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 chloride. 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. When available, mechanisms of action are discussed along with the health effects data; toxicokinetic mechanistic data are discussed in Section 3.1.

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 chloride, 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 chloride was also conducted; the results of this review are presented in Appendix C.

Human controlled exposure inhalation studies and animal inhalation studies are presented in Table 2-1 and Figure 2-2, and animal oral studies are presented in Table 2-2 and Figure 2-3; no dermal data were identified for vinyl chloride. Summaries of human observational studies are also provided by health effect in Tables 2-3 through 2-8.

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 chloride are indicated in Table 2-2 and Figure 2-3.

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

The health effects of vinyl chloride have been evaluated in epidemiological and laboratory animal studies. As illustrated in Figure 2-1, most of the health effects data come from inhalation exposure studies in humans and animals. Human and animal data are available for each health effect category and exposure duration category. The most examined endpoints were cancer (approximately 50%), hepatic (approximately 40%), and neurological (10%). Only five animal studies evaluated toxicity following oral exposure and these studies examined a limited number of endpoints (death, body weight, hematological, hepatic, and cancer). The oral animal data are derived from chronic-duration studies only. Many of the available human studies for vinyl chloride are characterized as case reports/series or occupational health studies of vinyl chloride workers. These studies are often limited by the absence of exposure data or a comparison group; however, they were conducted during a time period where workers were highly exposed to vinyl chloride and provide important information on vinyl chloride hazards. The human database also contains many cohort, cross-sectional, and case-control studies of vinyl chloride health effects, especially for hepatic and cancer outcomes.

The human and animal studies suggest several sensitive targets of vinyl chloride toxicity.

- **Hepatic endpoints:** Hepatic effects are a presumed health effect for humans based on evidence of fibrosis, cirrhosis, and steatohepatitis in vinyl chloride workers following chronic-duration inhalation exposure. Moderate evidence of hepatic effects in animals includes increased liver weight and histopathological liver lesions in rats and mice following intermediate- and chronic-duration inhalation and chronic-duration oral exposure.

- **Immune endpoints:** Immunological effects are a suspected health effect based on an increase in circulating immune complexes, immunoglobulins, complement factors, and levels of inflammatory cytokines in occupational worker studies. Limited evidence in animal studies includes increases in spleen weight and spontaneous and mitogen-stimulated lymphocyte proliferation.

- **Neurological endpoints:** Neurological effects are a presumed health effect for humans based on limited information including neurological symptom reporting and a single report of peripheral neuropathy in humans. There is a moderate level of evidence in animal studies based on clinical signs in multiple acute-duration inhalation studies.

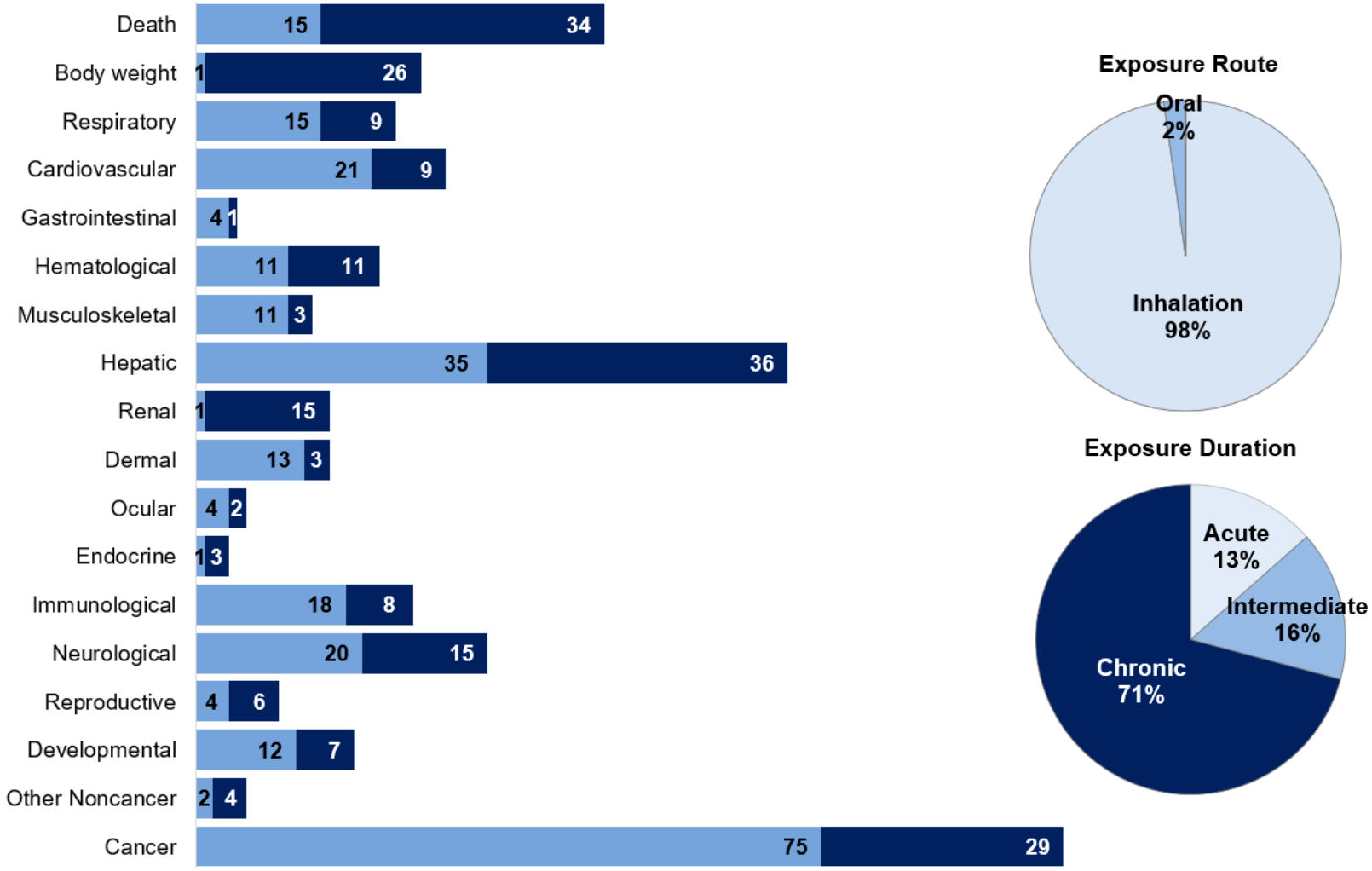
- **Developmental endpoints.** Developmental effects are a suspected health effect for humans based on strong evidence from acute-duration inhalation exposures in mice and rabbits. The most sensitive developmental endpoint was delayed ossification in mice following prenatal inhalation exposure. Human data were limited to a small number of ecological and case-control studies that did not report developmental effects.

- **Other noncancer endpoints.** Limited evidence of increased insulin resistance in humans was based on two epidemiology studies with altered serum biomarkers of this effect. Insulin resistance was not observed in several intermediate-duration inhalation studies in mice; however, these studies used only a single low concentration of vinyl chloride (0.85 ppm) and did not evaluate effects at higher concentrations.

- **Cancer endpoints.** The development of cancer in humans as a result of vinyl chloride exposure has been demonstrated in a number of studies of workers in the vinyl chloride production industry. The strongest evidence is for liver angiosarcoma; however, other liver tumors, including hepatocellular carcinoma and cholangiocellular carcinoma, have also been associated with occupational exposure to vinyl chloride. Data from studies in rats, mice, and hamsters support the conclusion that vinyl chloride is carcinogenic. Several tumor types were observed in animal studies, including hemangiosarcoma in liver, skin, and spleen, stomach angiosarcoma, mammary gland carcinoma, Zymbal’s gland carcinoma, and nephroblastoma.

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

Most studies examined the potential for cancer and hepatic and neurological effects of vinyl chloride
Fewer studies evaluated health effects in **animals** than **humans** (counts represent studies examining endpoint)



*Includes studies discussed in Chapter 2. A total of 224 studies (including those finding no effect) have examined toxicity; most studies examined multiple endpoints.

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
ACUTE EXPOSURE									
Lester et al. 1963									
1	Human 3 M, 3 F	3 days 2 times/day 5 minutes	0, 4,000, 8,000, 12,000, 16,000, 20,000	CS	Neuro	8,000	12,000		Dizziness
Patty et al. 1930									
2	Human 2 NS	3 minutes	25,000	CS	Neuro		25,000		Dizziness, disorientation
Hehir et al. 1981									
3	Rat (Fischer-344) 85–92M, 79–100 F	1 hour (WB)	0, 50, 500, 5,000, 50,000	CS, BW, GN, HP	Bd wt	50,000			
					Neuro	50,000			
Hehir et al. 1981									
4	Rat (Fischer-344) 50–90 M, 50–90 F	2 weeks 5 days/week 1 hour/day (WB)	0, 500	CS, BW, HP	Bd wt	500			
					Neuro	500			
Jaeger et al. 1974									
5	Rat (Sprague-Dawley) 2–5 M	1, 5 days 6 hours/day	0, 5,000, 50,000, 100,000	CS, BC, HP	Hepatic	50,000	100,000		Hepatocellular vacuolization, increased alanine-α-ketoglutarate transaminase and SDH
					Neuro	50,000		100,000	Anesthesia
John et al. 1977, 1981									
6	Rat (Sprague-Dawley) 16–31 F	GDs 6–15 10 days 7 hours/day (WB)	0, 500, 2,500	LE, BW, FI, OW, DX	Hepatic	500	2,500		9 or 10% increase in absolute and relative liver weight, respectively
					Develop	500	2,500		Ureter dilation

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Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Lester et al. 1963									
7	Rat (Sherman) 2 NS	2 hours	50,000, 60,000, 70,000, 100,000, 150,000	LE, CS, GN, HP	Death			150,000	½ died
					Resp			150,000	Edema and congestion in lungs
					Neuro		50,000	70,000	LOAEL: moderate intoxication SLOAEL: loss of righting reflex
Mastromatteo et al. 1960									
8	Rat (NS) 5 NS	30 minutes	0, 100,000, 200,000, 300,000	LE, CS, GN, HP	Death			300,000	5/5 died
					Resp		100,000		Lung hyperemia
					Hepatic	100,000	200,000		Fatty infiltration changes
					Renal	200,000	300,000		Renal congestion
					Neuro			100,000	Narcosis
Prodan et al. 1975									
9	Rat (NS) 10–30 NS	2 hours 1 time	146,625–205,275	LE, CS	Death			146,625	7/30 died
Reynolds et al. 1975a									
10	Rat (Holtzman) M	1, 5 days 6 hours/day	50,000	GN, HP	Hepatic	50,000			
Reynolds et al. 1975b									
11	Rat (NS) M	1 day 6 hours/day	50,000	BC, HP	Hepatic	50,000			
Thornton et al. 2002									
12	Rat (Sprague-Dawley) 25 F	GDs 6–19 6 hours/day (WB)	0, 10, 100, 1,100	LE, CS, BW, FI, GN, OW, DX	Bd wt	1,100			
					Hepatic	1,100			
					Renal	10	100		20% increase in relative kidney weight
					Develop	1,100			

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Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Hehir et al. 1981									
13	Mouse (ICR) 82 or 90 M, 88 or 90 F	1 hour (WB)	0, 50, 500, 5,000, 50,000	CS, BW, GN, HP	Bd wt	50,000			
					Resp	50	500	50,000	LOAEL: pneumonitis SLOAEL: hyperventilation, respiratory difficulties
					Cardio	50,000			
					Gastro	50,000			
					Musc/skel	50,000			
					Hepatic	50,000			
					Renal	50,000			
					Ocular	50,000			
					Immuno	50,000			
					Neuro	5,000		50,000	50% of males with twitching, ataxia; 25% of females with hyperactivity, ataxia
					Cancer			5,000	CEL: 24/143 bronchioalveolar adenoma
John et al. 1977, 1981									
14	Mouse (CF-1) 19–26 F	GDs 6–15 10 days 7 hours/day (WB)	0, 50, 500	LE, BW, FI, OW, DX	Death			500	5/29 died
					Hepatic	500			
					Develop	50[b]	500		Delayed ossification of skull and sternebrae; unfused sternebrae
Mastromatteo et al. 1960									
15	Mouse (NS) 5 NS	30 minutes	0, 100,000, 200,000, 300,000	LE, CS, GN, HP	Death			200,000	1/5 died
					Resp		100,000		Lung hyperemia
					Hepatic	200,000	300,000		Liver congestion
					Renal		100,000		Degenerative tubular epithelium
					Neuro			100,000	Narcosis

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Prodan et al. 1975									
16	Mouse (NS) 20–90 NS	2 hours 1 time	87,975–195,500	LE, CS	Death			107,525	15/61 died
John et al. 1977, 1981									
17	Rabbit (New Zealand) 5–20 F	GDs 6–18 13 days 7 hours/day	0, 500, 2,500	LE, BW, FI, OW, DX	Hepatic	2,500			
					Develop		500		38% of fetuses with delayed ossification of sternebrae; 16% of fetuses with delayed ossification at 2,500 ppm
Prodan et al. 1975									
18	Rabbit (NS) 4 NS	2 hours 1 time	195,500 to 273,700	LE, CS, GN	Death			224,825	¼ died
Mastromatteo et al. 1960									
19	Guinea pig (NS) 5 NS	30 minutes	0, 100,000, 200,000, 300,000, 400,000	LE, CS, GN, HP	Death			300,000	1/5 died
					Resp		100,000		Slight pulmonary hyperemia
					Cardio	400,000			
					Hepatic	200,000	300,000		Fatty degeneration
					Ocular	400,000			
					Endocr	400,000			
					Immuno	400,000			
					Neuro			100,000	Tremor, loss of consciousness
Patty et al. 1930									
20	Guinea pig (NS) 3–6, 18 NS	Up to 8 hours	0, 5,000, 10,000, 25,000, 50,000, 100,000, 150,000–250,000, 400,000	LE, CS, GN	Death			100,000	Death (incidence not reported)
					Neuro	10,000		25,000	Narcosis

