

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

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio that is greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) regulatory limit on the amount or concentration of a substance not to be exceeded in workplace air averaged over any 8-hour work shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests (insects or other organisms harmful to cultivated plants or animals).

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic endpoints. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—A type of physiologically based dose-response model that is comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information, including tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as blood:air partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which a group is followed over time and the pertinent observations are made on events occurring after the start of the study.

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation RfC is expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily oral exposure of the human population to a potential hazard that is likely to be without risk of deleterious noncancer health effects during a lifetime. The oral RfD is expressed in units of mg/kg/day.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). RQs are (1) ≥1 pound or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

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

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a hazardous substance.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, existing health condition, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio/Relative Risk—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio that is greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Serious LOAEL—A dose that evokes failure in a biological system and can lead to morbidity or mortality.

Short-Term Exposure Limit (STEL)—A STEL is a 15-minute TWA exposure that should not be exceeded at any time during a workday.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

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

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

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which it is believed that nearly all workers may be repeatedly exposed, day after day, for a working lifetime without adverse effect. The TLV may be expressed as a Time-Weighted Average (TLV-TWA), as a Short-Term Exposure Limit (TLV-STEL), or as a ceiling limit (TLV-C).

Time-Weighted Average (TWA)—An average exposure within a given time period.

Toxicokinetic—The absorption, distribution, metabolism, and elimination of toxic compounds in the living organism.

Toxics Release Inventory (TRI)—The TRI is an EPA program that tracks toxic chemical releases and pollution prevention activities reported by industrial and federal facilities.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL), Reference Dose (RfD), or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis (3 being the approximate logarithmic average of 10 and 1).

Xenobiotic—Any substance that is foreign to the biological system.

APPENDIX G. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

AAPCC	American Association of Poison Control Centers
ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ACMT	American College of Medical Toxicology
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AEGL	Acute Exposure Guideline Level
AIC	Akaike's information criterion
AIHA	American Industrial Hygiene Association
ALT	alanine aminotransferase
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BCF	bioconcentration factor
BMD/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
C	centigrade
CAA	Clean Air Act
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
cm	centimeter
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DWEL	drinking water exposure level
EAFUS	Everything Added to Food in the United States
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
ERPG	emergency response planning guidelines
F	Fahrenheit
F1	first-filial generation
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FR	Federal Register

FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GGT	γ-glutamyl transferase
GRAS	generally recognized as safe
HEC	human equivalent concentration
HED	human equivalent dose
HHS	Department of Health and Human Services
HPLC	high-performance liquid chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	kilokilogram; 1 kilokilogram is equivalent to 1,000 kilograms and 1 metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactate dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Level of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
MRL	Minimal Risk Level
MS	mass spectrometry
MSHA	Mine Safety and Health Administration
Mt	metric ton
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NCEH	National Center for Environmental Health
ND	not detected
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences

NIOSH	National Institute for Occupational Safety and Health
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NTP	National Toxicology Program
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PAC	Protective Action Criteria
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PEHSU	Pediatric Environmental Health Specialty Unit
PEL	permissible exposure limit
PEL-C	permissible exposure limit-ceiling value
pg	picogram
PND	postnatal day
POD	point of departure
ppb	parts per billion
ppbv	parts per billion by volume
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
REL-C	recommended exposure limit-ceiling value
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SD	standard deviation
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase (same as aspartate aminotransferase or AST)
SGPT	serum glutamic pyruvic transaminase (same as alanine aminotransferase or ALT)
SIC	standard industrial classification
SLOAEL	serious lowest-observed-adverse-effect level
SMR	standardized mortality ratio
sRBC	sheep red blood cell
STEL	short term exposure limit
TLV	threshold limit value
TLV-C	threshold limit value-ceiling value
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey

USNRC	U.S. Nuclear Regulatory Commission
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result