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

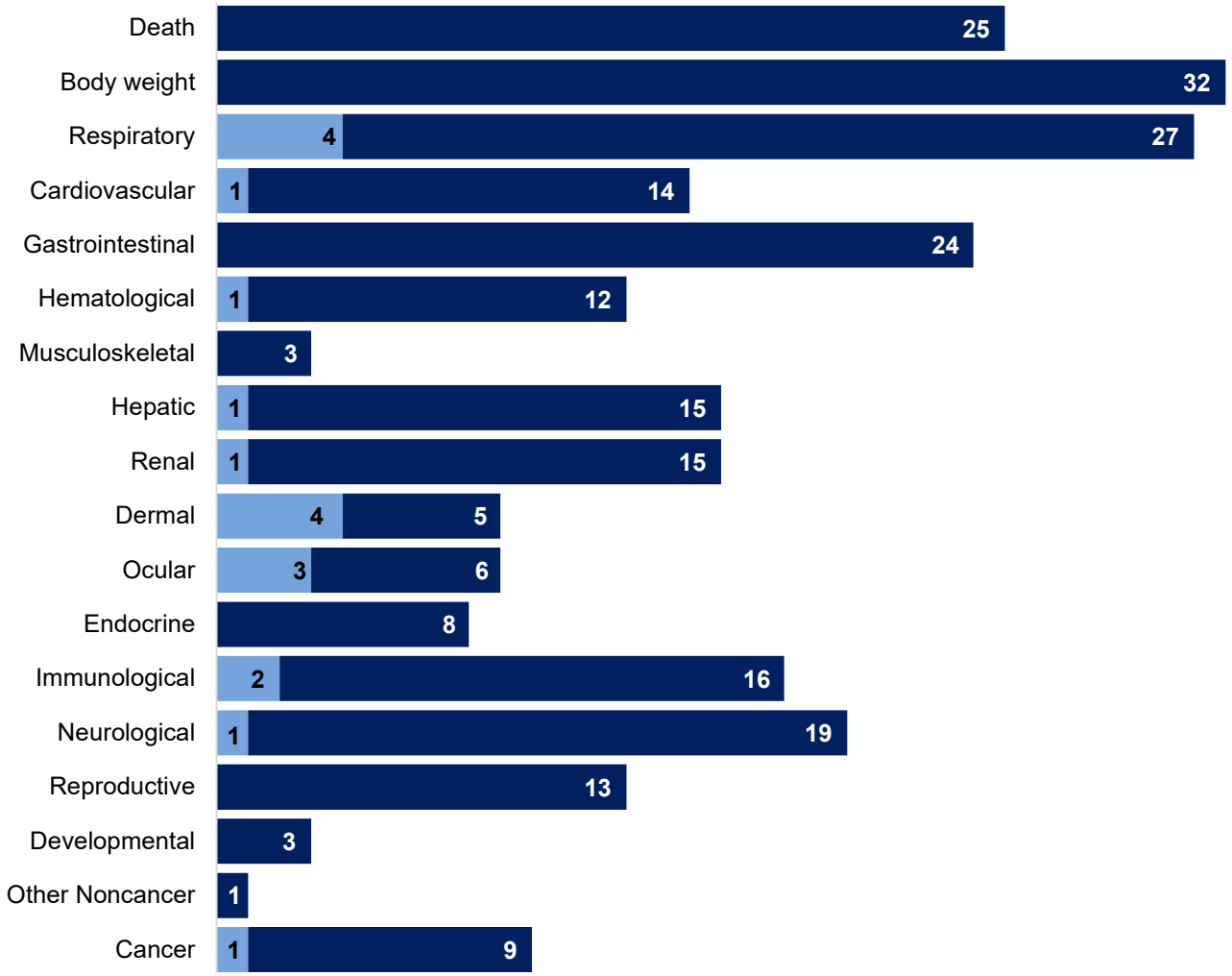
concomitant decreases in water and/or food intake. Based upon systematic review, the results of the animal studies, along with limited human data, support the following hazard identification conclusions:

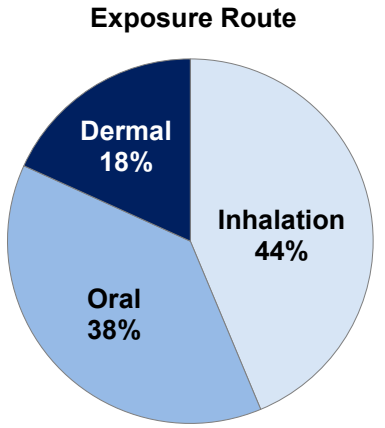
- **Respiratory Effects.** Respiratory effects are a presumed health effect for humans exposed to vinyl acetate based on inadequate evidence of respiratory effects in humans and a high level of evidence of upper and lower respiratory tract damage in laboratory animals following acute-, intermediate-, 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.

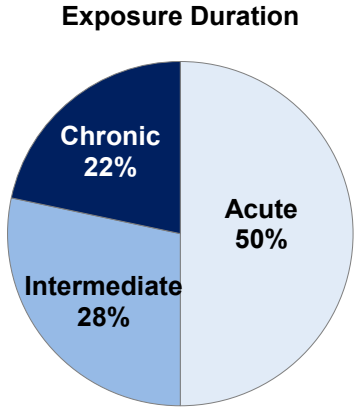
- **Developmental Effects.** Available data are inadequate to determine if developmental effects will occur in humans following exposure to vinyl acetate based on no human data and a low level of evidence in laboratory animals following oral exposure. There is some evidence for impaired growth and development 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)

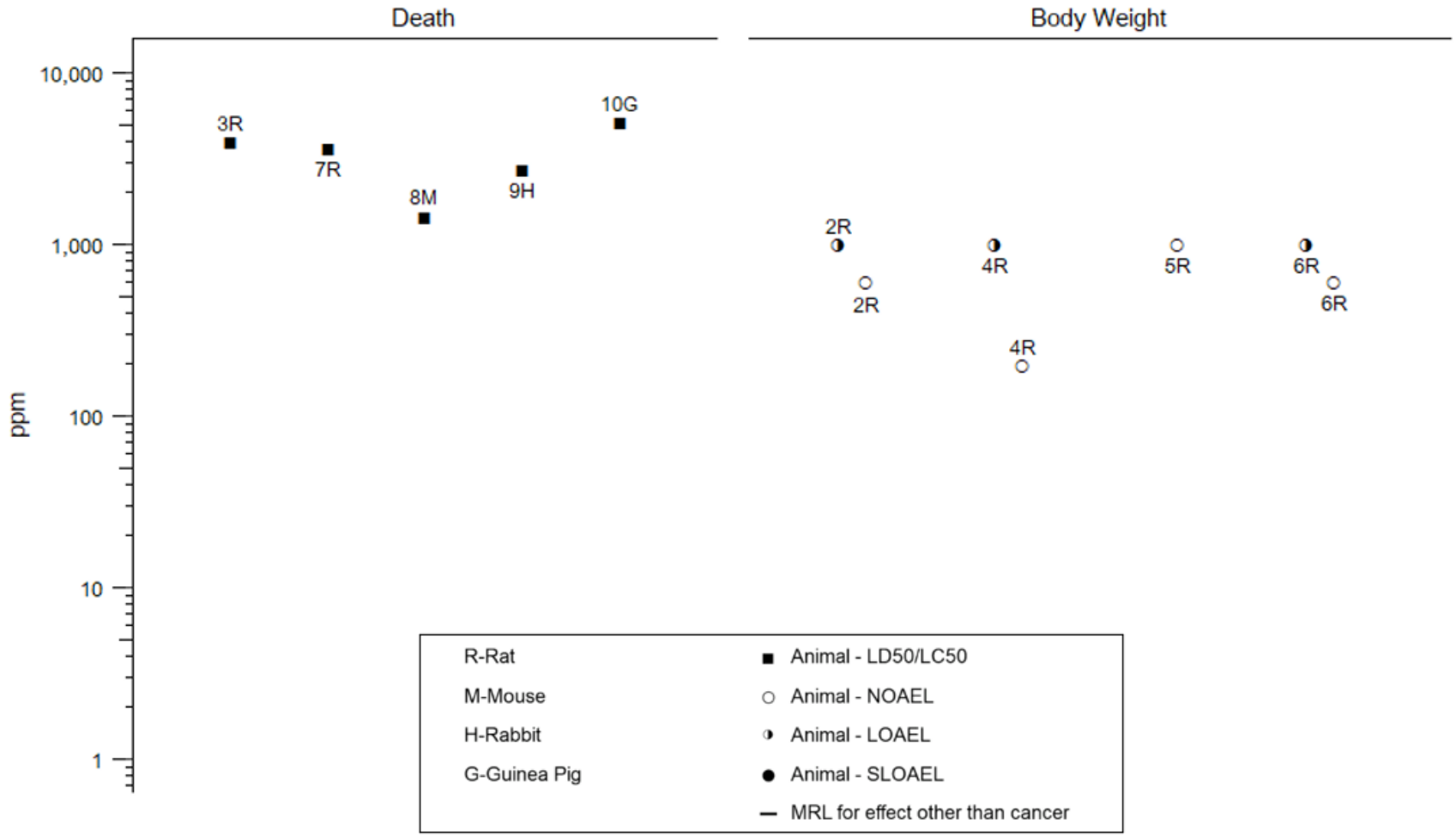


Figure 2-2. Levels of Significant Exposure to Vinyl Acetate – Inhalation Acute (≤14 days)