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Prodan et al. 1975									
21	Guinea pig (NS) 4–12 NS	2 hours 1 time	195,500–273,700	LE, CS	Death			224,825	1/6 died
INTERMEDIATE EXPOSURE									
Bi et al. 1985									
22	Rat (Wistar) 38 M	3, 6 months 6 days/week 6 hours/day	0, 11.1, 105.6, 2,918	BW, GN, OW, HP	Bd wt	11.1	105.6		15–17% decreased bodyweight at 3 and 6 months
					Cardio	2,918			
					Hepatic		11.1		Dose response with 14-68% increased relative liver weights at 6 months
					Renal		2,918		12% increased relative kidney weight at 3 months
					Immuno	2,918			
					Repro		105.6		8–11% decreased relative testes weight with testicular necrosis at 6 months
Drew et al. 1983									
23	Rat (Fischer-344) 112–224 F	6 months 5 days/week 6 hours/day	0, 100	LE, HP	Cancer			100	CEL: hepatic hemangiosarcoma, hepatocellular carcinoma, neoplastic nodules; mammary fibroadenoma
Froment et al. 1994									
24	Rat (Sprague-Dawley) 22 M, 22 F	33 days 6 days/week 8 hours/day	0, 500	LE, CS, GN, HP	Cancer			500 M	CEL: hepatocellular carcinoma, angiosarcoma of the liver, benign cholangioma, nephroblastoma, angiomyoma, leukemia, Zymbal gland carcinoma, pituitary adenoma, mammary carcinoma and fibroma

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Hehir et al. 1981									
25	Rat (Fischer-344) 50–90 M, 50–90 F	20 weeks 5 days/week 1 hour/day (WB)	0, 50	CS, BW	Bd wt	50			
					Neuro	50			
Hong et al. 1981									
26	Rat (CD) 4-16 M, 4–16 F	1–10 months 5 days/week 6 hours/day	0, 50, 250, 1,000	LE, BW, FI, HP	Death			50	17/26 died
					Cancer			250	CEL: liver hemangiosarcoma, neoplastic nodules
Sokal et al. 1980									
27	Rat (Wistar) 85 M	10 months 5 days/week 5 hours/day	0, 50, 500, 20,000	CS, BW, BC, BI, UR, GN, OW, HP	Bd wt			20,000	23% decrease in body weight
					Cardio		20,000		10% decrease in relative heart weight
					Musc/skel	20,000			
					Hepatic		50		Fatty change at 50 ppm; increased incidence of hepatocyte polymorphisms (53%) and proliferative reticuloendothelial cells (38%) at 500 ppm
					Renal	50	500		13% increase in relative kidney weight; 19% increase at 20,000 ppm
					Immuno		50		17% increase in relative spleen weight; 36% and 31% increase at 500 and 20,000 ppm, respectively
					Repro	50	500		Spermatogenic epithelial necrosis

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Thornton et al. 2002									
28	Rat (Sprague-Dawley) 30 M, 30 F	2 generations 13–16 weeks (M) 16–19 weeks (F) 6 hours/day (WB)	0, 10, 100, 1,100	LE, CS, BW, FI, GN, OW, HP, RX, DX	Bd wt	1,100			
					Hepatic		10 F[c]		Centrilobular hypertrophy in 6/30 F1 female rats ($BMCL_{10}$ = 2.05 ppm)
							10 M		Increase in absolute (13–17%) and relative (7–15%) liver weights in F0 males; at 100 ppm: centrilobular hypertrophy in 15/30 F0 males and 19/30 F1 males, increase in absolute (18–20%) and relative (11–13%) liver weight in F1 males
					Immuno	1,100			
					Repro	1,100			
Torkelson et al. 1961									
29	Rat (NS) 20–24 M, 24 F	6 months 5 days/week 0.5–7 hours/day	0, 100, 200	LE, CS, BW, BC, UR, GN, OW, HP	Bd wt	200			
					Hemato	200			
					Hepatic		100		Increased relative liver weight
					Renal	200			
Wisniewska-Knypl et al. 1980									
30	Rat (Wistar) 7–10 M	10 months 5 days/week 5 hours/day	0, 50, 500, 20,000	BI, OW, HP	Hepatic		50		Fatty changes
Adkins et al. 1986									
31	Mouse (A/J) 70–72 M, 30–70 F	6 months 5 days/week 6 hours/day	0, 50, 200, 500	LE, GN, HP	Death			500 F	23/70 died
								500 M	37/70 died
					Cancer			50	CEL: 74–88% of animals with pulmonary adenoma; 100% with pulmonary adenoma at 500 ppm with same result in repeat study

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Chen et al. 2019									
32	Mouse (C57BL/6J) 8–10 M	12 weeks 5 days/week 6 hours/day (low fat diet)	0, 0.85	BW, FI, BC, BI, HP	Bd wt	0.85			
					Hepatic	0.85			
					Other noncancer	0.85			
Drew et al. 1983									
33	Mouse (Swiss CD-1) 71–162 F	6 months 5 days/week 6 hours/day	0, 50	LE, GN, HP	Death			50	Mean survival time significantly less than controls (340 days versus 474 days)
					Cancer			50	CEL: hemangiosarcoma of skin, peritoneum; mammary gland carcinoma; lung carcinoma
Drew et al. 1983									
34	Mouse (B6C3F1) 69–162 F	6 months 5 days/week 6 hours/day	0, 50	LE, GN, HP	Death			50	Mean survival time significantly less than controls (316 days versus 780 days)
					Cancer			50	CEL: hemangiosarcoma of subcutis, peritoneum; mammary gland carcinoma
Hong et al. 1981									
35	Mouse (CD-1) 8–28 M, 8–28 F	1,3,6 months 5 days/week 6 hours/day	0, 50, 250, 1,000	LE, CS, HP	Death			50	15/16 died
					Cancer			50 F	CEL: mammary gland adenocarcinoma/carcinoma
Jia et al. 2022									
36	Mouse (C57BL/6J) 8 M	13 weeks 5 days/week 2 hours/day (WB, normal diet)	0, 63, 313	BW, BC, BI, OW, HP	Bd wt	313			
					Hepatic	63	313		Decreased absolute liver weight and hepatic steatosis

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Lang et al. 2018									
37	Mouse (C57BL/6J) 4–12 M	12 weeks 5 days/week 6 hours/day (low fat diet)	0, 0.85	BW, FI, BC, BI, HP	Bd wt	0.85			
					Hepatic	0.85			
					Other noncancer	0.85			
Lang et al. 2020									
38	Mouse (C56B1/6J) 8–10 NS	12 weeks 5 days/week 6 hours/day	0, 0.85	BW, FI, BC, BI, HP, OW	Bd wt	0.85			
					Hepatic	0.85			
Liang et al. 2018									
39	Mouse (C57BL/6J) 5–13M	12 weeks 5 days/week 6 hours/day	0, 0.85	BW, BC, BI, HP	Bd wt	0.85			
					Cardio	0.85			
Liu et al. 2023									
40	Mouse (C57BL/6J) 5 M	12 weeks 5 days/week 6 hours/day (WB, control diet)	0, 0.85	BW, FI, BC, OW, HP	Bd wt	0.85			
					Hepatic	0.85			
Maltoni et al. 1981									
41	Mouse (Swiss) 30–75 M, 30–75 F	30 weeks 5 days/week 4 hours/day	0, 50, 250, 2,500, 6,000, 10,000	BW, GN, HP	Cancer			50	CEL: liver angiosarcoma and angioma

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Schaffner 1978									
42	Mouse (NS) 3–14 M	1–6 months 5 days/week 5 hours/day	0, 2,500, 6,000	HP	Hepatic		2,500		Hyperplasia of hepatocytes and activated sinusoidal cells
Sharma and Gehring 1979									
43	Mouse (CD-1) 12 M	2–8 weeks 5 days/week 6 hours/day	0, 10, 101, 983	CS, BW, BC, OW	Bd wt	983			
					Hemato	983			
					Hepatic		983		Decreased relative liver weight
					Renal	983			
					Immuno		10		Increased spontaneous lymphocyte proliferation
Suzuki 1978, 1981									
44	Mouse (CD-1) 1–7 M	5–6 months 5 days/week 5 hours/day	0, 2500, 6,000	GN, HP	Resp		2,500		Proliferation and hypertrophy of bronchial epithelium; hypersecretion of mucin; hyperplasia of alveolar epithelium
Suzuki 1983									
45	Mouse (CD-1) 30–60M	4 weeks 5 days/week 6 hours/day	0, 1, 10, 100, 300, 600	HP	Cancer			100	CEL: lung alveoli tumors
Wahlang et al. 2020									
46	Mouse (C57BL/6N) 3–6 M, 3–6 F	12 weeks 5 days/week 6 hours/day	0, 0.85	BW, FI, WI, BC, BI, HP, OW	Bd wt	0.85			
					Hepatic	0.85			
					Repro	0.85			
					Other noncancer	0.85			

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Wang et al. 2019a									
47	Mouse (C57BL/6N) 10 M	16 weeks 5 days/week 2 hours/day	0, 57.3, 286.7, 1,433.6	BW, BC, BI, HP, OW	Bd wt	1,433.6			
					Hepatic	57.3	286.7		Fat droplets, eosinophilic changes, nuclear condensation; at 1,433.6 ppm: steatosis, large lipid droplets, hepatic edema, cytoplasmic loosening, and hepatocyte nuclear fragmentation
Zelko et al. 2022									
48	Mouse (C57BL/6) 25 M	12 weeks 5 days/week 6 hours/day	0, 0.8	BW, BC, HE, IX	Bd wt	0.8			
					Hemato	0.8			
					Immuno		0.8		Increased pulmonary interstitial macrophages
					Other noncancer		0.8		Impaired glucose tolerance
Drew et al. 1983									
49	Hamster (Golden Syrian) 143–224 F	6 months 5 days/week 6 hours/day	0, 200	LE, GN, HP	Death			200	Mean survival time significantly decreased in 2-month-old hamsters (390 days versus 463 days)
					Cancer			200	CEL: liver hemangiosarcoma; skin hemangiosarcoma, spleen hemangiosarcoma; mammary gland carcinoma
Maltoni et al. 1981									
50	Hamster (Golden Syrian) 30–62 M	30 weeks 5 days/week 4 hours/day	0, 50, 250, 500, 2500, 6,000, 10,000	BW, GN, HP	Cancer			500	CEL: liver angiosarcoma

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Sharma et al. 1980									
51	Rabbit (New Zealand) 5 M	8 weeks 5 days/week 6 hours/day (WB)	10, 101, 983	BW, OW, IX	Bd wt	983			
					Cardio	983			
					Hepatic	983			
					Renal	983			
					Endocr	983			
					Immuno		10		Increased spontaneous splenic lymphocyte proliferation
					Neuro	983			
Torkelson et al. 1961									
52	Rabbit (NS) 3 M, 3 F	6 months 5 days/week 7 hours/day	0, 100, 200	LE, BW, BC, UR, GN, OW, HP	Bd wt	200			
					Hepatic	100	200		Centrilobular degeneration and necrosis
					Renal	200			
CHRONIC EXPOSURE									
Bi et al. 1985									
53	Rat (Wistar) 35–36 M	12 months 6 days/week 6 hours/day (WB)	0, 11.1, 105.6, 2,918	BW, GN, OW, HP	Bd wt	11.1	105.6	2,918	Dose response with 10–35% decreased body weight at 9, 12, and 18 months for 105.6 and 2,918 ppm; 26–35% decreased body weight at 12 and 18 months at 2,918 ppm
					Hepatic		2,918		20% increase in relative liver weight
					Renal		2,918		17% increase in relative kidney weight

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
					Repro	11.1	105.6		27/74 with degenerative seminiferous tubule changes; incidence for testes damage 18.9, 29.7, 36.5, and 56%, respectively
					Cancer			105.6	CEL: 7/19 liver angiosarcoma and 2/19 lung angiosarcoma; at 2,918 ppm 17/19 liver angiosarcoma and 9/19 lung angiosarcoma
Drew et al. 1983									
54	Rat (Fischer-344) 112–280 F	12, 18, or 24 months 5 days/week 6 hours/day	0, 100	LE, GN, HP	Death			100	Mean survival time significantly less than controls (≤634 days versus 703 days)
					Cancer			100	CEL: hepatic hemangiosarcoma, hepatocellular carcinoma, neoplastic nodules; mammary gland fibroadenoma and adenocarcinoma
Holmberg et al. 1976									
55	Rat (albino) 12 M, 12 F	26 or 52 weeks 5 days/week 6 hours/day	0, 50, 500	CS, BW, GN, OW, HP	Cancer			50	CEL: lung, kidney, abdominal hemangiosarcoma
Lee et al. 1978									
56	Rat (CD) 36 M, 36 F	1–12 months 5 days/week 6 hours/day	0, 50, 250, 1,000	BW, FI, HE, GN, HP	Cancer			250 F	CEL: hepatic hemangiosarcoma

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Maltoni et al. 1981									
57	Rat (Sprague-Dawley) 30–300 B	52 weeks 5 days/week 4 hours/day	0, 1, 5, 10, 25, 50, 100, 150, 200, 250, 500, 2,500, 6,000, 10,000, 30,000	BW, GN, HP	Cancer			5 F	CEL: mammary gland carcinoma
Drew et al. 1983									
58	Mouse (Swiss CD-1) 71–216 F	12 or 18 months 5 days/week 6 hours/day	0, 50	LE, GN, HP	Death			50	Mean survival time significantly less than controls (≤347 days versus 474 days)
					Cancer			50	CEL: lung; hemangiosarcoma of peritoneum, subcutis; mammary gland carcinoma
Drew et al. 1983									
59	Mouse (B6C3F1) 69–216 F	12 months 5 days/week 6 hours/day	0, 50	LE, GN, HP	Death			50	Mean survival time significantly less than controls (301 days versus 780 days)
					Cancer			50	CEL: hemangiosarcoma of peritoneum, subcutis; mammary gland carcinoma
Lee et al. 1977a, 1978									
60	Mouse (CD-1) 36 M, 36 F	1–12 months 5 days/week 6 hours/day	0, 50, 250, 1,000	GN, HP	Cancer			50	CEL: hepatic hemangiosarcoma; bronchiolo-alveolar adenoma; malignant lymphoma
								50 F	CEL: mammary gland adenoma and adenocarcinoma

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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
Drew et al. 1983									
61	Hamster (Golden Syrian) 143–280 F	12, 18, or 24 months 5 days/week 6 hours/day	0, 200	LE, GN, HP	Death			200	Mean survival time significantly less than controls (≤355 days versus 463 days)
					Cancer			200	CEL: liver hemangiosarcoma; skin carcinoma, hemangiosarcoma; spleen hemangiosarcoma; mammary gland carcinoma; stomach adenoma

[a]The number corresponds to entries in Figure 2-2. The only human studies included in this table are controlled exposure studies. Other epidemiological studies are described in text and tables in the health effect sections below.
[b]Used to derive an acute-duration inhalation Minimal Risk Level (MRL) of 0.5 ppm. The NOAEL of 50 ppm was adjusted for continuous exposure and was converted to a human equivalency concentration using the default animal:human blood gas partition coefficient ratio of 1 (50 ppm x 7 hours/24 hours = 15 ppm) and divided by an uncertainty factor of 30 (3 for animal to human after dosimetric adjustment and 10 for human variability), resulting in an MRL of 0.5 ppm.
[c]Used to derive an intermediate-duration inhalation MRL of 0.02 ppm based on the $BMCL_{10HEC}$ of 0.5 ppm and an uncertainty factor of 30 (3 for animal to human after dosimetric adjustment and 10 for human variability).