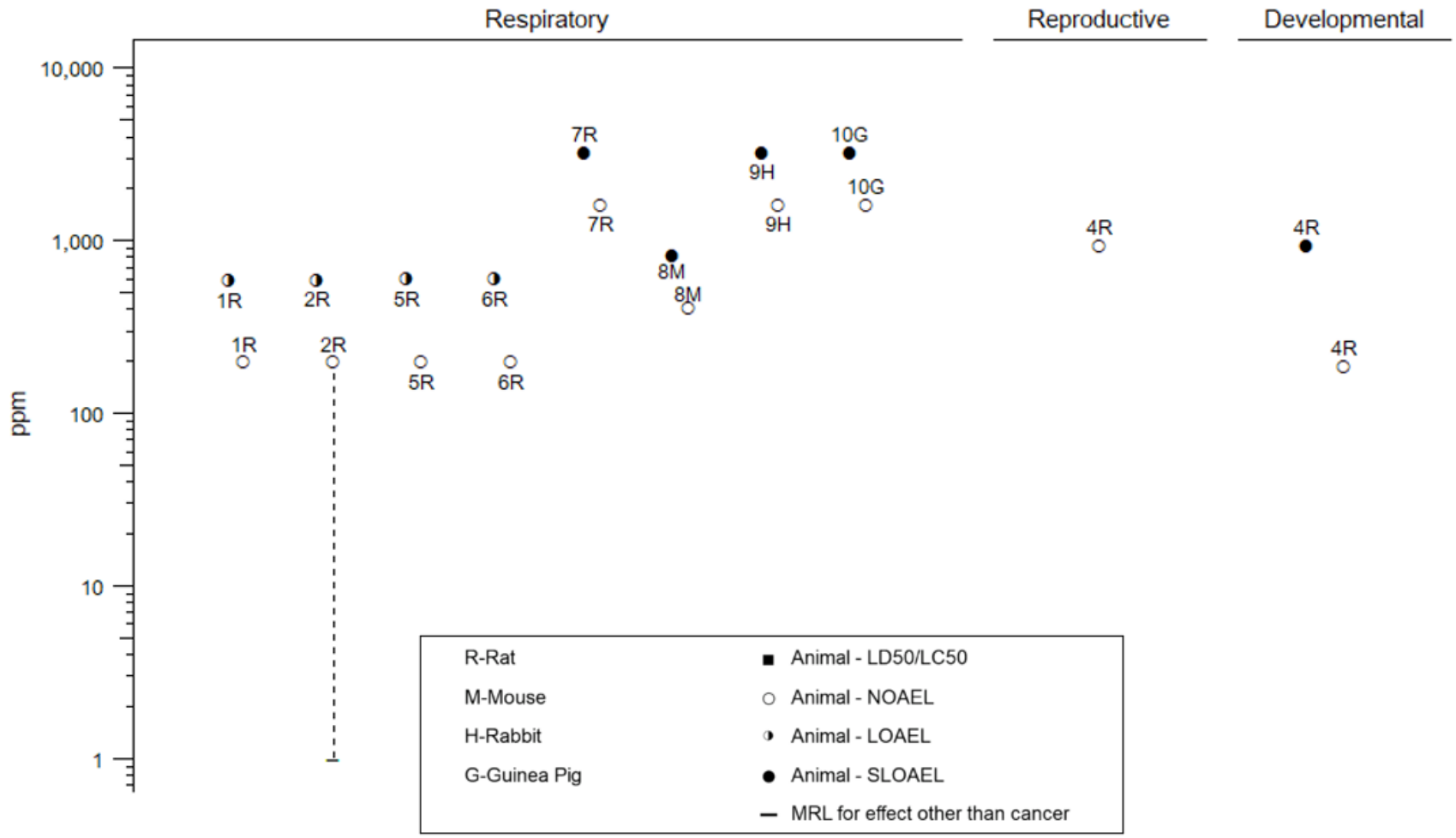


Figure 2-2. Levels of Significant Exposure to Vinyl Acetate – Inhalation Intermediate (15–364 days)

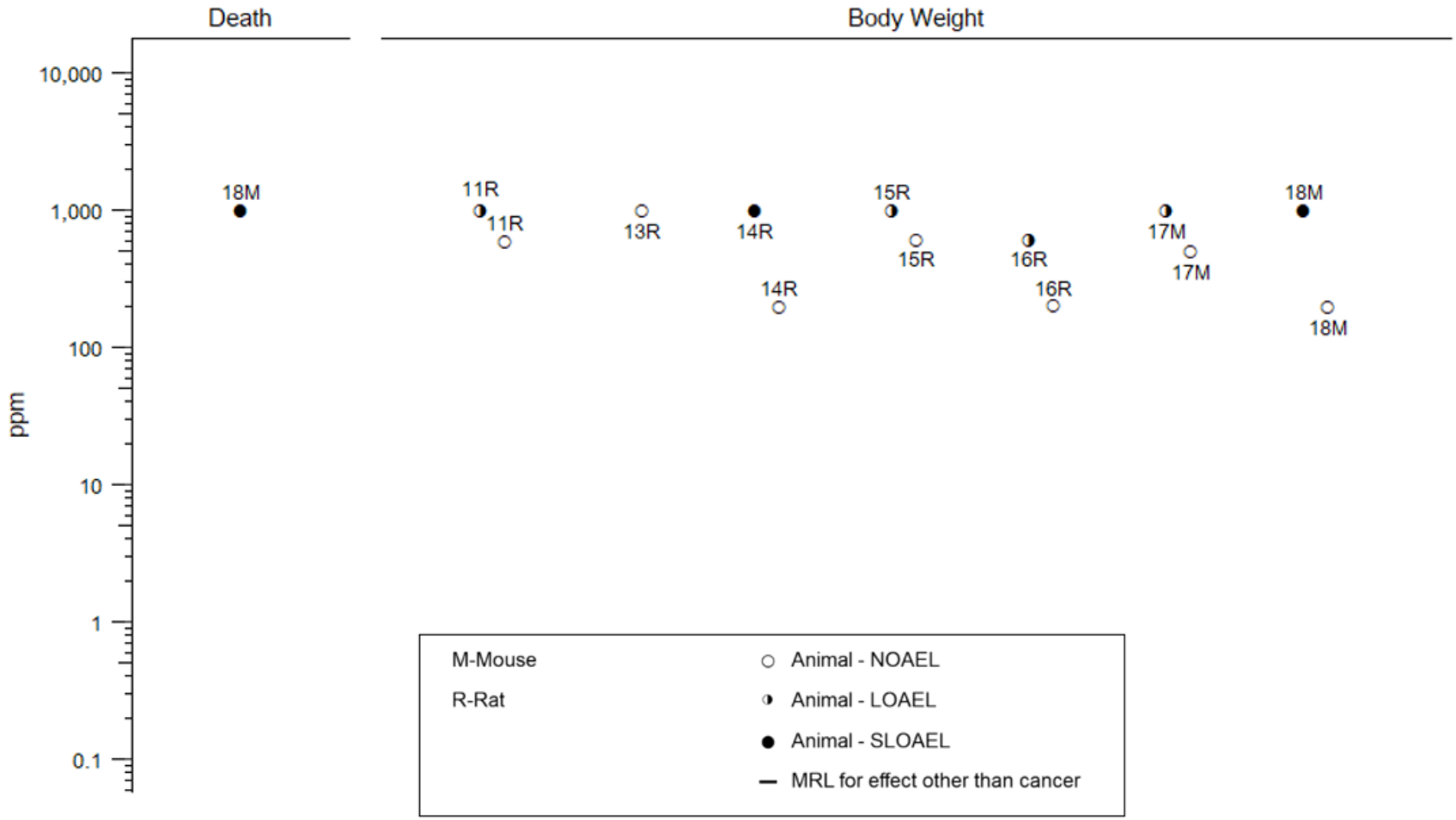


Figure 2-2. Levels of Significant Exposure to Vinyl Acetate – Inhalation Intermediate (15–364 days)

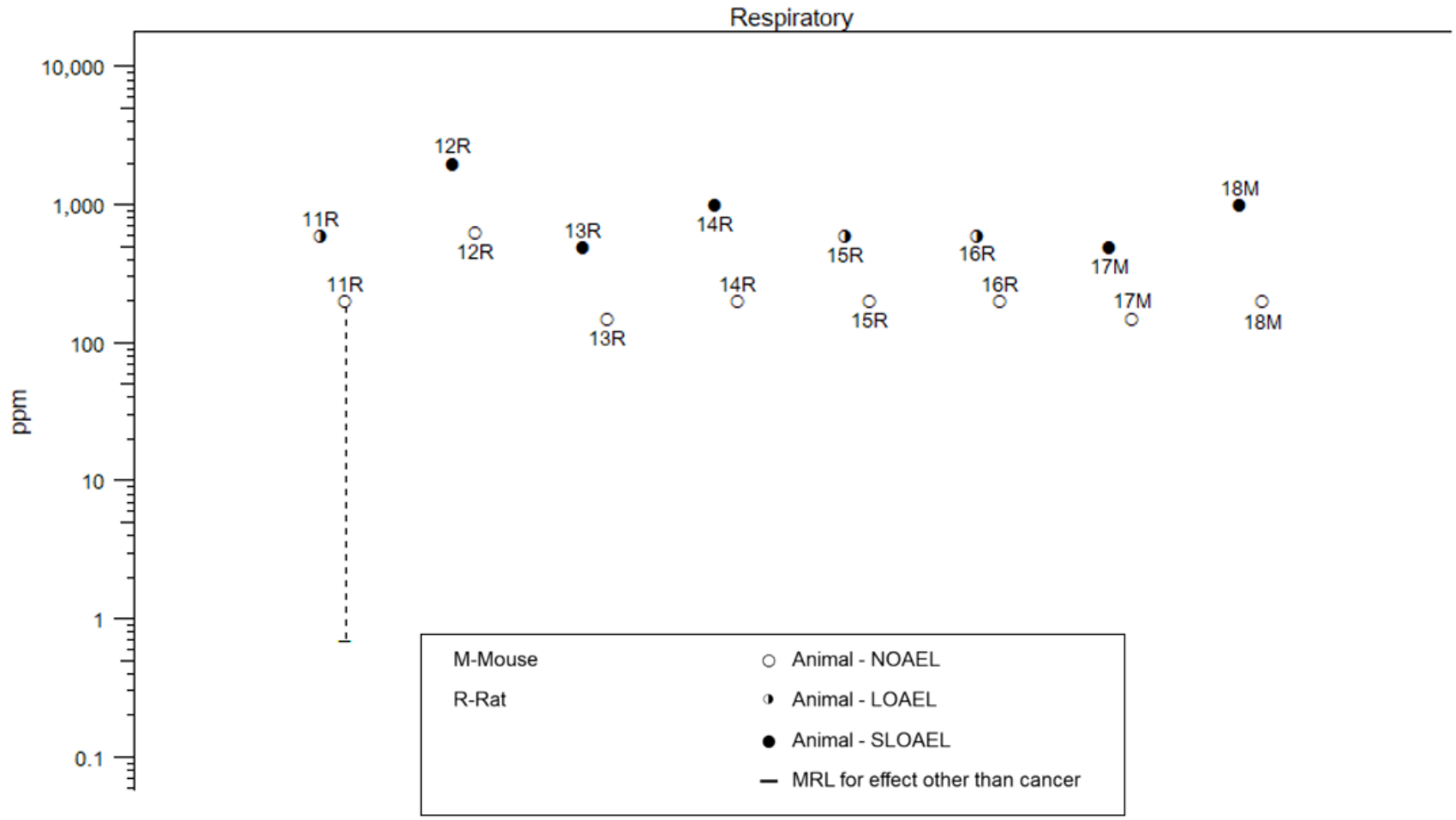


Figure 2-2. Levels of Significant Exposure to Vinyl Acetate – Inhalation Intermediate (15–364 days)

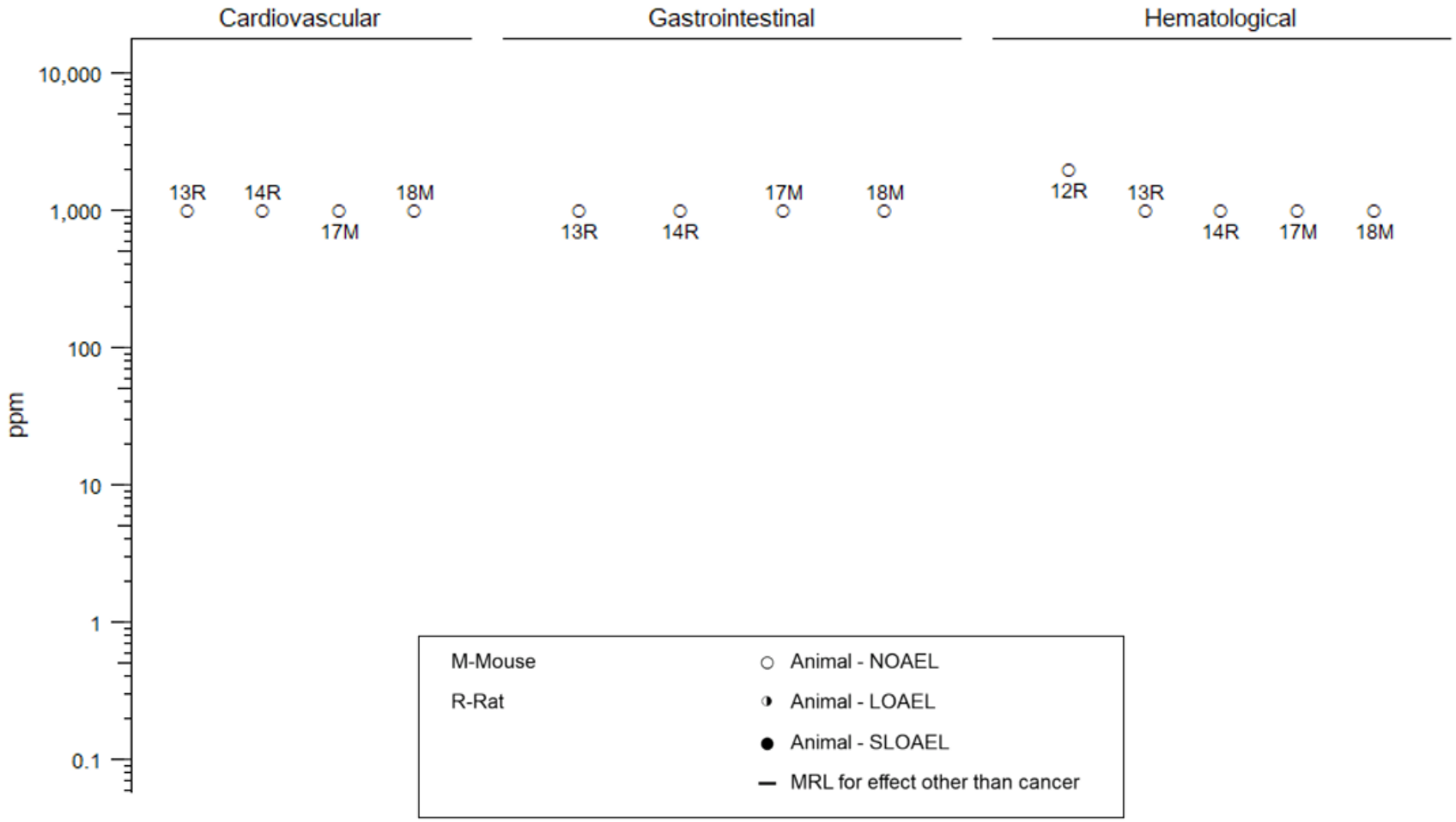


Figure 2-2. Levels of Significant Exposure to Vinyl Acetate – Inhalation Intermediate (15-364 days)

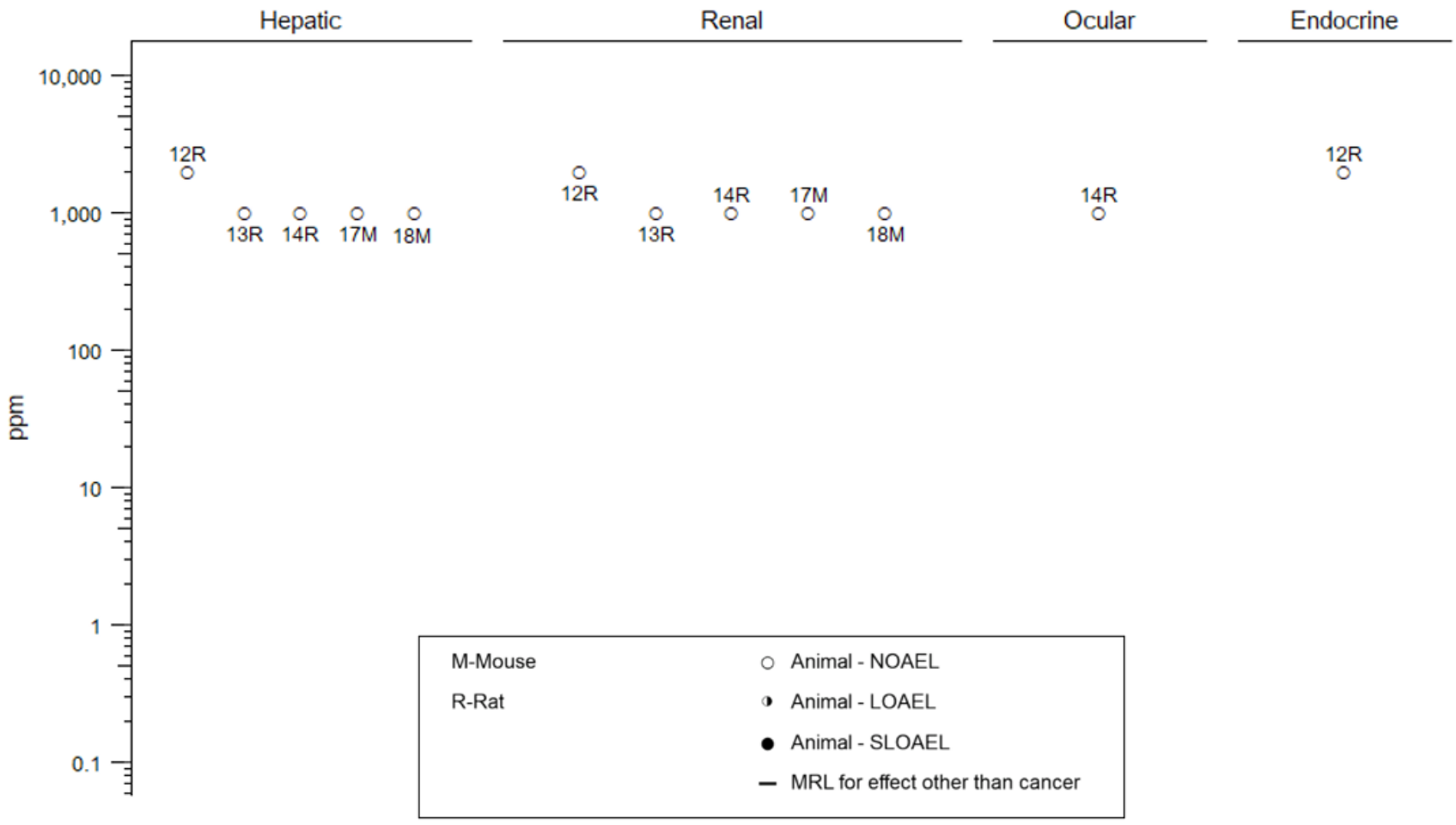


Figure 2-2. Levels of Significant Exposure to Vinyl Acetate – Inhalation Intermediate (15-364 days)

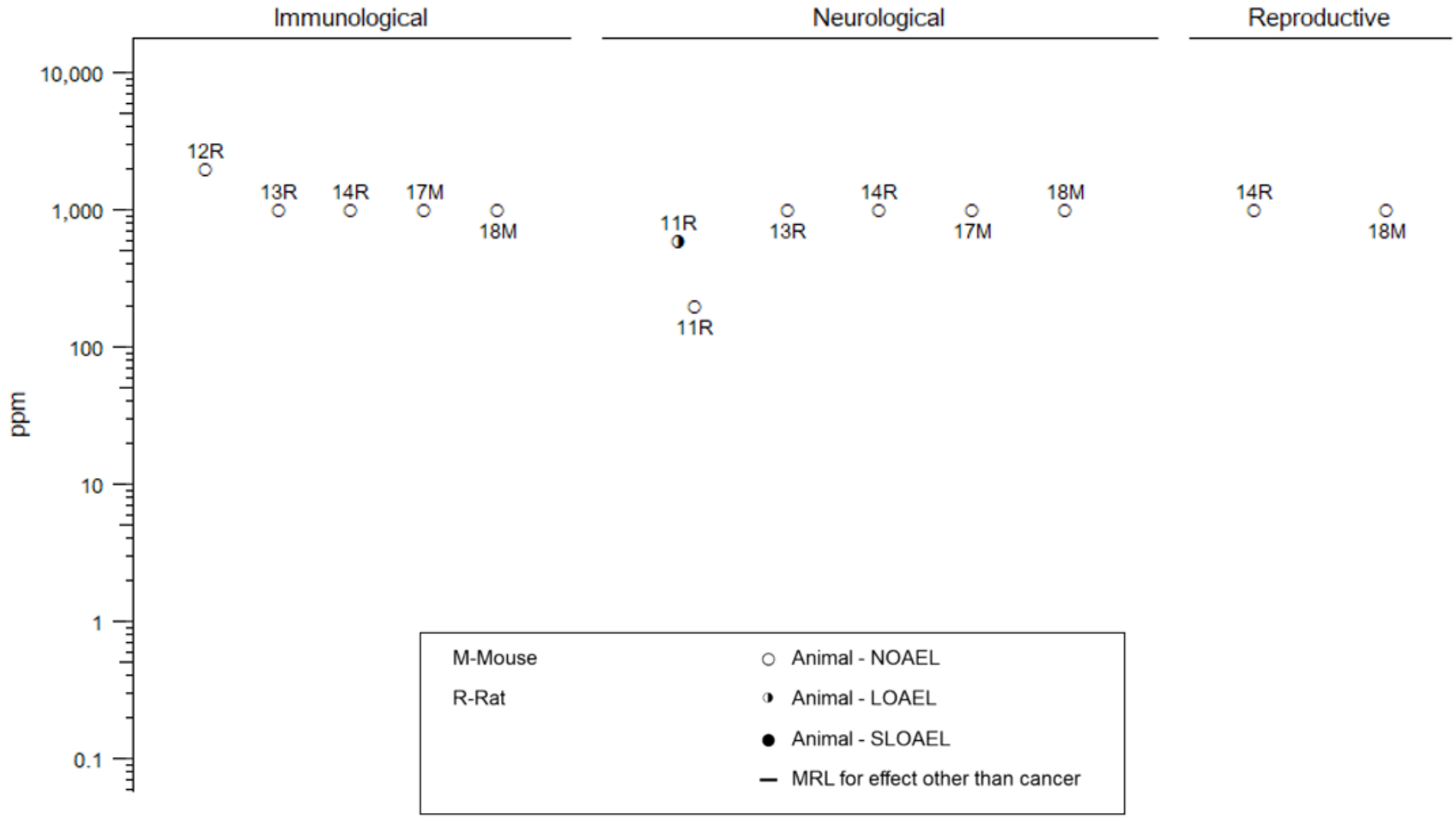


Figure 2-2. Levels of Significant Exposure to Vinyl Acetate – Inhalation Chronic (≥365 days)