BC = blood chemistry; Bd wt or BW = body weight; BI = biochemical changes; $BMCL_{10}$ = benchmark concentration lower confidence limit 10%; Cardio = cardiovascular; CEL = cancer effect level; CS = clinical signs; Develop = developmental; DX = developmental toxicity; Endocr = endocrine; F = female(s); FI = food intake; Gastro = gastrointestinal; GD = gestational day; GN = gross necropsy; Hemato = hematological; HP = histopathology; Immuno = immunological; IX = immune function; 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; Repro = reproductive; Resp = respiratory; RX = reproductive toxicity; SDH = sorbitol dehydrogenase; SLOAEL = serious lowest-observed-adverse-effect level; UR = urinalysis; (WB) = whole body; WI = water intake

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

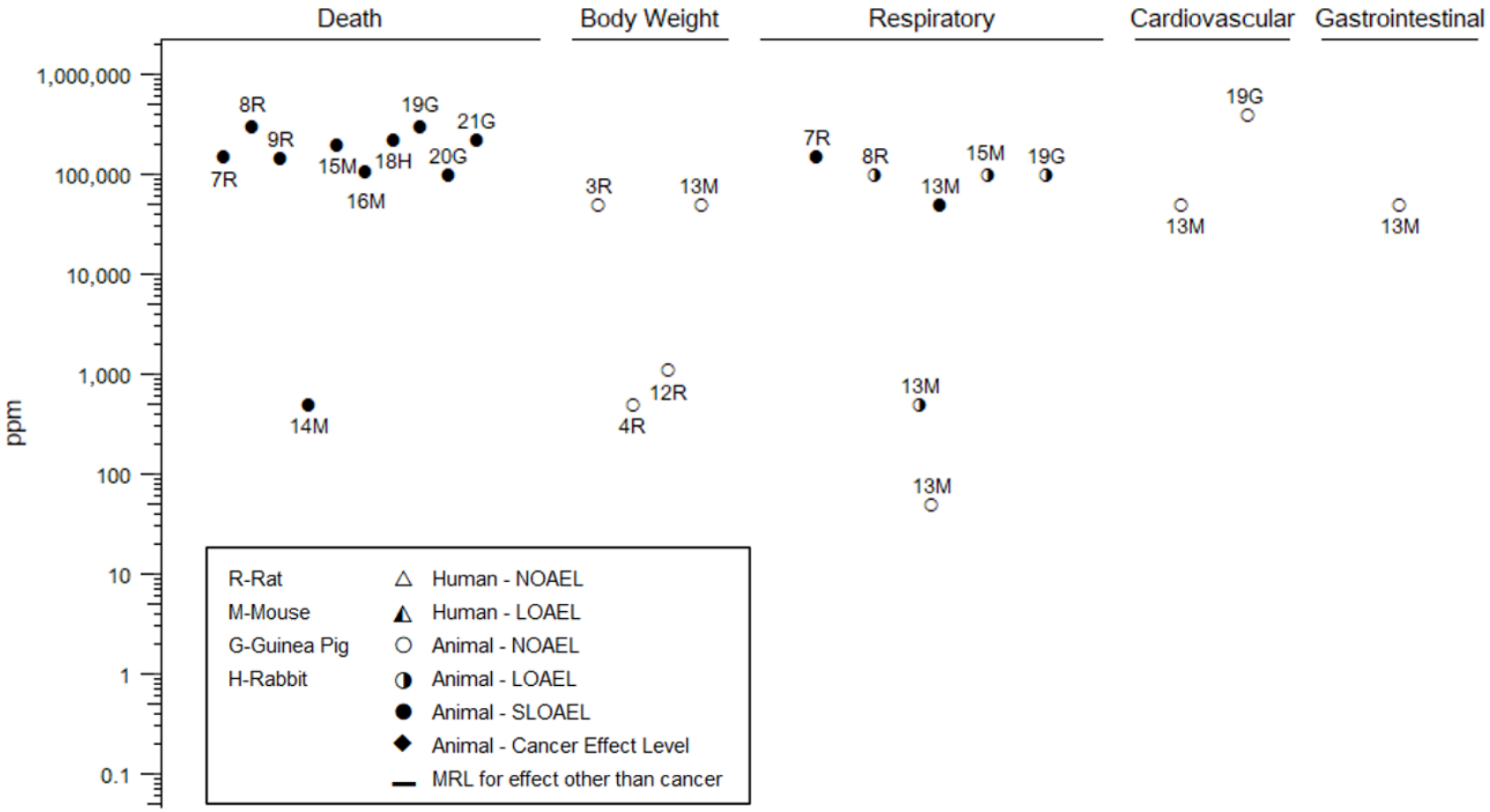


Figure 2-2. Levels of Significant Exposure to Vinyl Chloride – Inhalation
Acute (≤14 days)

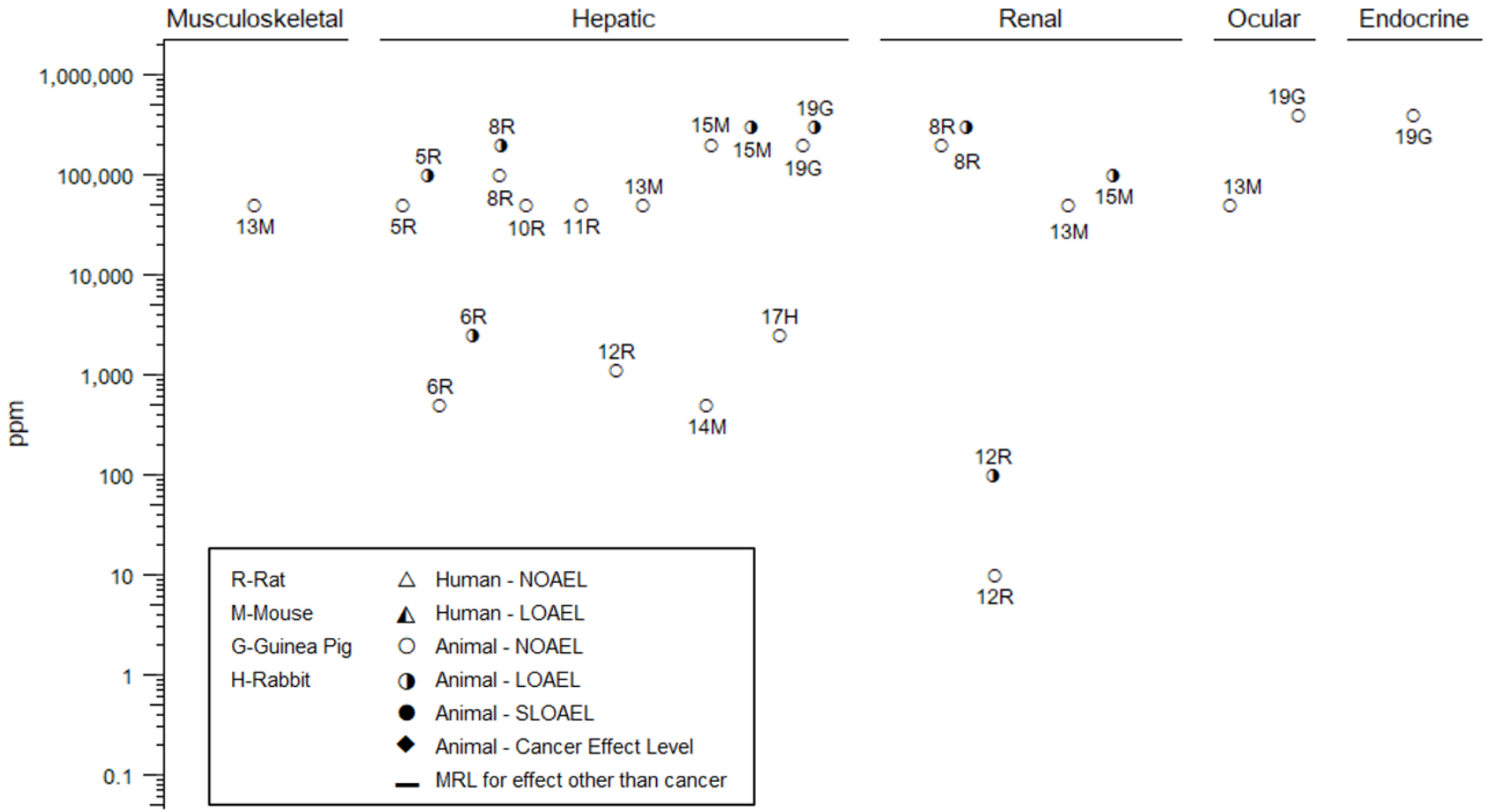


Figure 2-2. Levels of Significant Exposure to Vinyl Chloride – Inhalation
Acute (≤14 days)

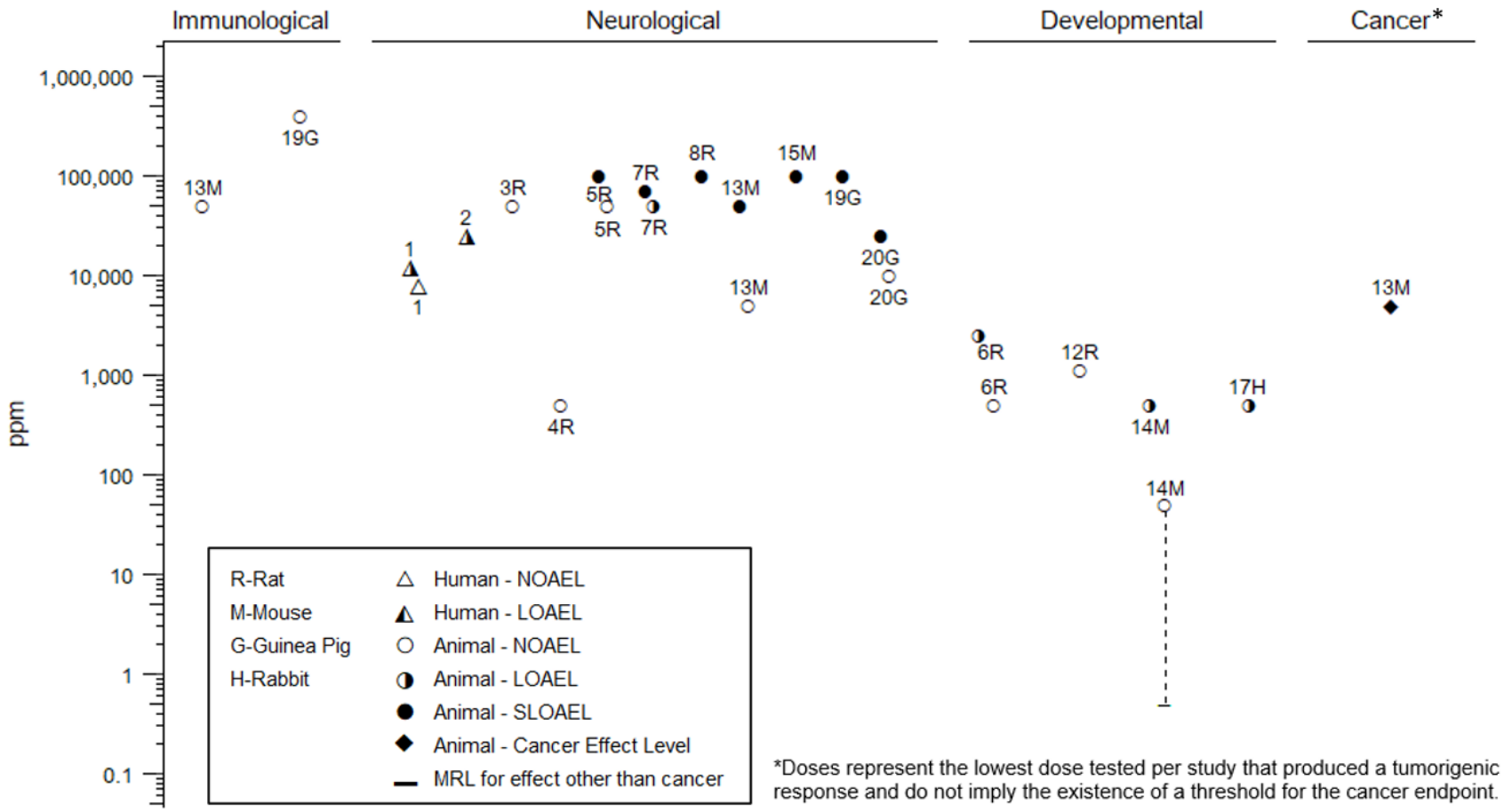


Figure 2-2. Levels of Significant Exposure to Vinyl Chloride – Inhalation
Intermediate (15–364 days)