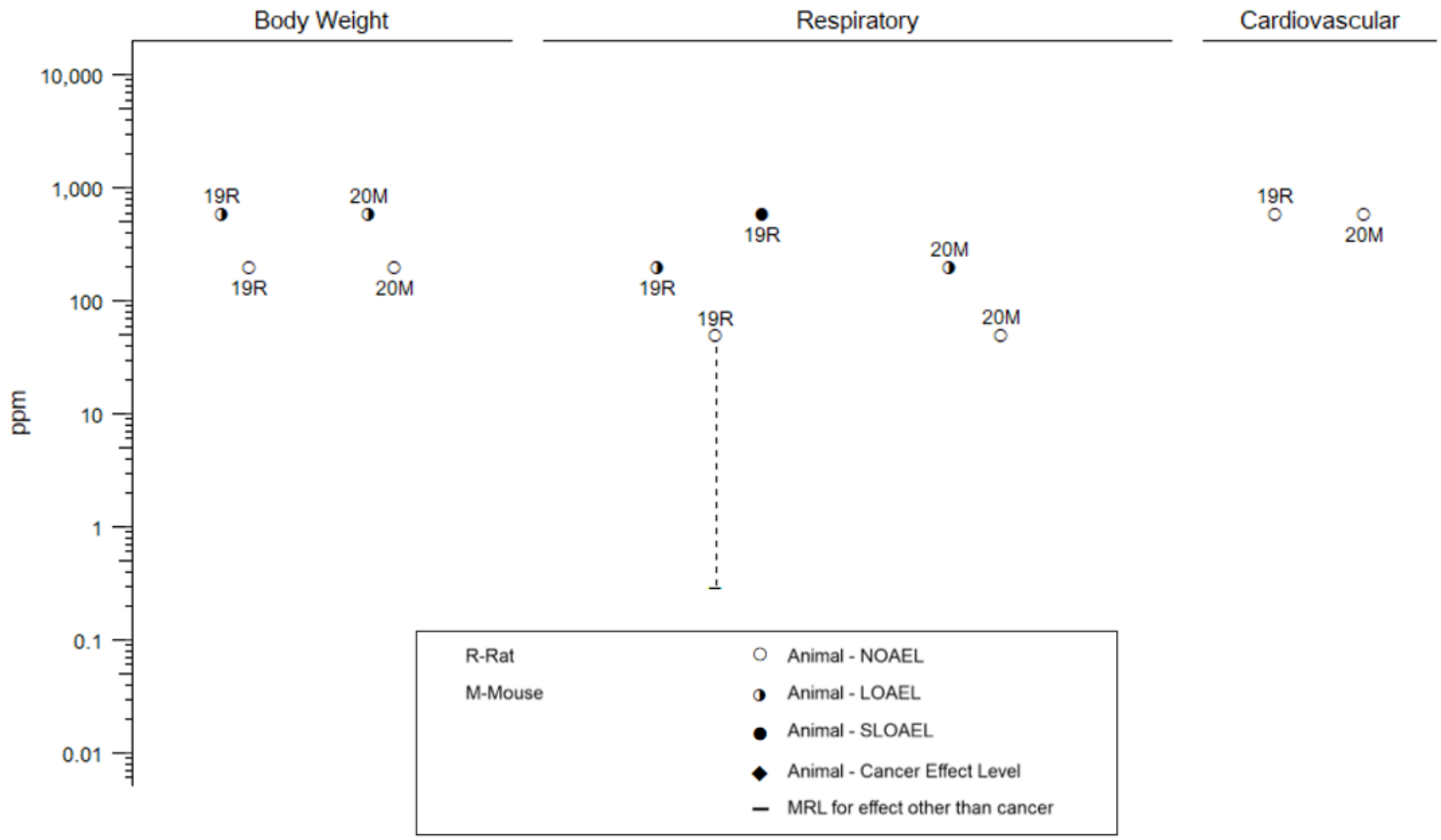


Figure 2-2. Levels of Significant Exposure to Vinyl Acetate – Inhalation Chronic (≥365 days)

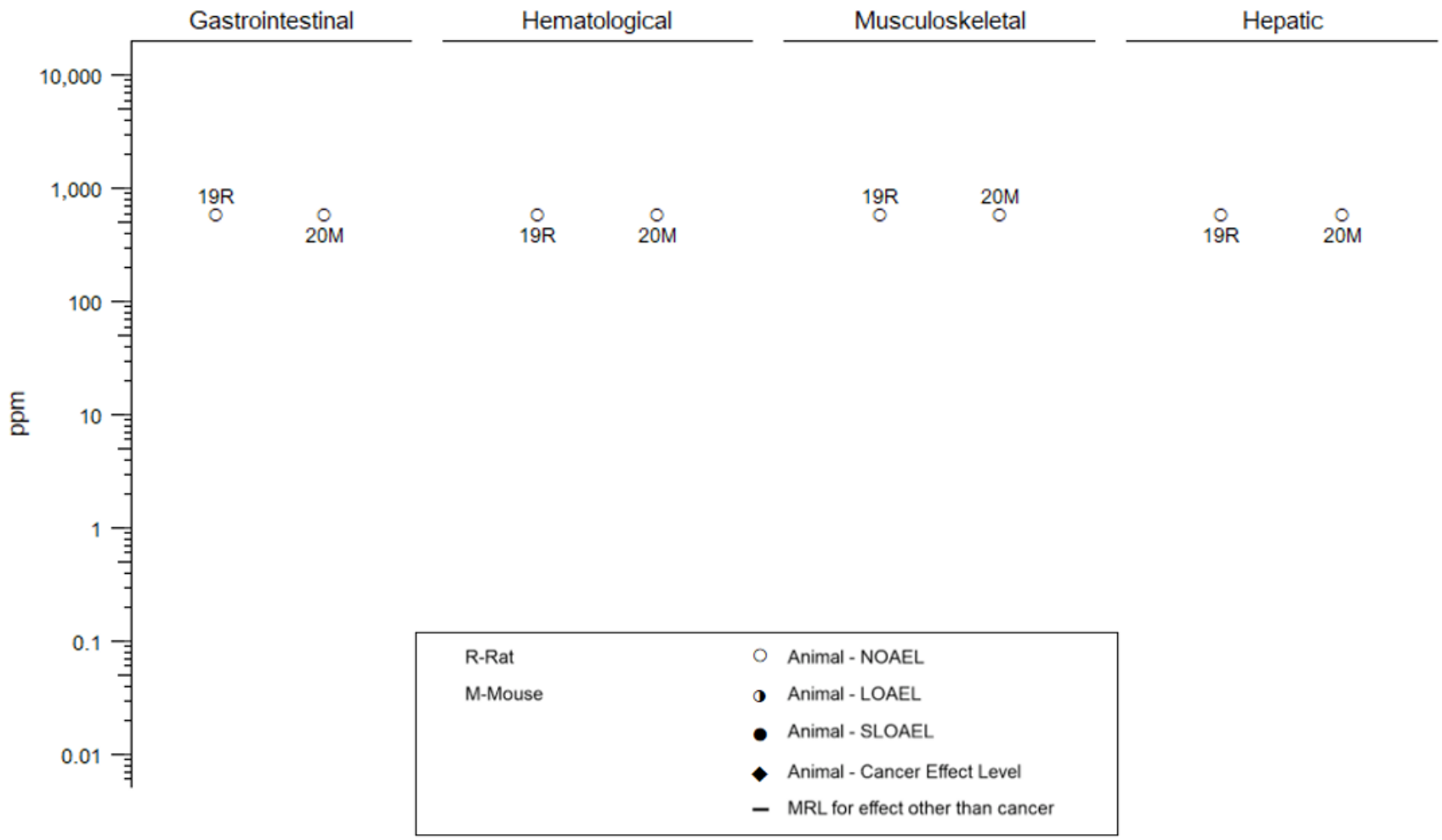


Figure 2-2. Levels of Significant Exposure to Vinyl Acetate – Inhalation Chronic (≥365 days)

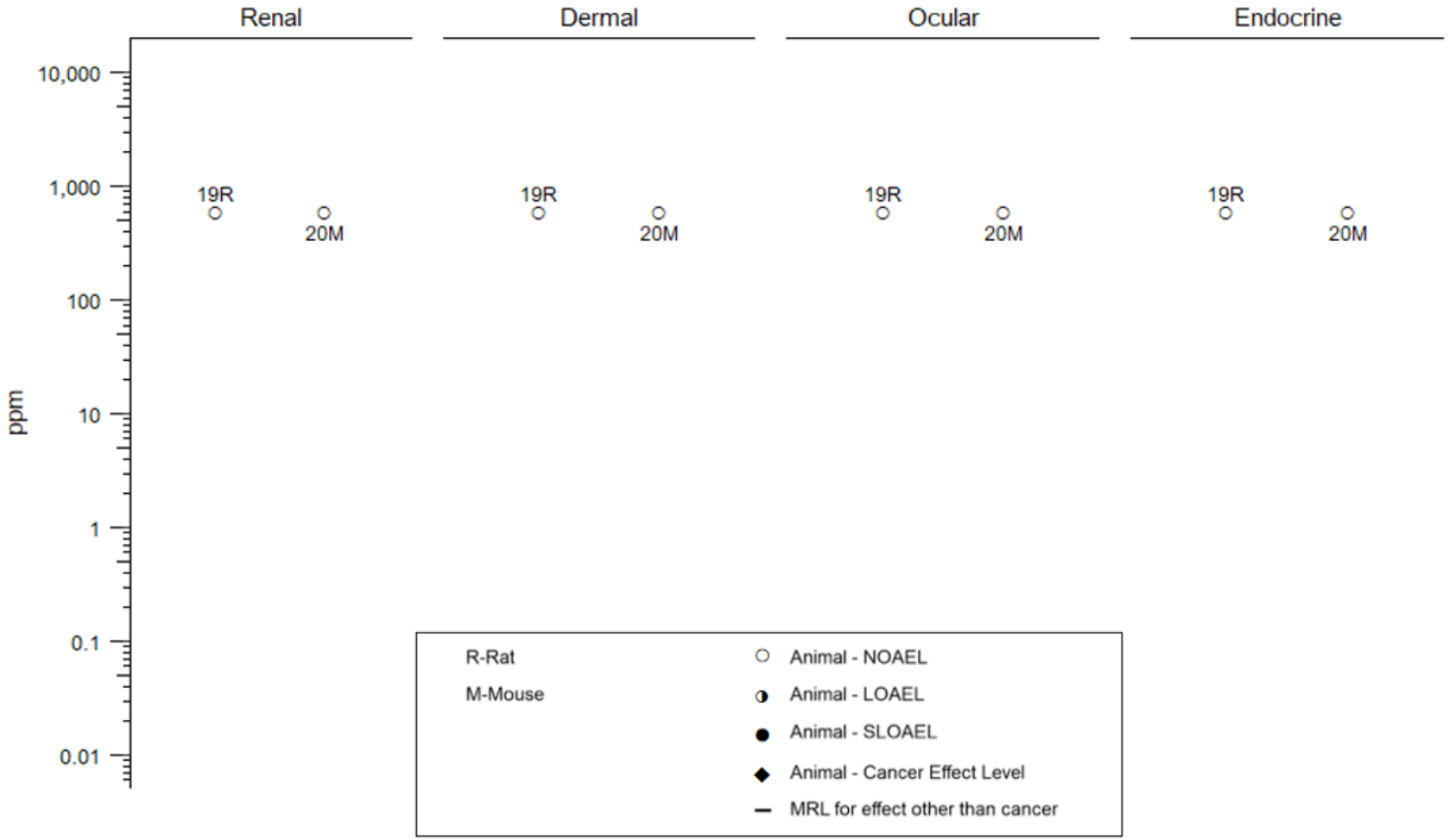
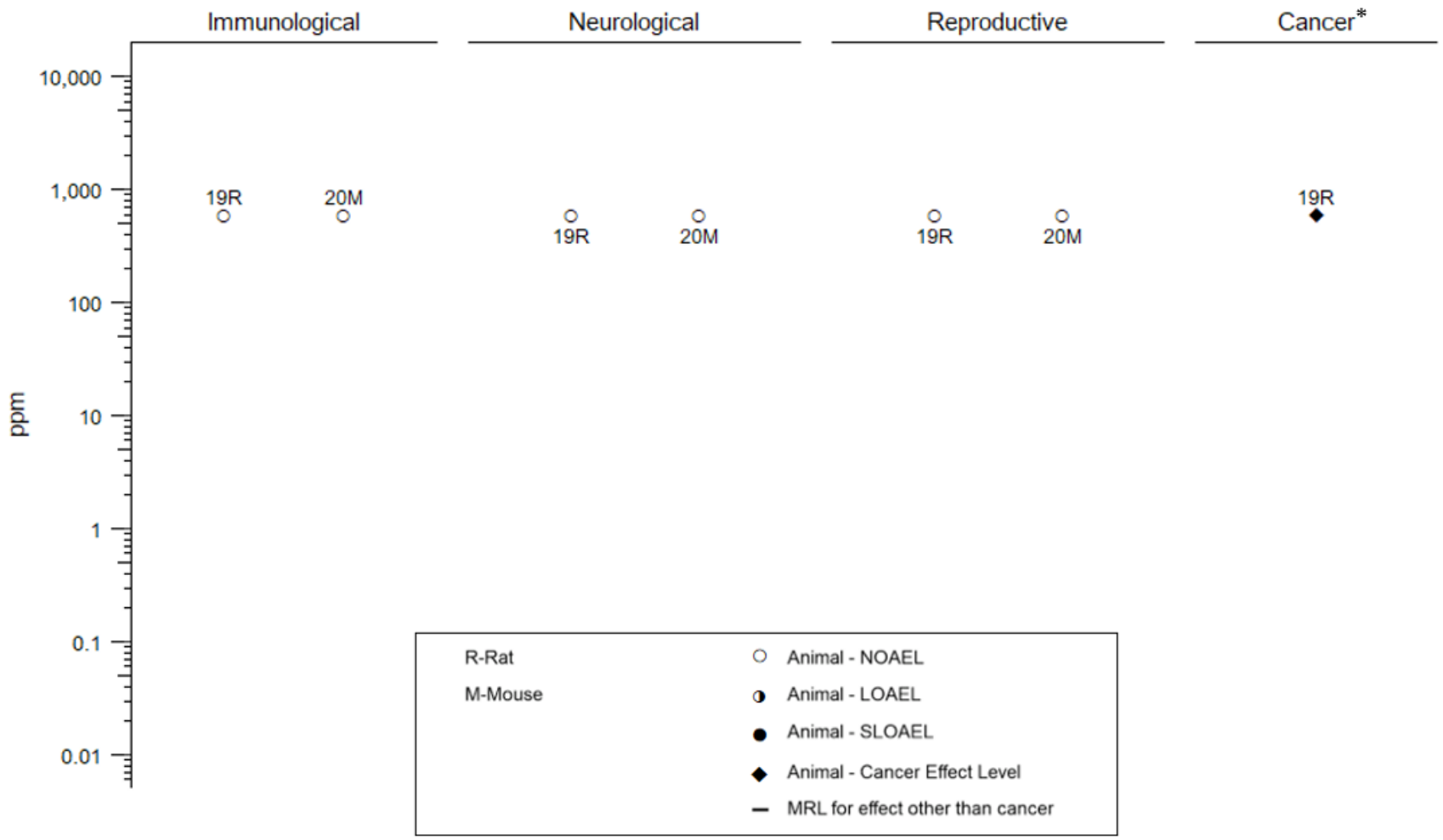