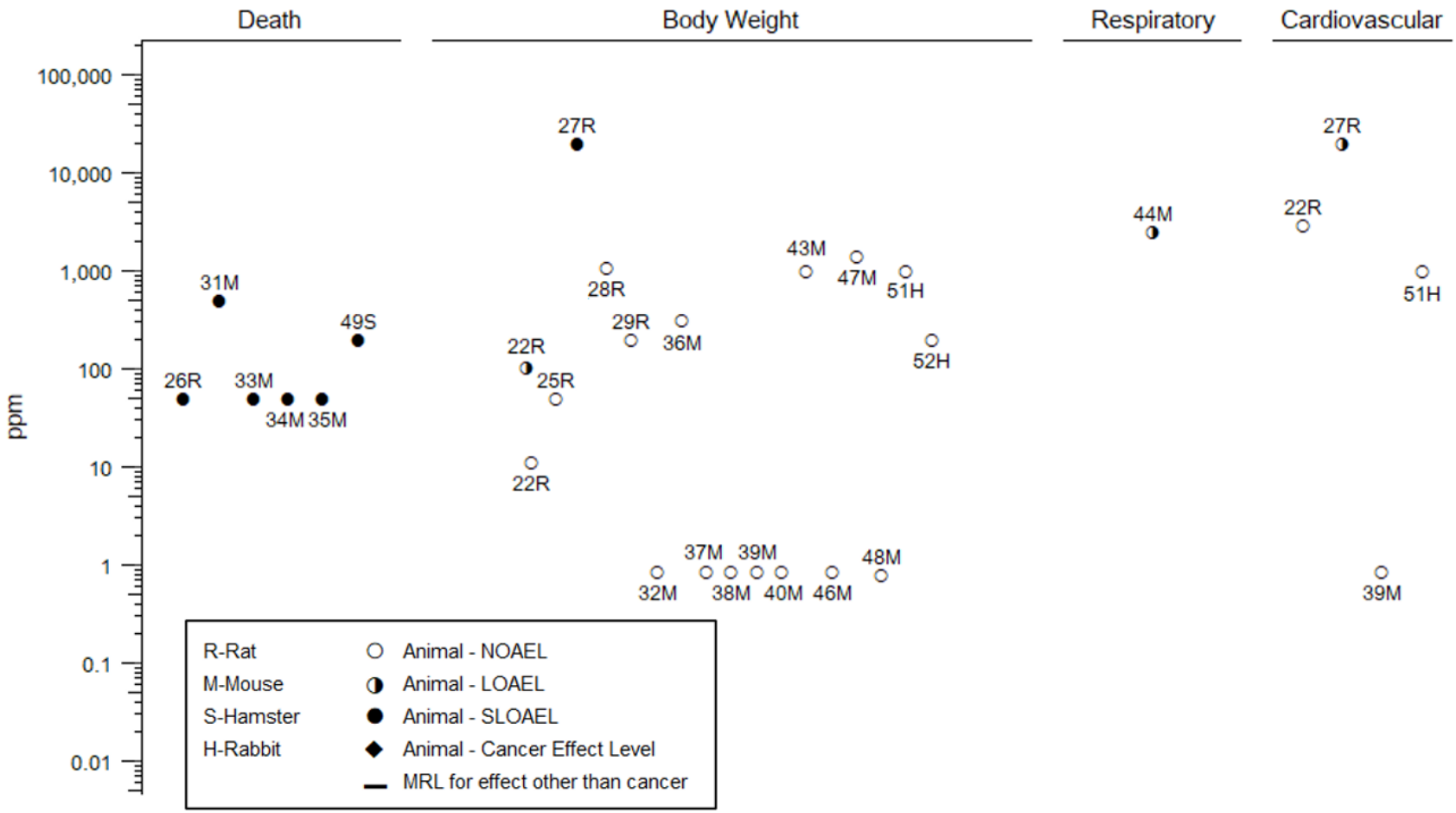


Figure 2-2. Levels of Significant Exposure to Vinyl Chloride – Inhalation
Intermediate (15–364 days)

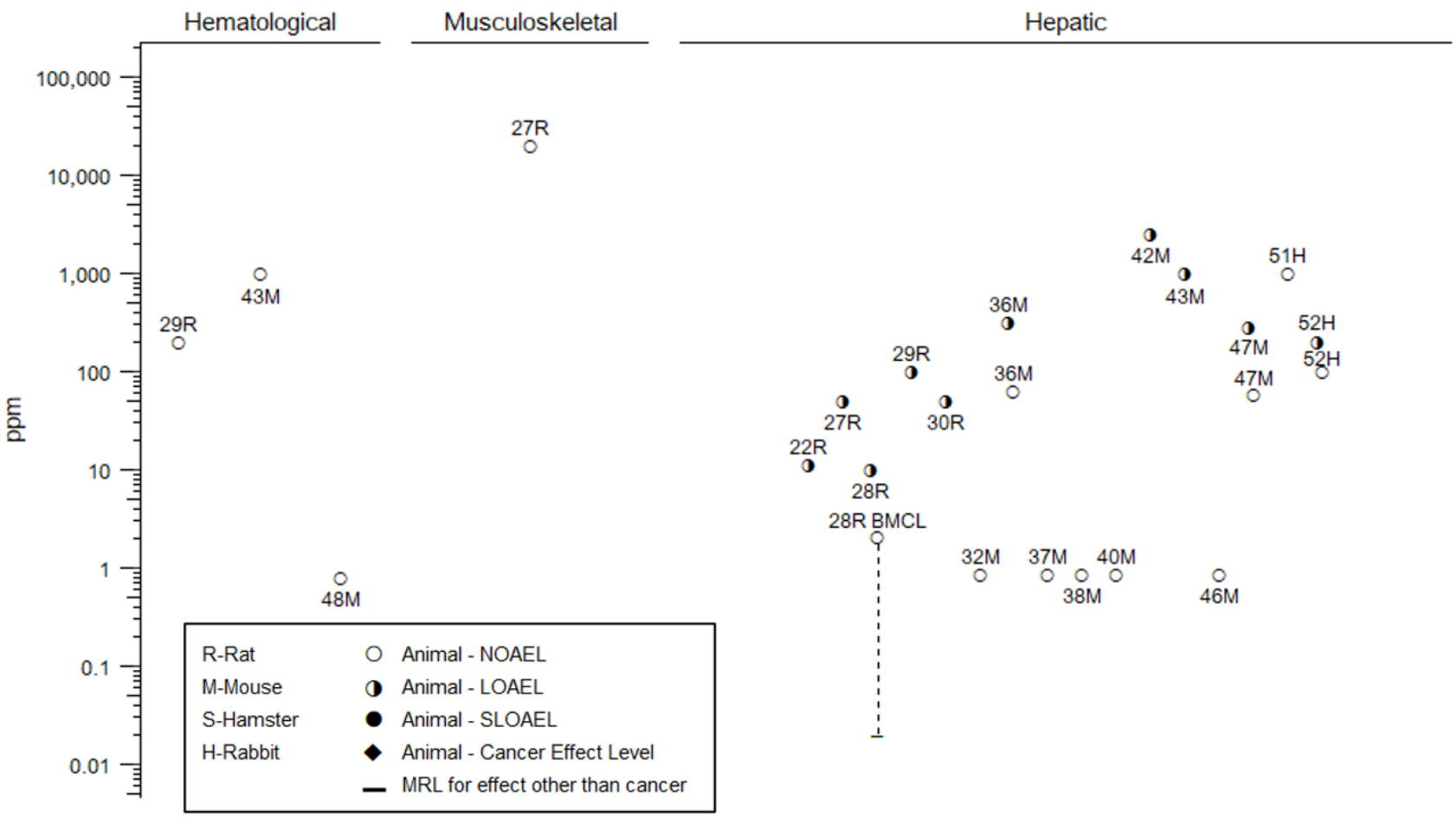


Figure 2-2. Levels of Significant Exposure to Vinyl Chloride – Inhalation
Intermediate (15–364 days)

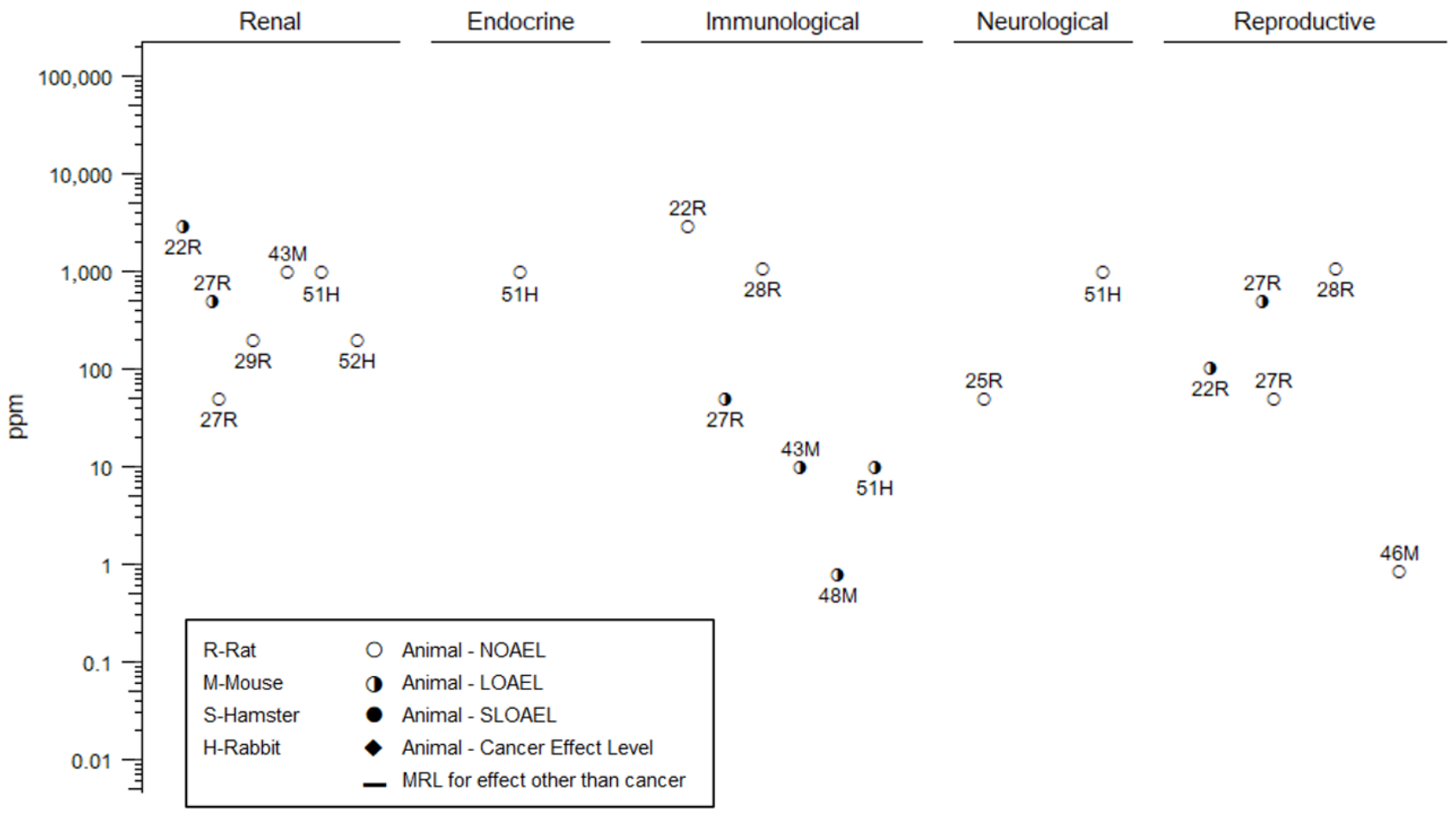


Figure 2-2. Levels of Significant Exposure to Vinyl Chloride – Inhalation
Intermediate (15–364 days)

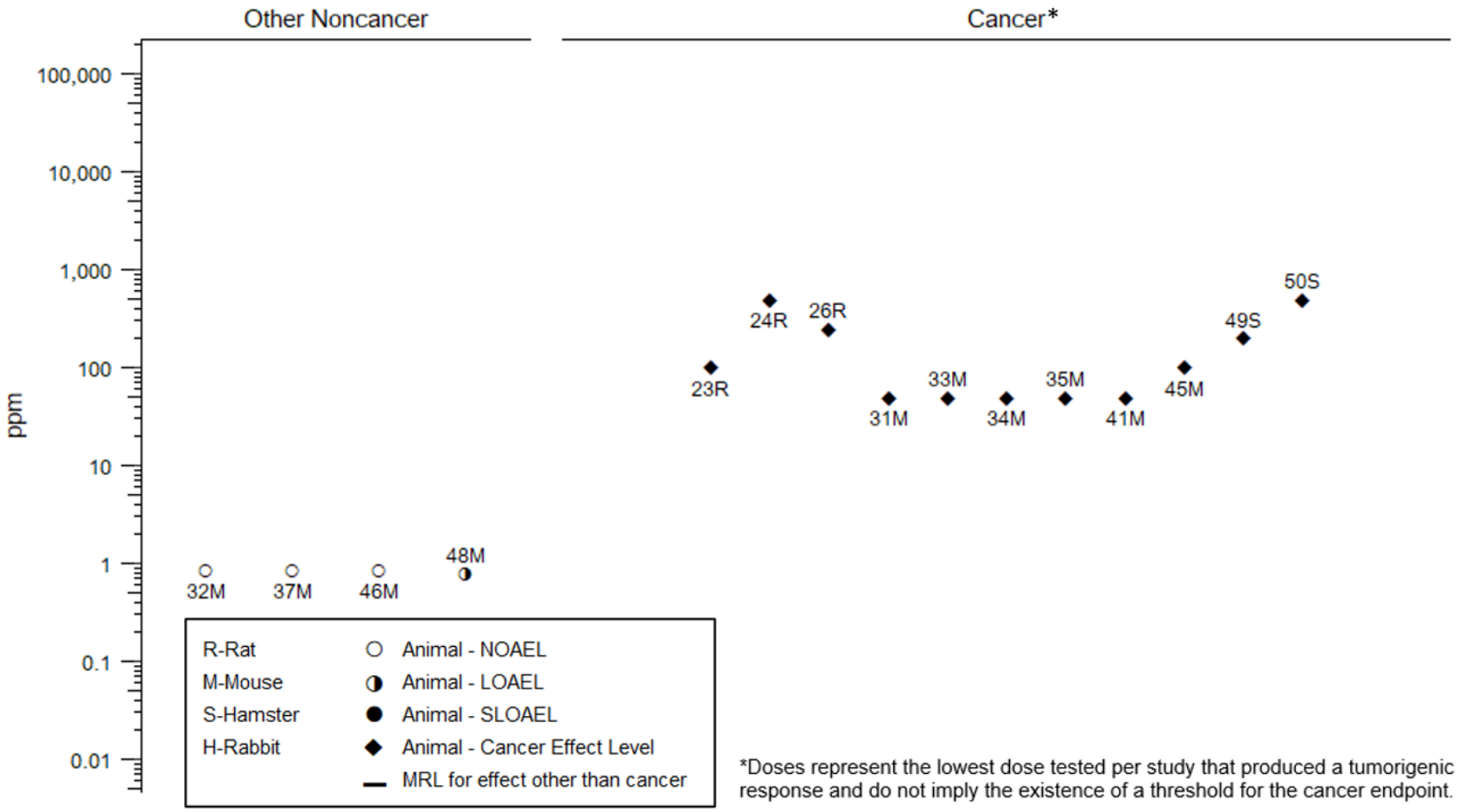


Figure 2-2. Levels of Significant Exposure to Vinyl Chloride – Inhalation
Chronic (≥365 days)