Figure 2-2. Levels of Significant Exposure to Vinyl Acetate – Inhalation Chronic (≥365 days)



*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)

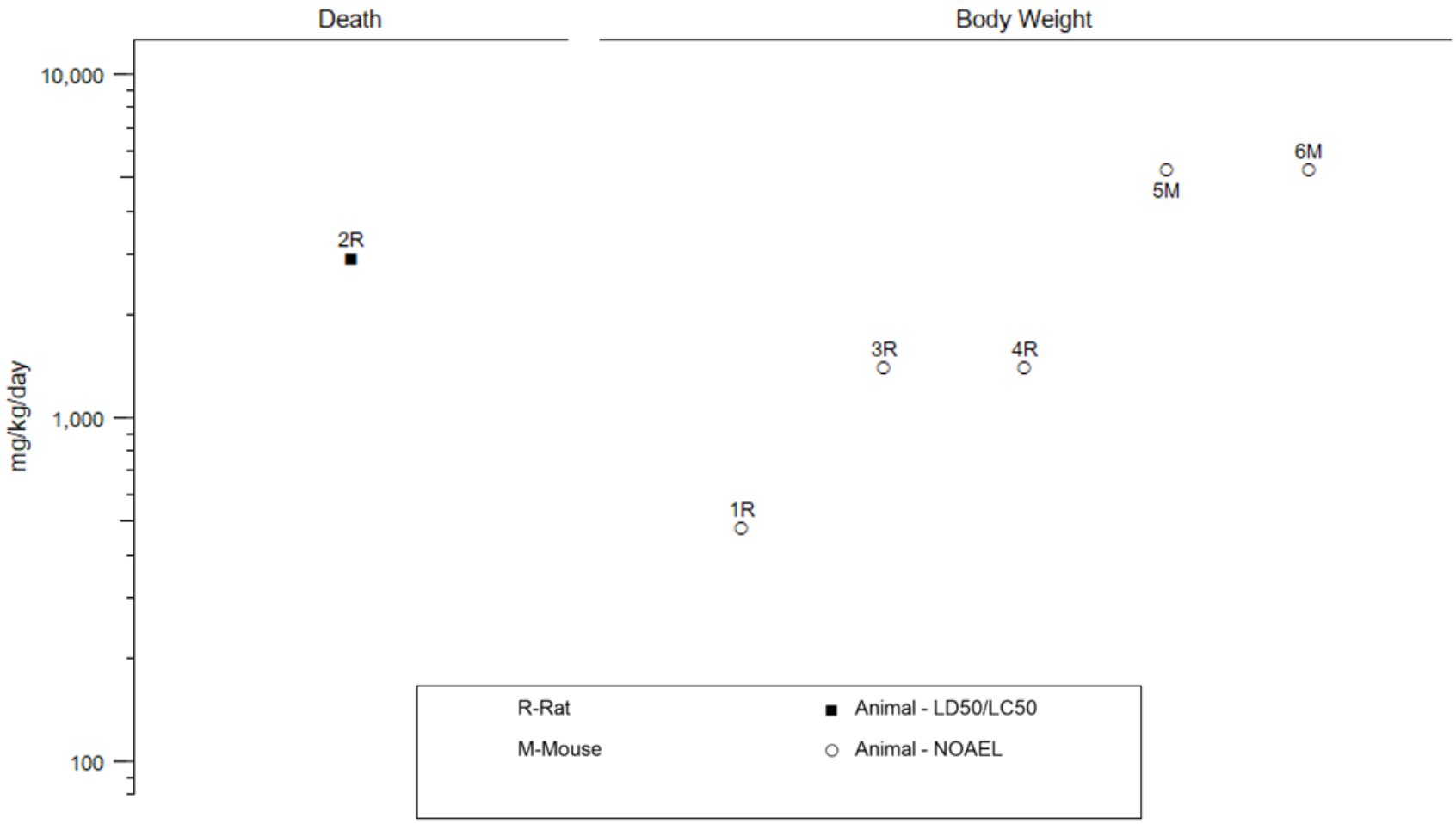


Figure 2-3. Levels of Significant Exposure to Vinyl Acetate – Oral Acute (≤14 days)

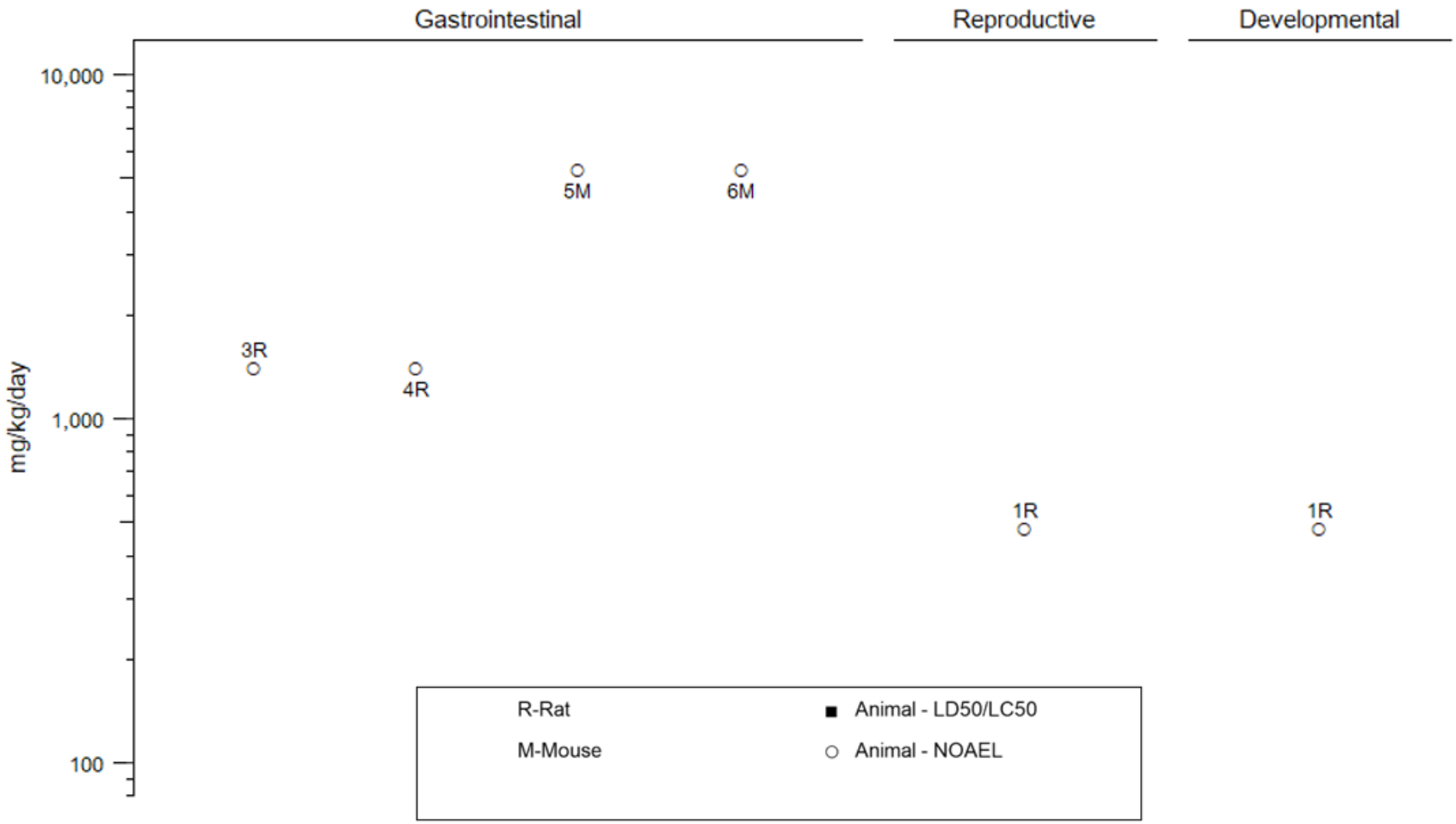


Figure 2-3. Levels of Significant Exposure to Vinyl Acetate – Oral Intermediate (15–364 days)

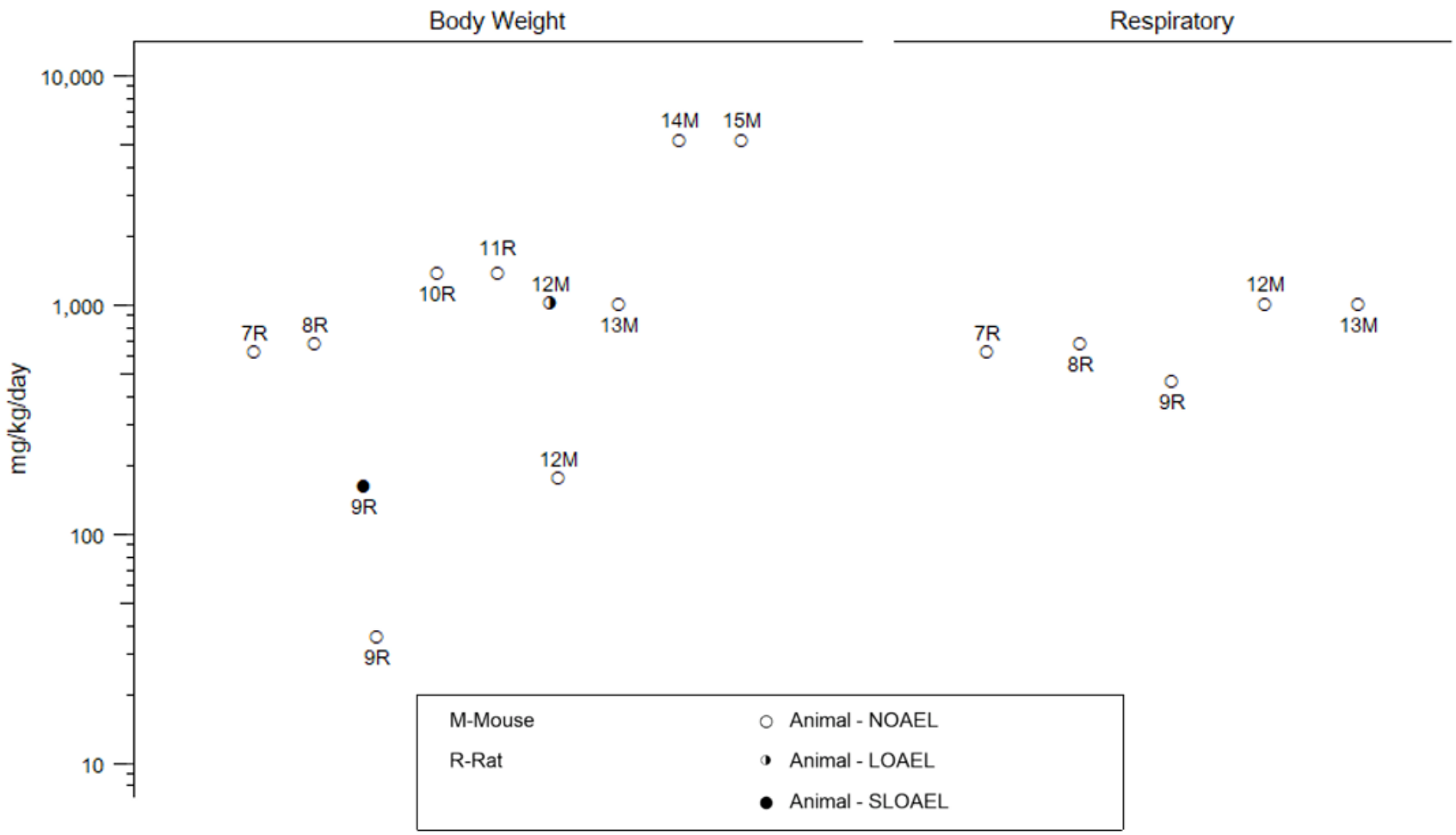


Figure 2-3. Levels of Significant Exposure to Vinyl Acetate – Oral Intermediate (15–364 days)

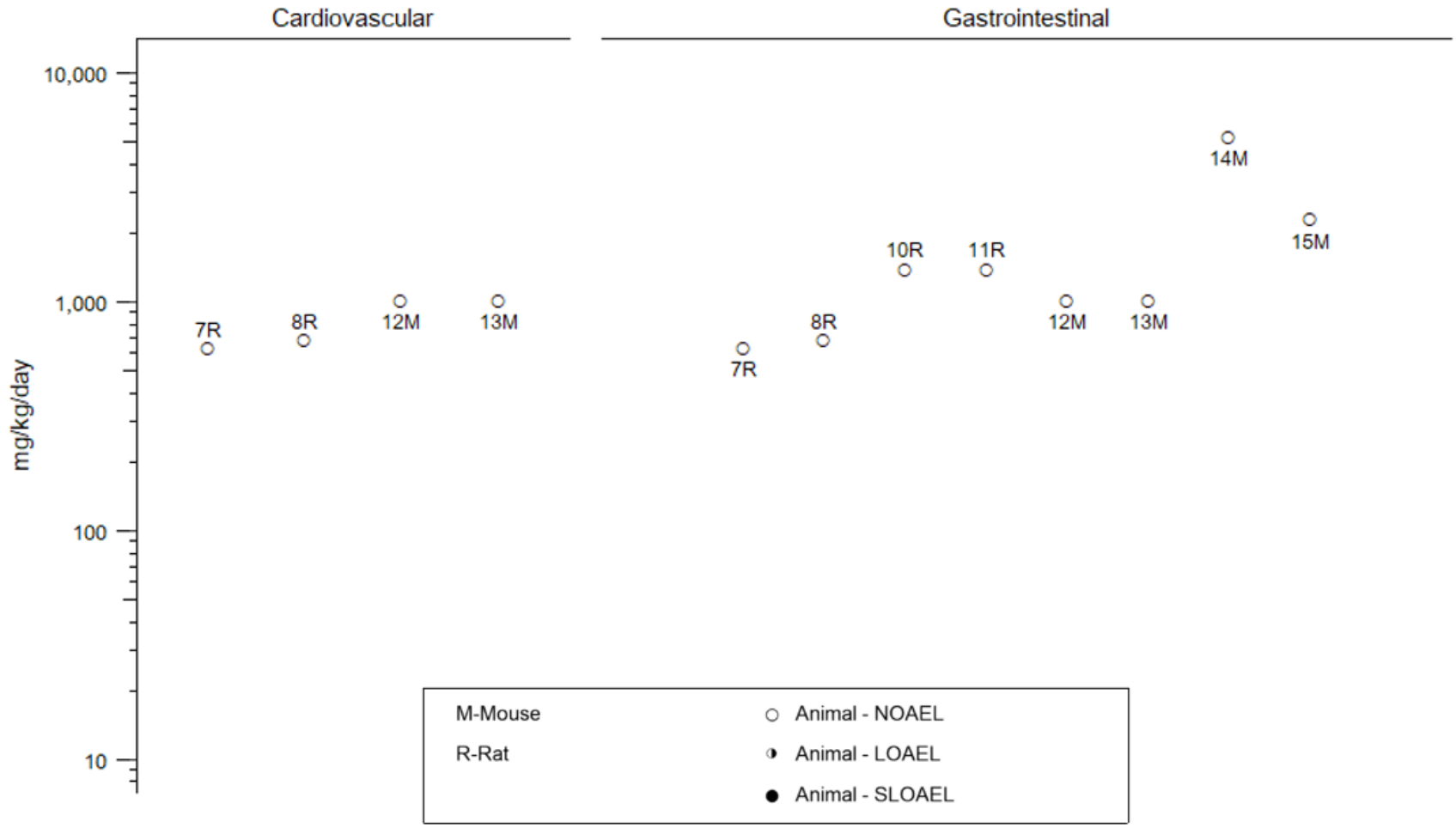


Figure 2-3. Levels of Significant Exposure to Vinyl Acetate – Oral Intermediate (15–364 days)

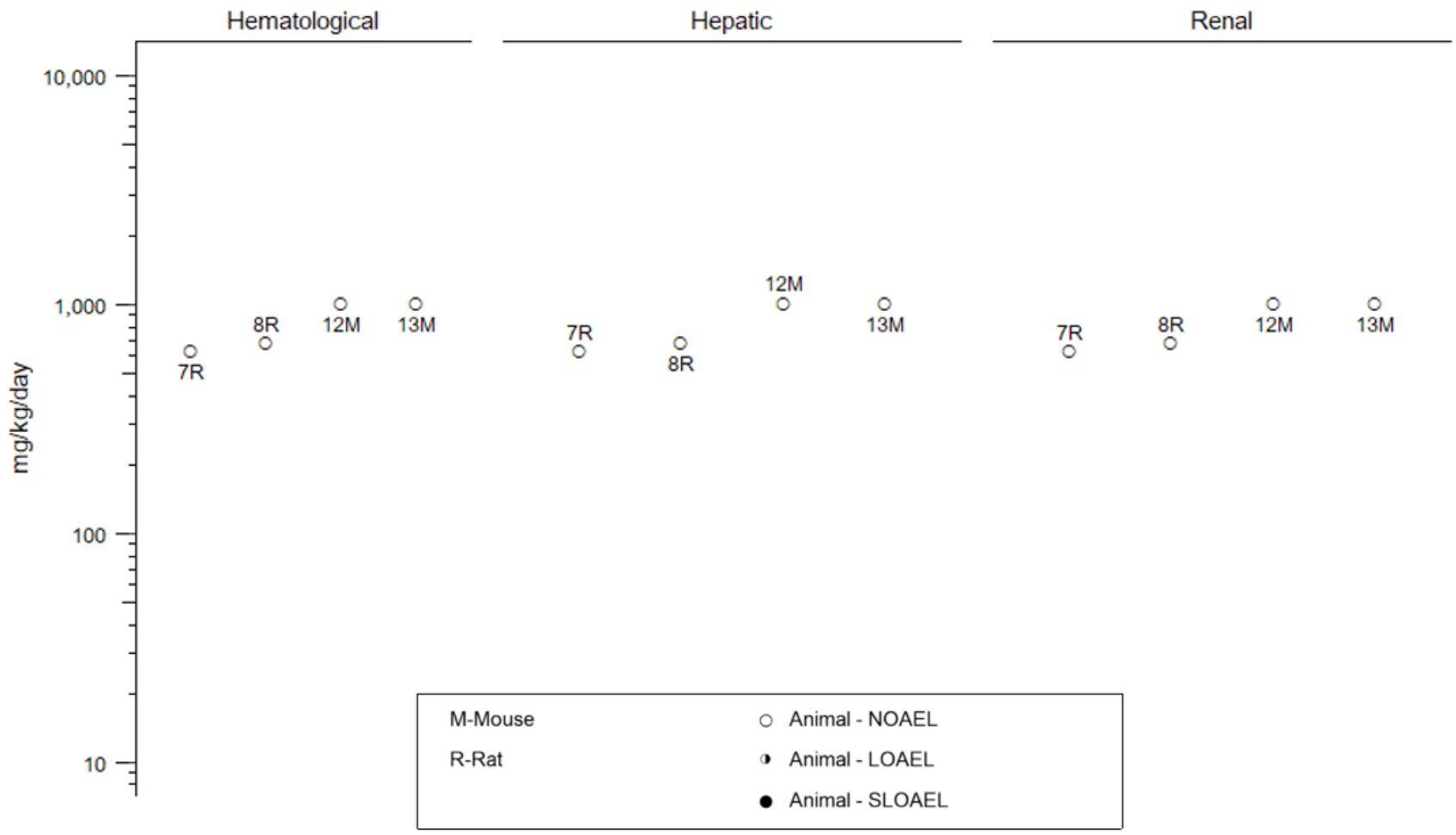


Figure 2-3. Levels of Significant Exposure to Vinyl Acetate – Oral Intermediate (15–364 days)