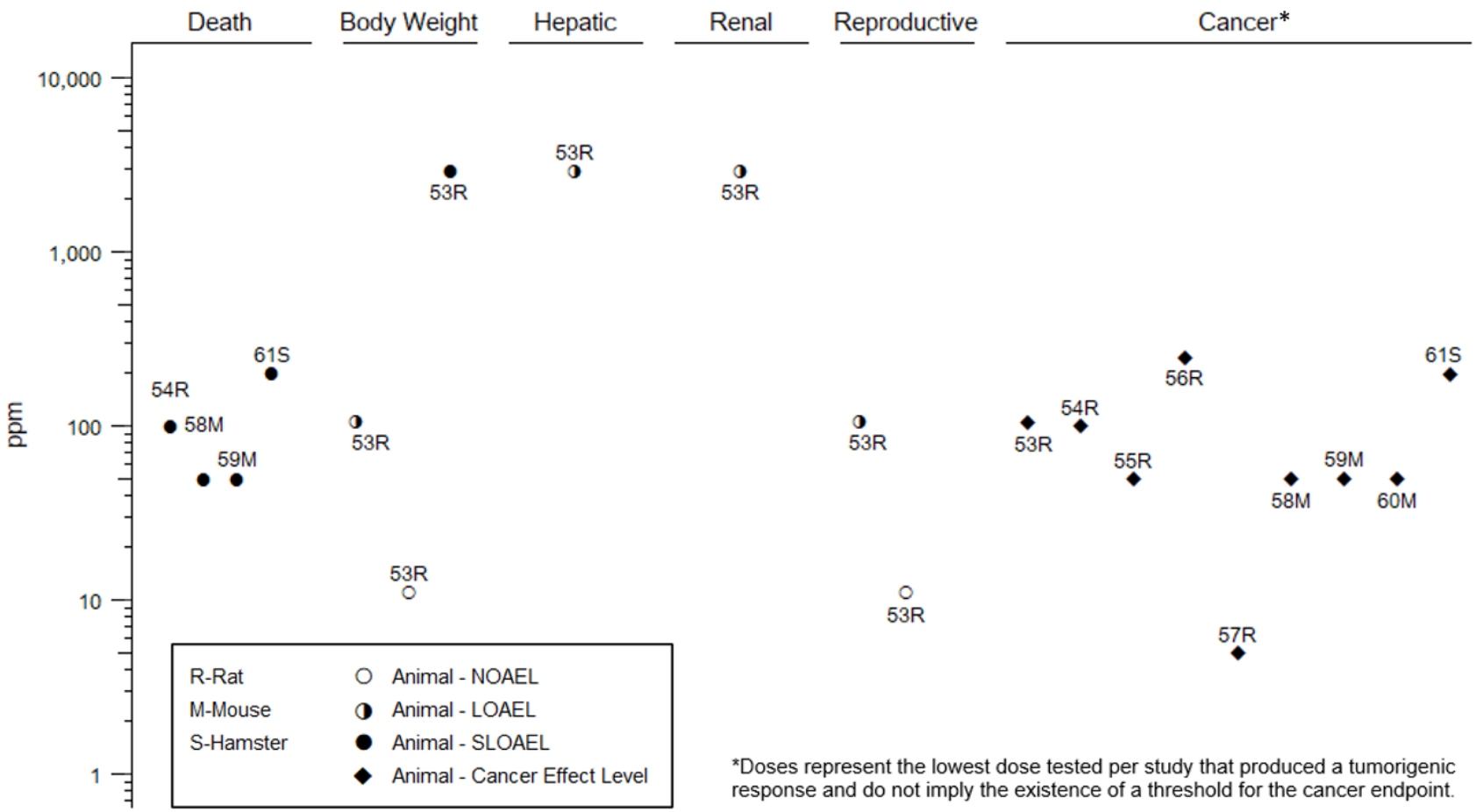


Table 2-2. Levels of Significant Exposure to Vinyl Chloride– Oral (mg/kg/day)

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses	Parameters monitored	Endpoint	NOAEL	Less serious LOAEL	Serious LOAEL	Effects
CHRONIC EXPOSURE									
Feron et al. 1981									
1	Rat (Wistar) 60–80 M, 60–80 F	84 weeks–2.7 years 5 days/week 4 hours/day (F), (GO)	0, 1.7, 5, 14.1, 300	LE, CS, BW, FI, BC, UR, GN, HP	Death			5 F	7/60 dead at 80 weeks
								14.1 M	8/60 dead at 80 weeks
					Resp			5	Breathing difficulties at 18 months
					Hemato	5	14.1		6–8% statistically significant decrease in clotting time
					Hepatic			5 F	Extensive necrosis
								14.1 M	Extensive necrosis
							1.7		Cellular alteration
					Neuro	5		14.1	Humpback position, lethargy, emaciation
					Cancer			5	Female CEL: 19/59 with hepatocellular carcinoma; 9/57 with liver angiosarcoma at 14.1 mg/kg/day Male CEL: 6/56 with liver angiosarcoma, 4/56 with lung angiosarcoma; 8/59 with hepatocellular carcinoma at 14.1 mg/kg/day
Knight and Gibbons 1987									
2	Rat (Wistar) 8–20 B NS	2 years 1 time/day (GO)	0, 3, 30, 300	LE, BW, BI, GN	Death			30	33% mortality
					Hepatic		3		Mottled appearance and hemorrhagic patches
					Dermal		30		Increased skin thickness, collagen
					Cancer			30	CEL: liver angiosarcoma
Maltoni et al. 1981									
3	Rat (Sprague-Dawley) 40 M, 40 F	52 weeks 5 times/week (GO)	0, 3.33, 16.65, 50	BW, GN, HP	Cancer			16.65 F	CEL: liver angiosarcoma

Table 2-2. Levels of Significant Exposure to Vinyl Chloride– 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. 1981									
4	Rat (Sprague-Dawley) 75 M,75 F	52 weeks 5 times/week (GO)	0, 0.03, 0.3, 1	BW, GN, HP	Cancer			0.3	CEL: liver angiosarcoma, hepatoma
Til et al. 1983, 1991									
5	Rat (Wistar) 50–100 M, 50–100 F	149 weeks 4 hours/day (F)	0, 0.018, 0.17, 1.7	LE, CS, BW, FI, BC, HP	Death			1.7 F	14% mortality
					Bd wt	1.7			
					Hemato	1.7			
					Hepatic	0.17[b]	1.7		33–34% increase in the incidence of liver cell polymorphism; cysts (females only)
					Cancer			1.7	CEL: 3/49 males and 3/49 females with hepatocellular carcinoma; 1/49 males and 2/49 females with liver angiosarcoma

[a]The number corresponds to entries in Figure 2-3.
[b]Used to derive a chronic-duration oral Minimal Risk Level (MRL) of 0.003 mg/kg/day based on the PBPK-modeled equivalent human NOAEL of 0.09 mg/kg/day and an uncertainty factor of 30 (3 for species extrapolation with a dosimetric adjustment and 10 for human variability).

BC = blood chemistry; Bd wt or BW = body weight; BI = biochemical changes; CEL = cancer effect level; CS = clinical signs; (F) = feed; F = female(s); FI = food intake; (GO) = gavage in oil; GN= gross necropsy; Hemato = hematological; HP = histopathology; LE = lethality; LOAEL = lowest-observed-adverse-effect level; M = male(s); NOAEL = no-observed-adverse-effect level; Neuro = neurological; NS = not specified; PBPK = physiologically based pharmacokinetic; Resp = respiratory; UR = urinalysis

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

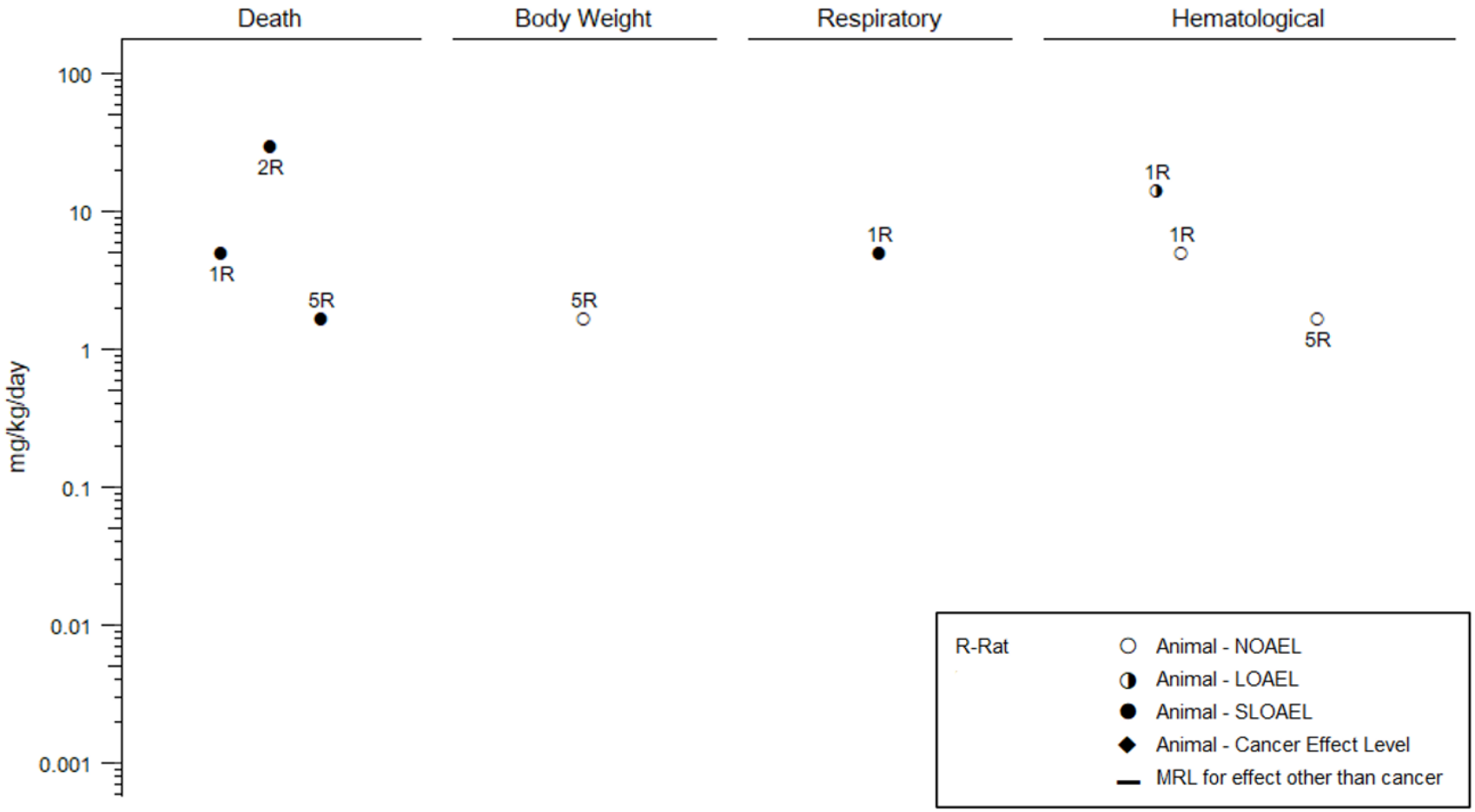
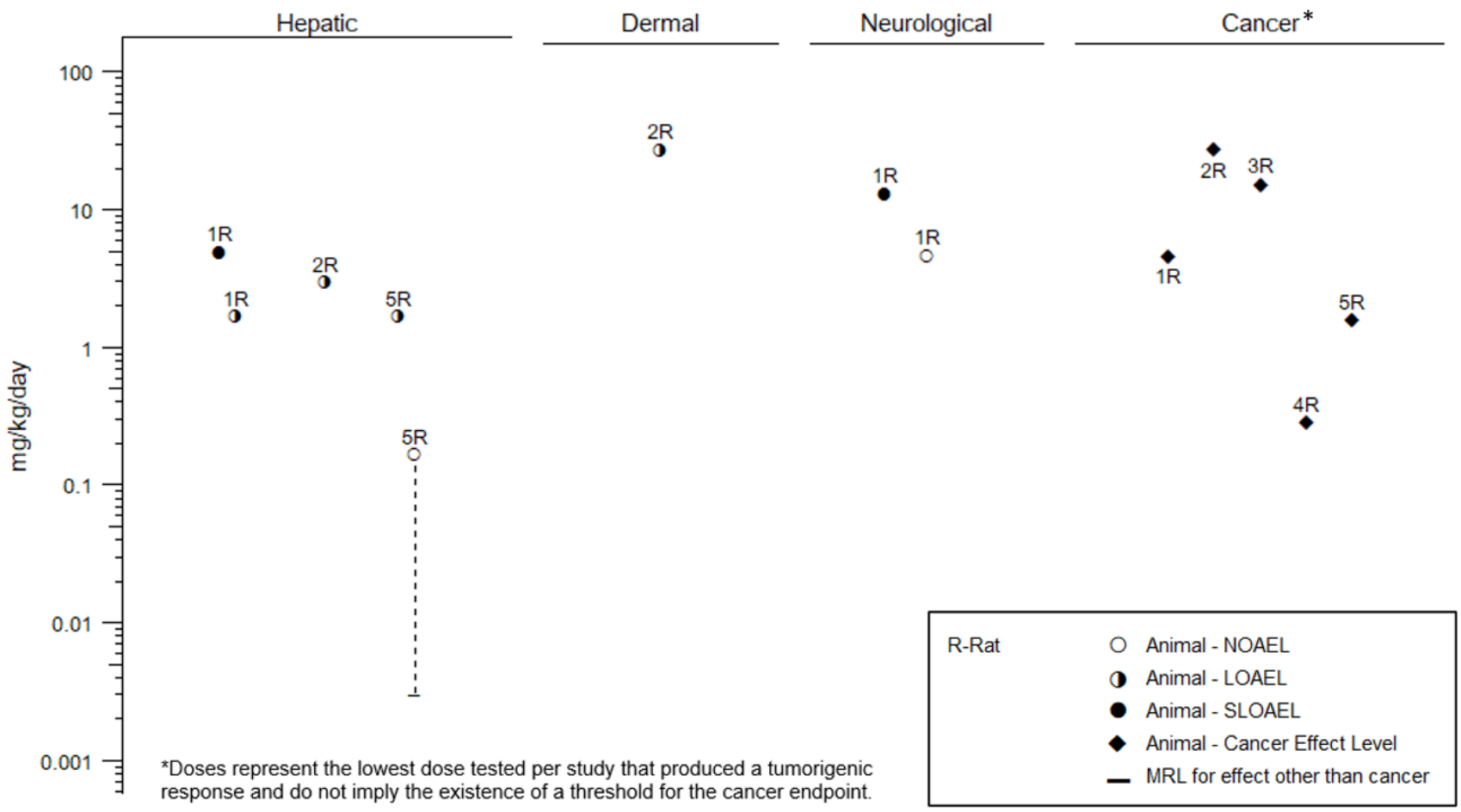


Figure 2-3. Levels of Significant Exposure to Vinyl Chloride – Oral
Chronic (≥365 days)



2.2 DEATH

Human Studies. A report by Danziger (1960) described the deaths of two vinyl chloride workers. In one case, a worker exposed to high concentrations of vinyl chloride emitted from an open valve was found dead. In another case, a worker responsible for cleaning a polymerization tank was found dead in the tank. Autopsies performed on these men showed congestion of the internal organs, particularly the lungs and kidneys, and failure of the blood to clot. Circumstances surrounding the deaths suggested that the deaths were due to breathing very high levels of vinyl chloride. Retrospective mortality studies associating exposure with cancer are described in Section 2.19. In general, epidemiology studies did not report an increase in all-cause mortality for workers exposed to vinyl chloride (Belli et al. 1987; Buffler et al. 1979; Carreón et al. 2014; Fedeli et al. 2019a; Hagmar et al. 1990; Hsieh et al. 2011; Laplanche et al. 1987, 1992; Mundt et al. 2000, 2017; Ott et al. 1975; Scarselli et al. 2022; Ward et al. 2001; Wong et al. 2002a).

Animal Studies. Brief exposures to concentrations of vinyl chloride ranging from 100,000 to 400,000 ppm have been shown to be fatal in rats (Lester et al. 1963; Mastromatteo et al. 1960; Prodan et al. 1975), guinea pigs (Mastromatteo et al. 1960; Patty et al. 1930; Prodan et al. 1975), mice (Mastromatteo et al. 1960; Prodan et al. 1975), and rabbits (Prodan et al. 1975). At these concentrations, deaths occurred within 30–60 minutes. An increased mortality rate was also observed at much lower concentrations in maternal mice in a developmental toxicity study (John et al. 1977, 1981). In this study, mortality was observed following exposure to 500 ppm for 10 days during gestation.

Decreased survival occurred in intermediate- and chronic-duration inhalation studies (Adkins et al. 1986; Drew et al. 1983; Feron et al. 1979a; Hong et al. 1981, Lee et al. 1977a, 1978). A treatment-related increase in the mortality rate was observed in mice exposed to 500 ppm of vinyl chloride for 6 hours/day, 5 days/week, for 6 months (Adkins et al. 1986). In mice and rats maintained for 12 months following a 6-month, 6 hour/day, 5 day/week exposure regime, survival was decreased at concentrations as low as 50 ppm (Hong et al. 1981). Substantial increases in the mortality rate of mice and rats exposed to 250 ppm vinyl chloride for 12 months were observed by Lee et al. (1977a, 1978). In addition, small increases in the mortality of mice and rats during the 12-month exposure period were observed at 50 ppm in these reports.

Drew et al. (1983) examined the influence of age on survival of female mice, rats, and hamsters exposed to 50, 100, or 200 ppm vinyl chloride, respectively. For a 12-month exposure duration (6 hours/day,

5 days/week), mortality was highest in younger animals where exposure began at 2 months of age compared to animals that were first exposed at 8 or 14 months of age. All animals were maintained for up to 24 months; therefore, the post-exposure period was considerably longer for the younger animals. Tumor incidence was higher in younger animals, suggesting that mortality may be related to carcinogenesis in this study (Section 2.19 Cancer). This study was limited in that only one dose of vinyl chloride was tested in each species.

Decreased survival has been observed in rats as a result of chronic oral ingestion of vinyl chloride. Significant increases in mortality were observed by Feron et al. (1981) when Wistar rats were allowed to consume vinyl chloride doses as low as 5 mg/kg/day in the diet for 4 hours/day over a 2.7-year period or when gavaged with 30 mg/kg/day for 2 years (Knight and Gibbons 1987) The effects of consumption of vinyl chloride during a lifespan study in Wistar rats lasting almost 3 years (149 weeks) were examined by Til et al. (1983, 1991). These authors found a decreased survival rate at a vinyl chloride dosage of 1.7 mg/kg/day. In both of these studies, vinyl chloride was administered by incorporating PVC resin that was high in vinyl chloride content into the diet.

2.3 BODY WEIGHT

Human Studies. An occupational health study (i.e., vinyl chloride worker study with no exposure measurements or comparison group) reported that workers exposed to high concentrations of vinyl chloride experienced anorexia (Suciu et al. 1975). No additional information on body weight is available from human studies of vinyl chloride exposure.

Animal Studies. No effects on body weight were noted in acute-duration studies of adult mice exposed to inhalation concentrations up to 10,000 ppm vinyl chloride 4 hours/day for 5–6 days (Kudo et al. 1990) or adult rats exposed to up to 50,000 ppm for 1 hour or 500 ppm 5 days/week, for 2 weeks (Hehir et al. 1981). Body weight decreases were observed in some, but not all, intermediate- and chronic-duration inhalation studies. Significant body weight decreases were found in rats exposed to 100 ppm vinyl chloride 6 hours/day, 6 days/week for 12 months (Bi et al. 1985), or 5,000 ppm vinyl chloride 7 hours/day, 5 days/week for 4–52 weeks (Feron et al. 1979a). Body weight was increased in mice fed a high-fat diet (not included in Levels of Significant Exposure, LSE, Tables); however, vinyl chloride exposure had no effect on body weight in mice fed a normal or high-fat diet (Chen et al. 2019; Lang et al. 2018, 2020; Liang et al. 2018; Wahlang et al. 2020).

No changes in body weight were noted in rats or rabbits exposed to 200 ppm vinyl chloride 7 hours/day, 5 days/week for 6 months (Torkelson et al. 1961) or in mice exposed up to 313 ppm 2 hours/day, 5 days/week for 13 weeks (Jia et al. 2022), 983 ppm 6 hours/day, 5 days/week for 8 weeks (Sharma and Gehring 1979; Sharma et al. 1980), or up to 1,433.6 ppm 2 hours/day, 5 days/week for 16 weeks (Wang et al. 2019a). No body weight change was observed in mice given a normal low-fat diet and exposed to 0.8 or 0.85 ppm vinyl chloride for 6 hours/day, 5 days/week for 12 weeks (Chen et al. 2019; Lang et al. 2018, 2020; Liang et al. 2018; Wahlang et al. 2020; Zelko et al. 2022). Exposure to 0.85 ppm vinyl chloride for 6 hours/day, 5 days/week for 12 weeks did not affect body weight gains of mice fed low-fat or high-fat diets 9 months after exposure ended (Liu et al. 2023). The vinyl chloride concentration used in these studies was anticipated to be nontoxic in low-fat diet mice and no other concentrations of vinyl chloride were used.

No changes in body weight were noted in Wistar rats fed 1.7 mg/kg/day vinyl chloride mixed with PVC powder in the diet for 149 weeks (Til et al. 1983, 1991).

2.4 RESPIRATORY

Human Studies. Limited information is available on the acute adverse effects from inhalation of vinyl chloride by humans. Autopsy findings from a man who died after being overcome by vinyl chloride revealed the irritating nature of a high-level inhalation exposure. The lungs were found to be intensely hyperemic, and some desquamation of the alveolar epithelium had occurred (Danziger 1960). Respiratory symptoms, including runny nose, burning sensation in the nose and throat, hoarseness, shortness of breath, chest tightness, wheezing, burning sensation in the lungs, coughing, and increased congestion or phlegm, were reported in first responders, refinery workers, and nearby residents following derailment of a train carrying vinyl chloride (Brinker et al. 2015; Shumate et al. 2017; Wilken et al. 2015).

Reports regarding respiratory effects in workers who are occupationally exposed to vinyl chloride are contradictory. Several epidemiology studies found no increased incidence of respiratory disease, respiratory symptom reporting, or pulmonary dysfunction among vinyl chloride workers (Gamble et al. 1976; Laplanche et al. 1987, 1992; NIOSH 1977). However, adverse respiratory effects were reported in cohort and case-control studies (Lloyd et al. 1984; Wong et al. 1991; Zhu et al. 2005a) and several occupational health studies, which often had no exposure measurements (Lilis et al. 1975, 1976; Suciu et al. 1975; Walker 1976). These effects included pharyngeal irritation (Zhu et al. 2005a), increased

incidence of emphysema (Suciu et al. 1975; Wong et al. 1991), decreased respiratory volume and vital capacity, respiratory insufficiency (Suciu et al. 1975), decreased respiratory oxygen and carbon dioxide transfer (Lloyd et al. 1984), pulmonary fibrosis of the linear type (Suciu et al. 1975), abnormal chest x-rays (Lilis et al. 1975, 1976), and dyspnea (Walker 1976). Interpretation of many of these results is confounded by the inclusion of smokers among those exposed to vinyl chloride and the concurrent exposure of many vinyl chloride workers to PVC resin dust, which is known to produce respiratory lesions (Mastrangelo et al. 1979).

Animal Studies. Brief inhalation of high concentrations of vinyl chloride produced respiratory inflammation in a variety of animals. A 30-minute exposure of guinea pigs, mice, and rats to 100,000 ppm of vinyl chloride produced hyperemia in all three species (Mastromatteo et al. 1960). Exposure to higher concentrations (200,000 and 300,000 ppm) produced increased congestion, edema, and at the highest concentrations, pulmonary hemorrhages in all three species (Mastromatteo et al. 1960). Tracheal epithelium was also eroded in one guinea pig exposed to 400,000 ppm for 30 minutes (Mastromatteo et al. 1960). Edema and congestion of the lungs of rats were also observed following a 2-hour exposure to 150,000 ppm (Lester et al. 1963).

Histopathologic examination of mice exposed to 2,500 ppm vinyl chloride 5 hours/day, 5 days/week for 5–6 months revealed proliferation and hypertrophy of the bronchiolar epithelium, hyperplasia of the alveolar epithelium, hypersecretion of mucin (Suzuki 1978, 1980, 1981), increased endoplasmic reticulum and free ribosomes in Clara cells, and mobilization of alveolar macrophages (Suzuki 1980). These changes were observed irrespective of the recovery period (2 or 37 days), indicating that they were not readily reversible. However, these studies were limited by the small number of animals tested and the absence of a statistical analysis.

Chronic-duration exposure of rats to 5,000 ppm 7 hours/day, 5 days/week for 12 months produced hyperplasia of the olfactory epithelium, increased cellularity of the interalveolar septa of the lungs, and an increased incidence of pulmonary hemorrhage (Feron and Kroes 1979). Interstitial pneumonia and hemorrhagic lungs were observed in rats exposed to 30,000 ppm of vinyl chloride 4 hours/day, 5 days/week for 12 months (Viola et al. 1971).

2.5 CARDIOVASCULAR

Human Studies. Cardiovascular symptoms (not further defined) were reported by residents living near the site of a train derailment resulting in a release of vinyl chloride (Shumate et al. 2017). Occupational exposure to vinyl chloride has been associated with the development of Raynaud's phenomenon, a condition in which the fingers blanch and become numb with discomfort upon exposure to the cold. It has also been reported in a worker exposed once to a vinyl chloride leak (Ostlere et al. 1992). Most of the evidence pertaining to Raynaud's phenomenon in vinyl chloride workers is derived from case reports and occupational health studies, which often had no exposure measurements and no comparison groups. Although only a small percentage of vinyl chloride workers develop Raynaud's phenomenon (Laplanche et al. 1987, 1992; Lilis et al. 1975; Marsteller et al. 1975; Suciu et al. 1975; Veltman et al. 1975; Walker 1976), the incidence is significantly higher than in unexposed workers (Laplanche et al. 1987, 1992). Investigation of the peripheral circulation of workers afflicted with Raynaud's phenomenon has revealed thickening of the walls of the digital arteries (Harris and Adams 1967), narrowing of the arterial lumen (Veltman et al. 1975), vascular occlusions (Walker 1976), arterial occlusions (Preston et al. 1976; Veltman et al. 1975), tortuosity (Preston et al. 1976), hypervascularity (Preston et al. 1976), inflammatory infiltration of the arterioles (Magnavita et al. 1986), deposition of immune products along the vascular endothelium (Ward 1976), and impaired capillary microcirculation (Magnavita et al. 1986; Maricq et al. 1976). Some reports indicate that upon removal from exposure, Raynaud's phenomenon gradually disappears (Freudiger et al. 1988; Suciu et al. 1975); however, abnormalities of microcirculation, as measured by capillaroscopy, were shown to persist in vinyl chloride workers 15 years after the cessation of exposure (Lopez et al. 2013). Genetic polymorphisms of glutathione transferase M1 and glutathione transferase T1 were not significantly associated with the presence of Raynaud's disease in a case-control study of French vinyl chloride workers (Fontana et al. 2006). For further discussion of Raynaud's phenomenon, refer to Section 2.14 (Immunological).

Splenomegaly, with evidence of portal hypertension (dilated peritoneal veins and esophageal varices), has been reported by investigators studying the effects of vinyl chloride exposure (Marsteller et al. 1975). In addition, hypertension among vinyl chloride workers (NIOSH 1977; Suciu et al. 1975) and significantly increased mortality rate due to cardiovascular and cerebrovascular disease (Byren et al. 1976) have been reported. Saad et al. (2017) reported that vinyl chloride workers had increased serum lipoprotein concentrations compared to healthy unexposed controls. Serum levels of total cholesterol, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, and triglycerides were similar between

vinyl chloride workers and controls. Conclusive evidence was not provided for an association of vinyl chloride with coronary heart disease (Kotseva 1996).

Animal Studies. Investigators studying the anesthetic properties of vinyl chloride in dogs have observed that doses producing anesthesia (100,000 ppm, Oster et al. 1947; 150,000–900,000 ppm, Carr et al. 1949) also produced cardiac arrhythmias. Arrhythmias were characterized by intermittent tachycardia, extra ventricular systoles, vagal beats, ventricular fibrillation, and atrioventricular block. However, the statistical significance of these effects was not reported. At high concentrations (>150,000 ppm), vinyl chloride was shown to sensitize the heart to epinephrine, resulting in cardiac arrhythmias in dogs (Carr et al. 1949). No histopathological changes in the heart were noted in guinea pigs exposed to 400,000 ppm of vinyl chloride for 30 minutes (Mastromatteo et al. 1960).

Bi et al. (1985) examined relative heart weight in rats after 3 or 6 months of exposure to 0–2,918 ppm vinyl chloride, 6 hours/day, 6 days/week. Findings did not exhibit a clear dose-response relationship. No changes in heart weights were reported when immunized rabbits were exposed up to 983 ppm vinyl chloride 6 hours/day, 5 days/week for 8 weeks (Sharma et al. 1980). Chronic-duration exposure of rats to 5,000 ppm vinyl chloride 7 hours/day, 5 days/week for 1 year resulted in increases in areas of myodegeneration in the heart and thickening of the walls of arteries (Feron and Kroes 1979). There were no significant findings reported in the transthoracic echocardiography examination of mice exposed to 0.85 ppm vinyl chloride 6 hours/day, 5 days/week for 12 weeks (Liang et al. 2018). Other cardiovascular parameters in these mice including gross cardiac dimensions, heart weight to tibia length ratio, left ventricular mass collected index, intraventricular septal thickness, left ventricular posterior wall, and cardiomyocyte cross-sectional area were similar to measurements in control mice.