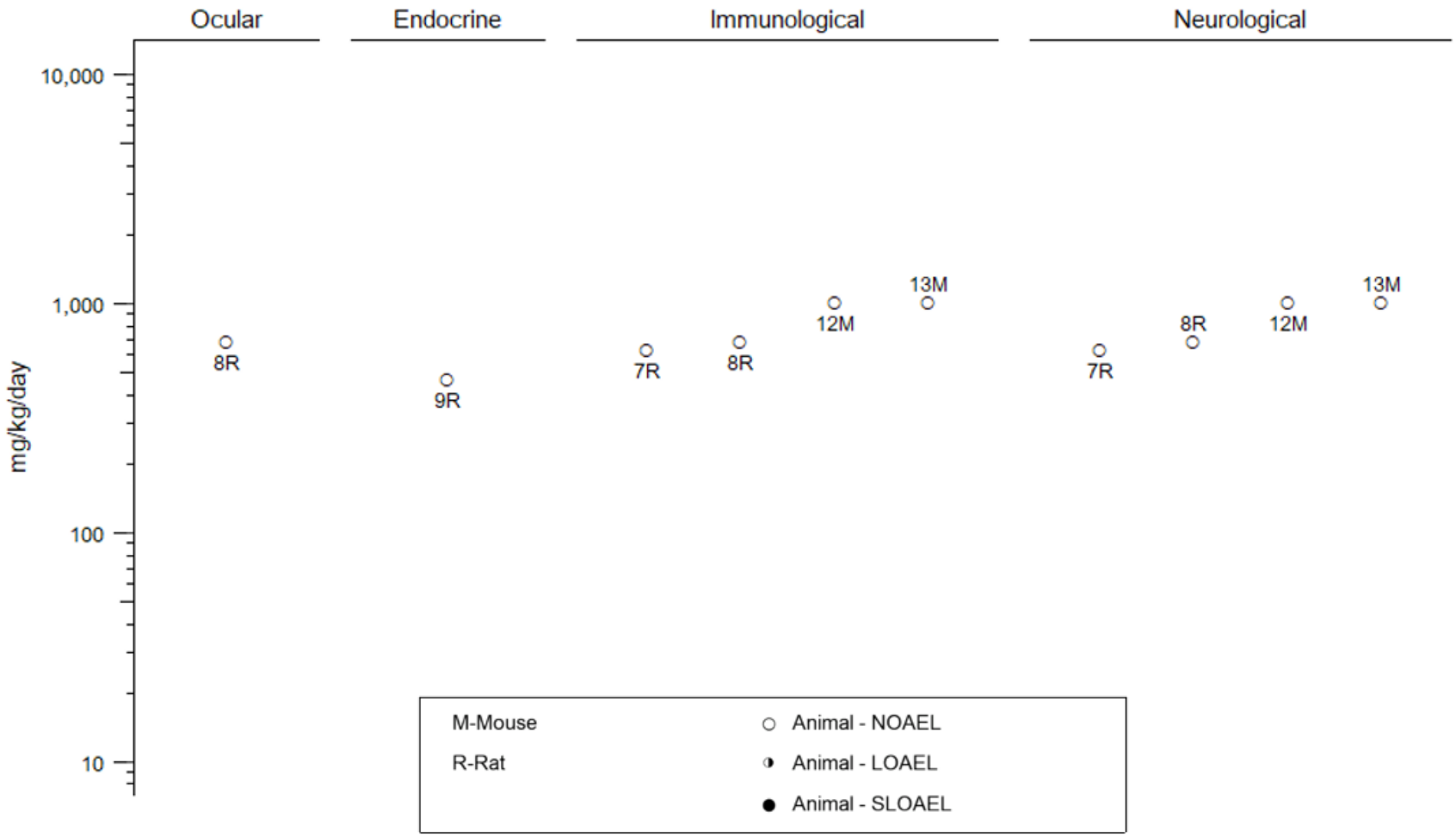


Figure 2-3. Levels of Significant Exposure to Vinyl Acetate – Oral Intermediate (15–364 days)

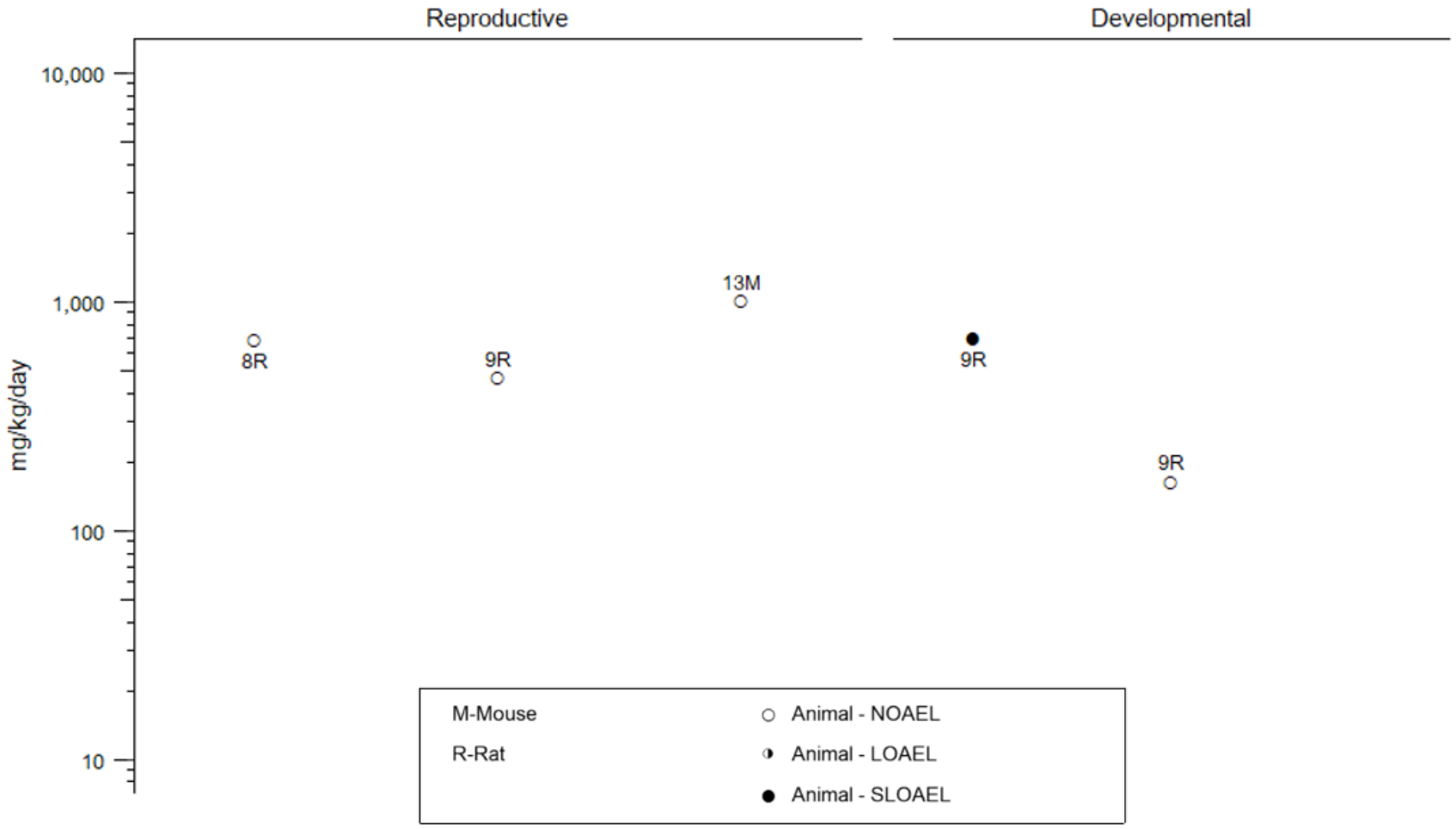


Figure 2-3. Levels of Significant Exposure to Vinyl Acetate – Oral Chronic (≥365 days)

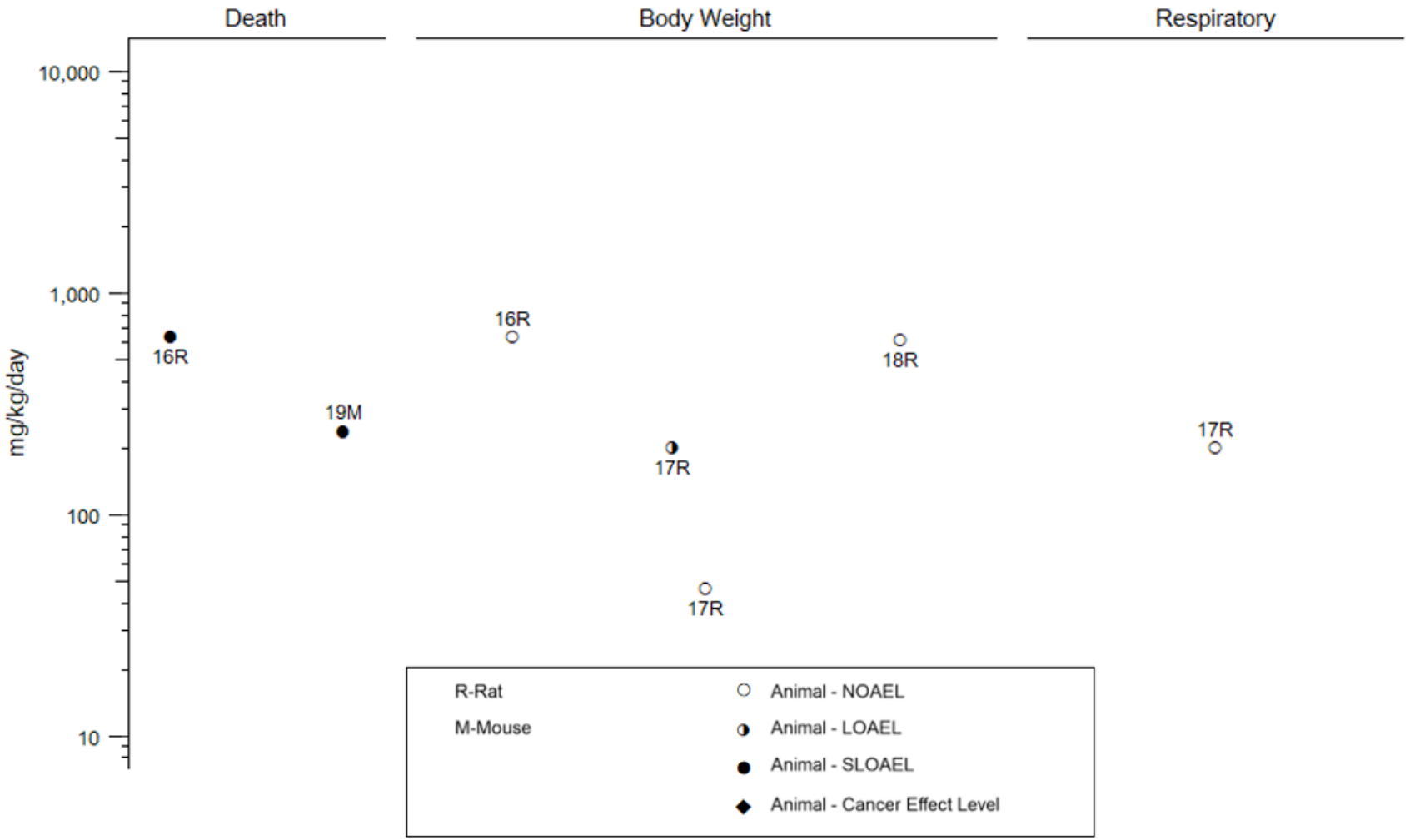


Figure 2-3. Levels of Significant Exposure to Vinyl Acetate – Oral Chronic (≥365 days)