Exposure of LDL receptor-knockout (KO) mice fed a western diet (42% kcal from fat) to 0.8 ppm vinyl chloride 6 hours/day, 5 days/week for 12 weeks did not affect the atherosclerotic lesion area in the aortic valves of the innominate artery (Zelko et al. 2022).

Mechanisms. It has been hypothesized that cardiac arrhythmia reported after vinyl chloride exposure may result from sensitization of the heart to circulatory catecholamines, as occurs with other halogenated hydrocarbons. This was demonstrated in a dog study where the EC_{50} for cardiac sensitization for vinyl chloride was determined to be 50,000 ppm (Clark and Tinston 1973). Cardiac sensitization by halogenated hydrocarbons generally occurs at very high air concentrations (0.5–90%) when the

compounds were tested as anesthetic agents in experimental studies (Brock et al. 2003). Therefore, it appears unlikely that individuals exposed to low levels of vinyl chloride will experience these effects.

2.6 GASTROINTESTINAL

Human Studies. Gastrointestinal symptoms including nausea and/or vomiting were reported in people working and living near the site of a train derailment (Shumate et al. 2017; Wilken et al. 2015). Approximately 32% of the vinyl chloride workers examined by Lilis et al. (1975) reported a history of "gastritis, ulcers (gastric and duodenal), and upper gastrointestinal bleeding." Because these subjects were not compared to workers who had not been exposed to vinyl chloride, the significance of these findings is unknown. Other symptoms reported by vinyl chloride workers included nausea, abdominal distension, and heartburn. Loss of appetite and nausea have been reported in a case series of Singapore workers exposed to 1–21 ppm vinyl chloride (Ho et al. 1991).

Animal Studies. No studies were located regarding gastrointestinal effects in animals exposed to vinyl chloride.

2.7 HEMATOLOGICAL

Human Studies. Blood tests performed at autopsy of two workers whose deaths were believed to be due to exposure to extremely high levels of vinyl chloride revealed that blood clotting did not occur (Danziger 1960). Slight-to-severe thrombocytopenia in workers exposed to vinyl chloride was reported in several occupational health studies, which often had no exposure measurements or a comparison group (Marsteller et al. 1975; Micu et al. 1985; Veltman et al. 1975). Thrombocytopenia was found in patients who both did and did not present with splenomegaly (Veltman et al. 1975) but Lilis et al. (1975) found no increased incidence of thrombocytopenia in their vinyl chloride worker study. A prospective cohort study of female workers exposed to vinyl chloride at levels ranging from 0.2 to 130.7 ppm showed that the exposed workers had a significantly lower number of platelets than the nonexposed controls during the early part of their pregnancies (weeks 8–10) but that this effect had abated by the end of the pregnancy (34–38 weeks) following a period free from exposure (Bao et al. 1988). Hemoglobin disorders (not further defined) were diagnosed in a higher number of vinyl chloride-exposed workers compared with unexposed controls in a cohort study (Zhu et al. 2005a). Splenomegaly was reported in a number of case reports and occupational health studies (Ho et al. 1991; Marsteller et al. 1975; Popper and Thomas 1975; Suciu et al. 1975; Veltman et al. 1975). Increased levels of two plasma proteins (α_1- and α_2-globulin)

were reported in case reports and occupational health studies examining the effects of exposure to vinyl chloride in workers (Harris and Adams 1967; Suciu et al. 1975).

Animal Studies. A brief (30-minute) exposure of guinea pigs to 400,000 ppm vinyl chloride resulted in a failure of the blood to clot in the animals that died during the exposure (Mastromatteo et al. 1960). Mice that were exposed to 5,000 ppm (4 hours/day for 6 days) or 10,000 ppm (4 hours/day for 5 days) showed an increased emergence of basophilic stippled erythrocytes (Kudo et al. 1990). This effect was also noted in mice that were exposed for 10 weeks to 50 ppm intermittently (4 hours/day for 4–5 days/week) or to 30–40 ppm continuously for 62 days (Kudo et al. 1990). Exposure of rats to either 50,000 ppm for 8 hours/day for 19 consecutive days or 20,000 ppm for 8 hours/day, 5 days/week for 92 days resulted in a decrease in white blood cells (Lester et al. 1963); this study was not included in Table 2-1 or Figure 2-2 due to colony contamination. Exposure of dogs and rats to 200 ppm for 7 hours/day, 5 days/week, for 6 months had no effect on hematologic values (Torkelson et al. 1961). An 8-week exposure of mice to 983 ppm for 6 hours/day, 5 days/week also had no effect on erythrocyte or leukocyte counts (Sharma and Gehring 1979). Exposure of rats to 5,000 ppm vinyl chloride for 7 hours/day, 5 days/week for 1 year produced increased hematopoiesis in the spleen (Feron and Kroes 1979). Blood clotting time was decreased in rats exposed to 5,000 ppm for 7 hours/day for 1 year (Feron et al. 1979a).

Wistar rats fed 14.1 mg/kg/day for up to 2.7 years showed decreased clotting time of the blood, which was not observed at 5 mg/kg/day (Feron et al. 1981). No changes in thrombocyte count or prothrombin times were noted in Wistar rats fed diets containing low concentrations of vinyl chloride in PVC resin (1.7 mg/kg/day) for 149 weeks (Til et al. 1983, 1991).

No changes in hematological parameters were reported in C57BL/6 mice exposed to 0.8 ppm vinyl chloride for 6 hours/day, 5 days/week for 12 weeks (Zelko et al. 2022).

2.8 MUSCULOSKELETAL

Human Studies. Case reports and occupational health studies, which often had no exposure measurements or comparison groups, reported that acroosteolysis, or resorption of the terminal phalanges of the finger, was observed in a small percentage of workers occupationally exposed to vinyl chloride (Dinman et al. 1971; Lilis et al. 1975; Marsteller et al. 1975; Sakabe 1975; Veltman et al. 1975; Wilson et al. 1967). Bone lesions were most often confined to the terminal phalanges of the fingers, but in a few cases the bones of the toes (Harris and Adams 1967), feet (Preston et al. 1976), sacroiliac joint (Harris

and Adams 1967), and arms, legs, pelvis, and mandible (Preston et al. 1976) were also involved. Development of acroosteolysis was most often preceded by Raynaud's phenomenon (Dinman et al. 1971; Freudiger et al. 1988; Harris and Adams 1967; Magnavita et al. 1986; Markowitz et al. 1972; Preston et al. 1976; Sakabe 1975; Veltman et al. 1975; Wilson et al. 1967). In two reports, bone resorption was observed to progress despite discontinuation of exposure (Markowitz et al. 1972; Preston et al. 1976). However, in two other reports, improvement was observed after exposure ceased (Veltman et al. 1975; Wilson et al. 1967). Joint pain was also reported by Lilis et al. (1975).

Animal Studies. Although Sokal et al. (1980) found no alterations in the bones of male rats exposed to 20,000 ppm for 5 hours/day, 5 days/week for 10 months, Viola et al. (1971) observed skeletal changes (i.e., osteochondroma) in the bones of rats exposed to 30,000 ppm for 4 hours/day, 5 days/week for 12 months.

Mechanisms. Impaired capillary microcirculation has been observed in vinyl chloride workers with Raynaud's phenomenon (Magnavita et al. 1986; Maricq et al. 1976). Because impaired microcirculation in the fingertips has been associated with resorptive bone loss, it has been hypothesized that activation of osteoclasts may be secondary to vascular insufficiency (Grainger et al. 1980; Ward 1976); however, no data investigating this possible mechanism are available.

2.9 HEPATIC

Human Studies. A potential association between vinyl chloride exposure and liver toxicity was evaluated in eight cohort studies, nine cross-sectional studies, four case-control studies (Table 2-3), and many occupational health case reports and case series (i.e., studies of vinyl chloride workers with no exposure measurements or relative to a comparison group) (not tabulated). Routine, noninvasive techniques revealed hepatomegaly (14–37%) in a limited number of workers (Ho et al. 1991; Lilis et al. 1975; Maroni et al. 2003; Marsteller et al. 1975; NIOSH 1977; Suciu et al. 1975). However, when peritoneoscopy was performed or biopsies were obtained from exposed workers, Marsteller et al. (1975) found a much higher prevalence of hepatic abnormalities. Only 37% of the workers studied by Marsteller et al. (1975) were diagnosed with hepatomegaly, but peritoneoscopy revealed a 50% incidence of granular changes in the liver surface and an 86% incidence of capsular fibrosis with increased numbers of capsular vessels. Histopathological examination of the biopsied tissue from these workers revealed an 80% incidence of collagenization of the sinusoidal walls, a 90% incidence of proliferation of cells lining the sinusoids, a 30% incidence of septal fibrosis, and degeneration of hepatocytes (incidence not specified).

A number of other investigators observed fibrotic changes in liver tissues obtained from workers exposed to vinyl chloride or detected by liver ultrasonography of exposed workers (Cave et al. 2010; Falk et al. 1974; Gedigke et al. 1975; Hsiao et al. 2004; Hsieh et al. 2007; Lee et al. 1977b; Maroni et al. 2003; Popper and Thomas 1975; Tamburro et al. 1984). Steatosis (i.e., fatty liver) and steatohepatitis (i.e., fatty liver with inflammatory changes) was also observed in studies of exposed workers (Cave et al. 2010; Hsiao et al. 2004; Maroni et al. 2003; Zhu et al. 2005a).

Table 2-3. Results of Epidemiological Studies Evaluating Exposure to Vinyl Chloride and Liver Effects (Noncancer)

Reference, study type, and population	Exposure or biomarker	Outcome evaluated	Result[a]
Lee et al. 2020 Cross-sectional, 108 male and 5 female workers (Taiwan)	2,065 μg/m^3; mean of high-VCM group	Albumin, AST, ALT, GGT, total and direct bilirubin, total cholesterol, TG, ALP	↔
Yuan et al. 2020 Cross-sectional, 447 adult residents (Taiwan)	Urinary TdGA >232.7 μg/g creatinine; residents living 10–20 km from petrochemical complex[b]	FIB-4	↑
Fedeli et al. 2019a Cohort (mortality), 1,658 male workers (Italy)	Cumulative exposure >2,378 ppm-years; workers in vinyl chloride production and polymerization facility	Cirrhosis	↑
Wang et al. 2019b Cross-sectional, 303 school-aged children (6–13 years) (Taiwan)	Urinary TdGA ≥160 μg/g creatinine; children living within 10 km of a petrochemical complex	AST	↑
		ALT, FIB-4, APRI	↔
Mundt et al. 2017 Cohort (mortality), 9,951 vinyl chloride workers (35 facilities in the United States)	287 to <2,271 ppm-year (3rd and 4th quintiles of cumulative exposure)	Cirrhosis	↑
Cave et al. 2010 Case-control, 16 male, non-obese, highly-exposed workers with steatohepatitis, 26 healthy worker controls, and 11 unexposed, healthy volunteers (Kentucky, United States)	11,319 ppm-years, estimated mean cumulative, long-term exposure (mean 18.9 years)	CK-18 (whole)	↑
		AST, ALT, CK-18 (caspase-cleaved fragments), TG	↔

Table 2-3. Results of Epidemiological Studies Evaluating Exposure to Vinyl Chloride and Liver Effects (Noncancer)

Reference, study type, and population	Exposure or biomarker	Outcome evaluated	Result[a]
Attarchi et al. 2007 Cross-sectional, 52 male PVC plant workers and 48 male office workers (Iran)	mean 0.8 ppm, long-term exposure (mean 9 years)	ALP, GGT	↑
		ALT, AST, total and direct bilirubin	↔
Hsieh et al. 2007 Cohort, 320 male workers in PVC plants (Taiwan); disease incidence determined by ultrasound	Significant exposure-response trend for 40–400, 400–800, and >800 ppm-years compare to <40 ppm-years	Fibrosis (cirrhosis and pre-cirrhosis)	↑
Maroni and Fanetti 2006 Cohort, 735 male and 22 female workers in vinyl chloride/PVC plants (Italy)	>1,000 ppm-years, cumulative exposure, or 500 ppm, historical maximum yearly average exposure	GGT, AST, ALT, total and conjugated bilirubin, TG, cholesterol, AST/ALT ratio >1	↔
Zhu et al. 2005a Cohort, 163 male and 75 female workers at a vinyl chloride polymerization plant (China); disease incidence determined by ultrasound	>15,000 mg, mean cumulative exposure dose	Liver ultrasonography abnormality	↑
		Fatty liver, hepatic hemangioma	↔
Hsiao et al. 2004 Cohort, 347 male workers (Taiwan); disease incidence determined by ultrasound	Cumulative exposure 2,400 ppm-months; workers with history of high exposure jobs	Fibrosis	↑
		Pre-cirrhosis	↑
		Cirrhosis	↔
		Fatty liver	↔
	Current exposure ≥10 ppm	AST, ALT, GGT	↔
Mastrangelo et al. 2004 Case-control (nested in a VCM worker cohort), 40 cases of cirrhosis, 139 controls without chronic liver diseases/cancers (Italy)	>2,500 ppm-years, cumulative exposure	Cirrhosis	↑
Maroni et al. 2003 Cohort, 735 male and 22 female workers in vinyl chloride/PVC plants (Italy); disease incidence determined by ultrasound	200 ppm (historical maximum yearly average exposure) or 100–1,000 ppm-years (cumulative exposure)	Periportal fibrosis	↑
	500 ppm, historical maximum yearly average exposure	Hepatomegaly, steatosis, GGT, ALT, TG	↔

Table 2-3. Results of Epidemiological Studies Evaluating Exposure to Vinyl Chloride and Liver Effects (Noncancer)