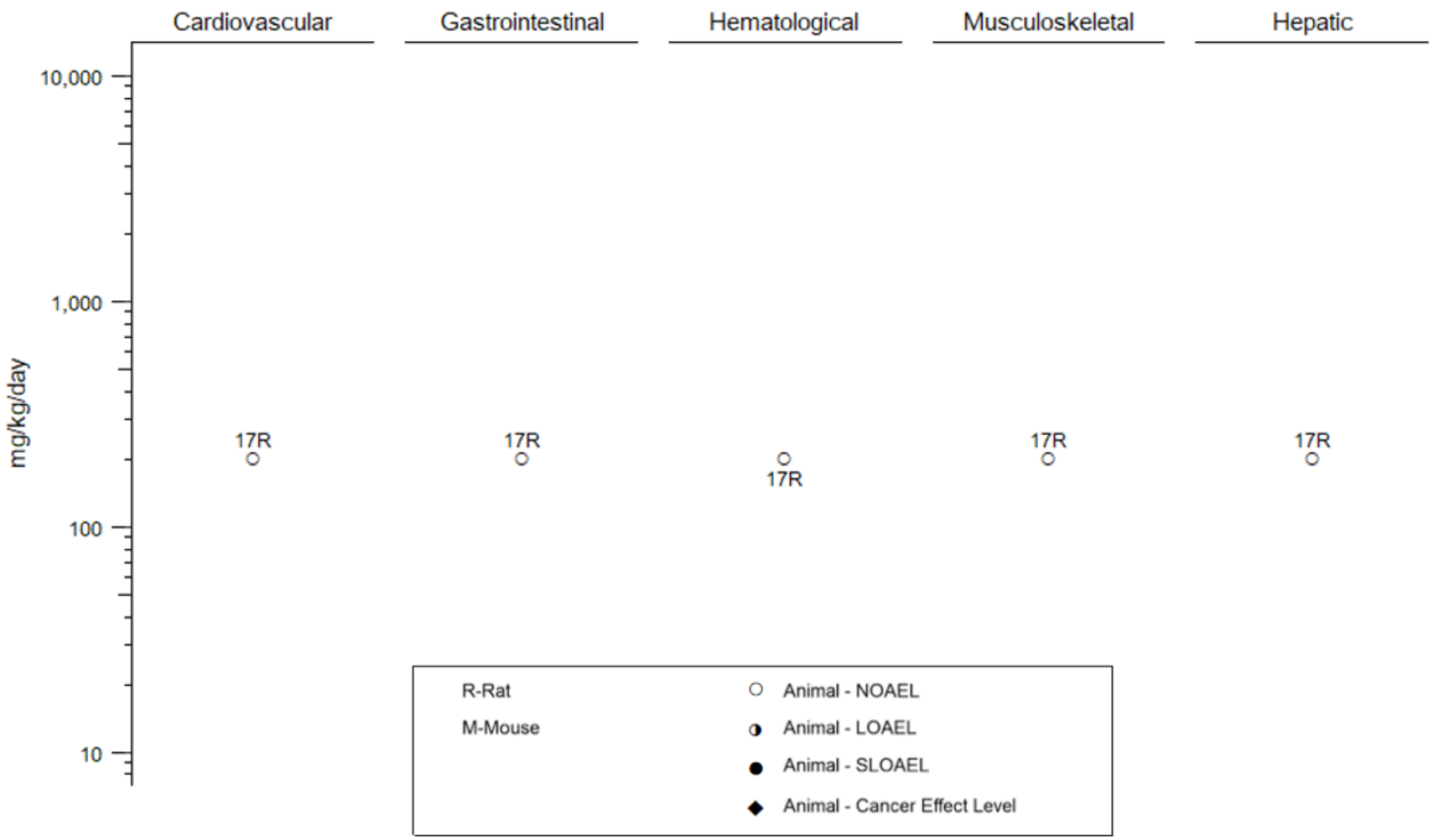


Figure 2-3. Levels of Significant Exposure to Vinyl Acetate – Oral Chronic (≥365 days)

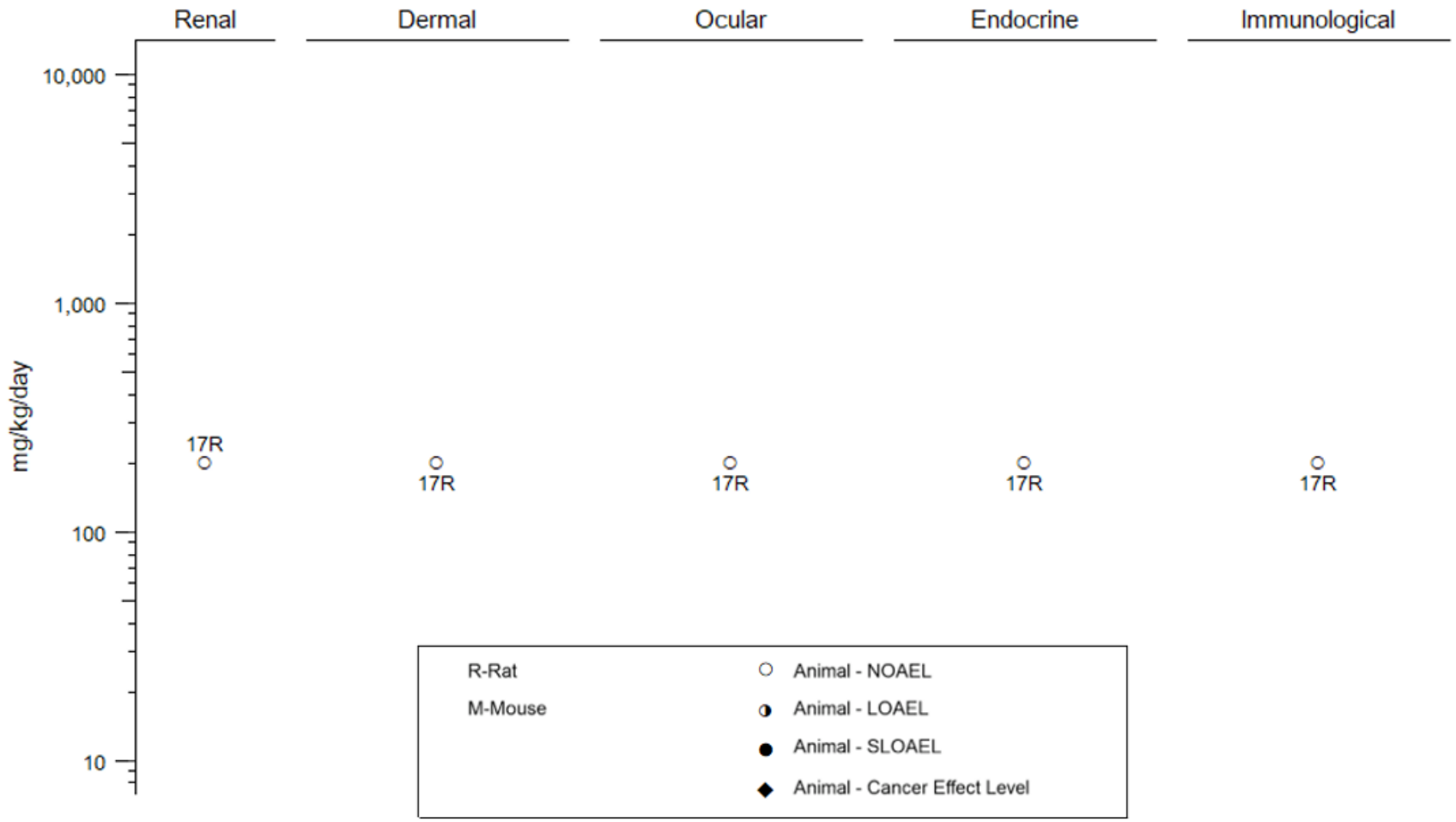
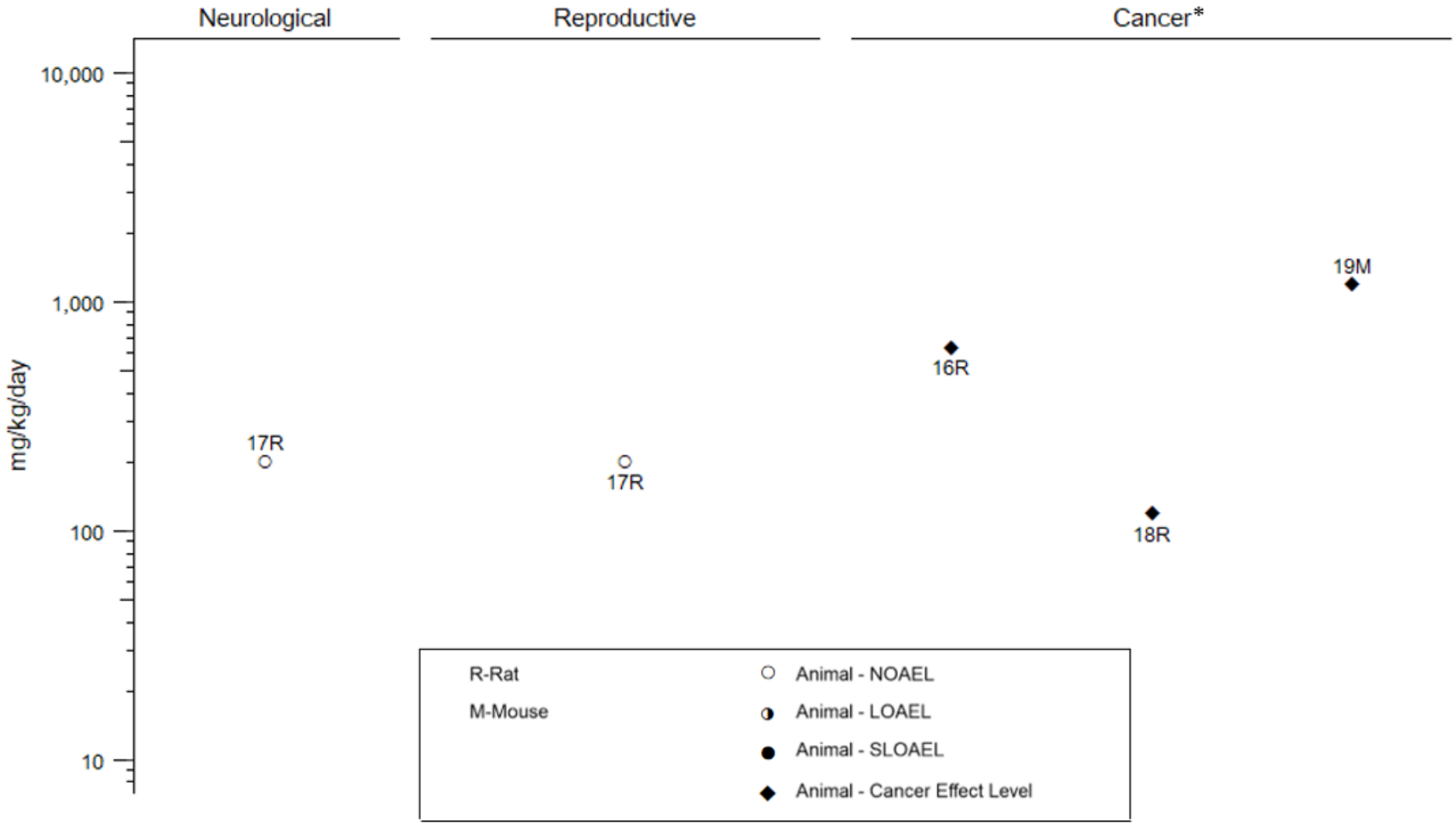


Figure 2-3. Levels of Significant Exposure to Vinyl Acetate – Oral Chronic (≥365 days)



*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).