Reference, study type, and population	Exposure or biomarker	Outcome evaluated	Result[a]
Ward et al. 2001 Cohort (mortality), 12,700 male workers in the vinyl-chloride industry (Italy, Norway, Sweden, United Kingdom)	≥524 ppm-years, estimated cumulative exposure	Cirrhosis	↑
Cheng et al. 1999b Cross-sectional, 251 male workers in vinyl chloride manufacturing plants with low to moderate vinyl chloride exposure (Taiwan)	0.44–1.63 ppm, range of median vinyl chloride concentrations from area sampling (moderate-VCM-low-EDC group; range of median EDC concentrations from area sampling 0.32–0.44 ppm)[c]	ALT, AST, GGT	↔
Du and Wang 1998 Case-control, 1,058 male workers (current and former) at PVC factories with vinyl chloride exposure admitted to hospitals from January 1985 to March 1994 (Taiwan)	Exposed cases versus unexposed controls (VCM workers compared to optical workers or motorcycle manufacturers)	Cirrhosis, chronic liver diseases (unspecified)	↑
Du et al. 1995 Cross-sectional, 244 workers (7 females, 237 males) in PVC manufacturing factories (Taiwan)	56.3 ppm, current mean exposure for high exposure group	GGT	↑
		AST, ALP, ALT	↔
Liss et al. 1985 Case-control, workers in vinyl chloride/synthetic rubber manufacturing plants; 15 cases of chemical liver injury and 25 healthy worker controls (United States)	Workers with biopsy evidence of vinyl chloride-associated liver damage (50% with exposure ranking ≥4)	Cholylglycine, conjugates of cholic acid, indocyanine green clearance, and serum bile acids	↑
		ALP, ALT, AST and GGT	↔
Tamburro et al. 1984 Cross-sectional, 48 vinyl chloride monomer workers (United States); biopsy samples	Cumulative exposure indices of ≥3.5 (on a scale from 1 to 6)	Focal hepatocyte hyperplasia (histological evidence of chemical liver injury)	↑

Table 2-3. Results of Epidemiological Studies Evaluating Exposure to Vinyl Chloride and Liver Effects (Noncancer)

Reference, study type, and population	Exposure or biomarker	Outcome evaluated	Result[a]
Vihko et al. 1984 Cross-sectional, 76 workers with low to moderate occupational exposures to vinyl chloride (location not reported)	Up to 1 ppm, mean exposure time 3 years	ALT, chenodeoxycholic acid (bile acid)	↑
		GGT, LDH, conjugated and total bilirubin, cholic acid (bile acid)	↔
NIOSH 1977 Cross-sectional, 126 current and 71 former male workers with vinyl chloride exposure (United States)	Current or former workers with vinyl chloride exposure (exposure estimates not reported)	Hepatomegaly	↑
		AST, ALP, and total bilirubin	↔
	Former vinyl chloride workers	LDH	↑

[a]Up and down arrows were based on statistically significant results only.
[b]Used TdGA as a biomarker for vinyl chloride and ethylene dichloride exposure.
[c]Workers exposed to vinyl chloride and ethylene dichloride.

↑ = association with increase; ↓ = association with decrease; ↔ = no association; ALP = alkaline phosphatase; ALT = alanine amino transferase; APRI = AST to platelet ratio index; AST = aspartate amino transferase; CK-18 = serum cytokeratin 18; EDC = ethylene dichloride; FIB-4 = fibrosis-4 liver fibrosis index model considering age, AST, ALT, and platelet count as variables; GGT = gamma-glutamyl transferase; LDH = lactate dehydrogenase; PVC = polyvinyl chloride; TdGA = thiodiglycolic acid; TG = serum triglycerides; VCM = vinyl chloride monomer

Hepatic lesions in workers exposed to vinyl chloride generally include the following features identified by liver biopsy: hypertrophy and hyperplasia of hepatocytes, activation and hyperplasia of sinusoidal lining cells, fibrosis of the portal tracts and the septa and intralobular perisinusoidal regions, sinusoidal dilation, and focal areas of hepatocellular degeneration (Berk et al. 1975; Falk et al. 1974; Gedigke et al. 1975; Ho et al. 1991; Jones and Smith 1982; Lilis et al. 1975; Liss et al. 1985; Marsteller et al. 1975; NIOSH 1977; Popper and Thomas 1975; Suciu et al. 1975; Tamburro et al. 1984; Vihko et al. 1984). The incidence and severity of the effects correlated well with the duration of exposure (Gedigke et al. 1975; Lilis et al. 1975; NIOSH 1977).

Standard biochemical liver function tests appear to have low sensitivity for detecting liver injury produced by vinyl chloride (Berk et al. 1975; Cave et al. 2010; Cheng et al. 1999b; Hsiao et al. 2004; Lee et al. 1977b, 2020; Maroni and Fanetti 2006; Maroni et al. 2003; Marsteller et al. 1975; NIOSH 1977; Tamburro et al. 1984; Vihko et al. 1984). For example, the values obtained in several standard biochemical liver function tests (e.g., activities of serum alkaline phosphatase [ALP], aspartate aminotransferase [AST], alanine aminotransferase [ALT], gamma-glutamyltransferase [GGT]) from

workers with biopsy or ultrasonographic evidence of vinyl chloride-associated liver damage were not significantly higher than those from unexposed controls (Cave et al. 2010; Hsiao et al. 2004; Liss et al. 1985). Cytokeratin 18 (CK-18) was elevated in vinyl chloride workers with steatohepatitis (Cave et al. 2010). Serum ALP, ALT, and/or GGT levels were increased in some studies of workers exposed to high concentrations of vinyl chloride (1–20 ppm) (Du et al. 1995; Ho et al. 1991; Lilis et al. 1975). Serum ALP and GGT levels were increased by 10 and 29%, respectively, in workers exposed for at least 2 years to concentrations <1 ppm (Attarchi et al. 2007). Serum bile acids (Berk et al. 1975; Liss et al. 1985) and/or the results from the indocyanine green clearance test (Liss et al. 1985; Tamburro et al. 1984) correlated with liver injury. Furthermore, investigators were able to demonstrate that levels of chenodeoxycholic acid (a serum bile acid) in asymptomatic vinyl chloride workers were elevated when compared to the 95% interval of values from a healthy reference population (Vihko et al. 1984). The serum hyaluronic acid concentration was elevated in workers with angiosarcoma of the liver, even when other liver function tests were normal (McClain et al. 2002). The fibrosis-4 (FIB-4) score, which evaluates liver fibrosis based on a model considering age, platelet count and AST and ALT levels, was elevated in residents living near a petrochemical complex in Taiwan (Yuan et al. 2020). Vinyl chloride exposure in this study was estimated using thiodiglycolic acid as a urinary biomarker. Children with elevated urinary thiodiglycolic acid concentrations living near the same petrochemical complex did not exhibit significantly increased FIB-4 scores or an elevated AST to platelet ratio (APRI) (Wang et al. 2019b); however, these indices may not be accurate predictors of liver fibrosis or injury in children (Alkhouri et al. 2014). AST levels were significantly elevated in highly exposed children, suggesting a potential for toxicity in this population.

An increase in mortality from liver cirrhosis was demonstrated in several cohort studies of vinyl chloride workers (Fedeli et al. 2019a; Hsieh et al. 2007; Mastrangelo et al. 2004; Ward et al. 2001). Morbidity associated with liver cirrhosis was also reported to be elevated among vinyl chloride workers (Du and Wang 1998). Alcohol intake was not evaluated as a critical confounding factor in these studies. Mastrangelo et al. (2004) evaluated the possible interaction between alcohol consumption, hepatitis infection, and liver cirrhosis in a large cohort of vinyl chloride workers. Vinyl chloride was suggested to be an independent risk factor for liver cirrhosis with a synergistic interaction described for alcohol consumption and an additive interaction observed for hepatitis infection. Liver ultrasonography revealed an increase in the incidence of periportal fibrosis in vinyl chloride workers compared to unexposed workers from the same plants (Maroni et al. 2003). Portal fibrosis and portal hypertension were considered to contribute to mortality in several studies (Lee et al. 1996; Lelbach 1996). A meta-analysis of seven studies that included >40,000 vinyl chloride workers did not demonstrate increased mortality

from liver cirrhosis (Frullanti et al. 2012); however, that may have resulted from cirrhosis not being included on death certificates when a person died from liver cancer (Fedeli et al. 2019b; Mastrangelo et al. 2013).

Animal Studies. Brief exposures of animals to extremely high concentrations of vinyl chloride lead to hepatic damage. For example, acute-duration exposure (30 minutes) of guinea pigs and mice to 300,000 ppm of vinyl chloride produced liver congestion or severe fatty degeneration, while 200,000 ppm caused fatty infiltration in rats (Mastromatteo et al. 1960). Exposure to 100,000 ppm for 6 hours produced centrilobular vacuolization and increased alanine serum α-ketoglutarate transaminase activity in rats (Jaeger et al. 1974). However, exposure of rats to 50,000 ppm for 6 hours produced no observable effects on the liver (Reynolds et al. 1975a, 1975b). In contrast, a single-concentration study in which pregnant rats were continuously exposed to 1,500 ppm for 7–9 days during either the first or second trimester of pregnancy resulted in an increase in the liver-to-body-weight ratio (Ungvary et al. 1978). Absolute and relative liver weight was also increased (by 9 or 10%, respectively) in pregnant rats exposed to 2,500 ppm vinyl chloride for 7 hours/day on gestational days (GDs) 6–15 (John et al. 1977, 1981).

In studies with longer durations of exposure, lower concentrations of vinyl chloride have produced hepatic toxicity. Histopathological signs of hepatotoxicity observed in rats have included fatty liver and hepatocellular degeneration (Sokal et al. 1980; Torkelson et al. 1961; Wisniewska-Knypl et al. 1980), swelling of hepatocytes with compression of sinusoids (Lester et al. 1963), dilation of the rough endoplasmic reticulum (Du et al. 1979), nuclear polymorphism (Sokal et al. 1980), hypertrophy of smooth endoplasmic reticulum (Thornton et al. 2002; Wisniewska-Knypl et al. 1980), and proliferation of reticulocytes (Sokal et al. 1980). Changes in metabolic enzyme activities, such as cytochrome P-450, glucose-6-phosphatase, glutathione reductase, and glucose-6-phosphate dehydrogenase, occurred after inhalation exposure in rats (Du et al. 1979; Wisniewska-Knypl et al. 1980). Increased liver-to-body-weight ratio was observed in several studies following intermediate-duration exposure (Bi et al. 1985; Lester et al. 1963; Sokal et al. 1980; Thornton et al. 2002; Torkelson et al. 1961). Lester et al. (1963) was not included in Table 2-1 or Figure 2-2 due to parasitic liver cysts present in all animals, suggesting colony contamination. Histopathological liver lesions in mice have included lipid droplets, eosinophilic changes, nuclear condensation, steatosis, hepatic edema, cytoplasmic loosening, and hepatocyte nuclear fragmentation (Jia et al. 2022; Wang et al. 2019a). Mice exposed to vinyl chloride and fed a high-fat diet experienced liver damage (steatosis), neutrophil infiltration, apoptosis, and oxidative and endoplasmic reticulum stress compared to exposed mice fed a normal or low-fat diet (Chen et al. 2019; Fujiwara 2018; Jia et al. 2022; Lang et al. 2018, 2020; Liang et al. 2018; Liu et al. 2023; Wahlang et al. 2020).

Exposure of rats to 500 ppm for 7 hours/day, 5 days/week for 4.5 months resulted in an increase in liver-to-body-weight ratio and granular tissue degeneration (Torkelson et al. 1961). An increased liver-to-body-weight ratio was also found in rats exposed to 100 ppm vinyl chloride for 7 hours/day, 5 days/week for 6 months (Torkelson et al. 1961). The liver-to-body-weight ratio was increased (14–68%) in a dose-related manner at concentrations of 11.1, 105.6, and 2,918 ppm vinyl chloride in male rats exposed for 6 hours/day, 6 days/week for 6 months (Bi et al. 1985). In contrast, relative liver weight was decreased in mice exposed to 983 ppm vinyl chloride for 6 hours/day, 5 days/week for 8 weeks (Sharma and Gehring 1979). No changes in liver weights were reported when immunized rabbits were exposed up to 983 ppm vinyl chloride 6 hours/day, 5 days/week for 8 weeks (Sharma et al. 1980). Exposure of rats to 500 ppm for 5 hours/day, 5 days/week for 10 months produced swelling of hepatocytes and proliferation of reticuloendothelial cells, increased liver weight, and cellular degeneration; at 50 ppm, small lipid droplets and proliferation of smooth endoplasmic reticulum were noted (Sokal et al. 1980). Histopathological examination of rats exposed to either 50,000 ppm vinyl chloride for 8 hours/day for 19 consecutive days or 20,000 ppm vinyl chloride for 8 hours/day, 5 days/week, for 92 days showed hepatocellular hypertrophy, vacuolization, and sinusoidal compression (Lester et al. 1963); this study was not included in Table 2-1 or Figure 2-2 due to colony contamination.

Mice exposed to 313 ppm of vinyl chloride for 2 hours/day, 5 days/week for 13 weeks had decreased absolute liver weight and increased number of fat droplets in the liver (Jia et al. 2022). Histopathological changes in the liver that included hyperplasia of hepatocytes and activated sinusoidal cells were seen in mice exposed to 2,500 ppm vinyl chloride 5 hours/day, 5 days/week for up to 6 months (Schaffner 1978). Centrilobular necrosis and degeneration were noted in rabbits exposed to 200 ppm vinyl chloride 7 hours/day, 5 days/week for 6 months but not at 100 ppm vinyl chloride in this regimen (Torkelson et al. 1961). Exposure of rats to 50 ppm for 5 hours/day, 5 days/week for 10 months produced fatty degeneration and proliferation of the smooth endoplasmic reticulum (Wisniewska-Knypl et al. 1980). In contrast, no hepatic effects were seen in mice fed a control diet and exposed to 0.85 ppm vinyl chloride for 12 weeks (0.85 ppm, 6 hours/day, 5 days/week) examined immediately after the exposure period or 9 months later (Liu et al. 2023). Liver effects were observed in a 2-generation reproductive toxicity study where rats were exposed to ≥10 ppm vinyl chloride (6 hours/day for a 10-week premating period and a 3-week mating period, through GD 20, and from lactation day 4 through weaning [females only]) (Thornton et al. 2002). Absolute and relative mean liver weights were significantly increased at all exposure levels in F0 males and in 100- and 1,100-ppm F1 males. Centrilobular hypertrophy, considered to be a minimal adverse effect, was noted in the livers of all 1,100-ppm male and female F0 and F1 rats,

most 100-ppm male and female F0 and F1 rats, and 2/30 and 6/30 of the 10-ppm F0 male and F1 female rats, respectively. Centrilobular hypertrophy was not noted in the 30 female rats of the control group. Histopathological alterations occurring at 100 and 1,100 ppm included centrilobular hypertrophy and acidophilic, basophilic, and clear cell foci.

The NOAELs for liver effects in a number of species following a 6-month exposure to vinyl chloride indicated that mice and rats were the most sensitive (NOAEL of 50 ppm), rabbits were the next most sensitive (NOAEL of 100 ppm), and dogs and guinea pigs were the least sensitive (NOAEL of >200 ppm) (Torkelson et al. 1961).

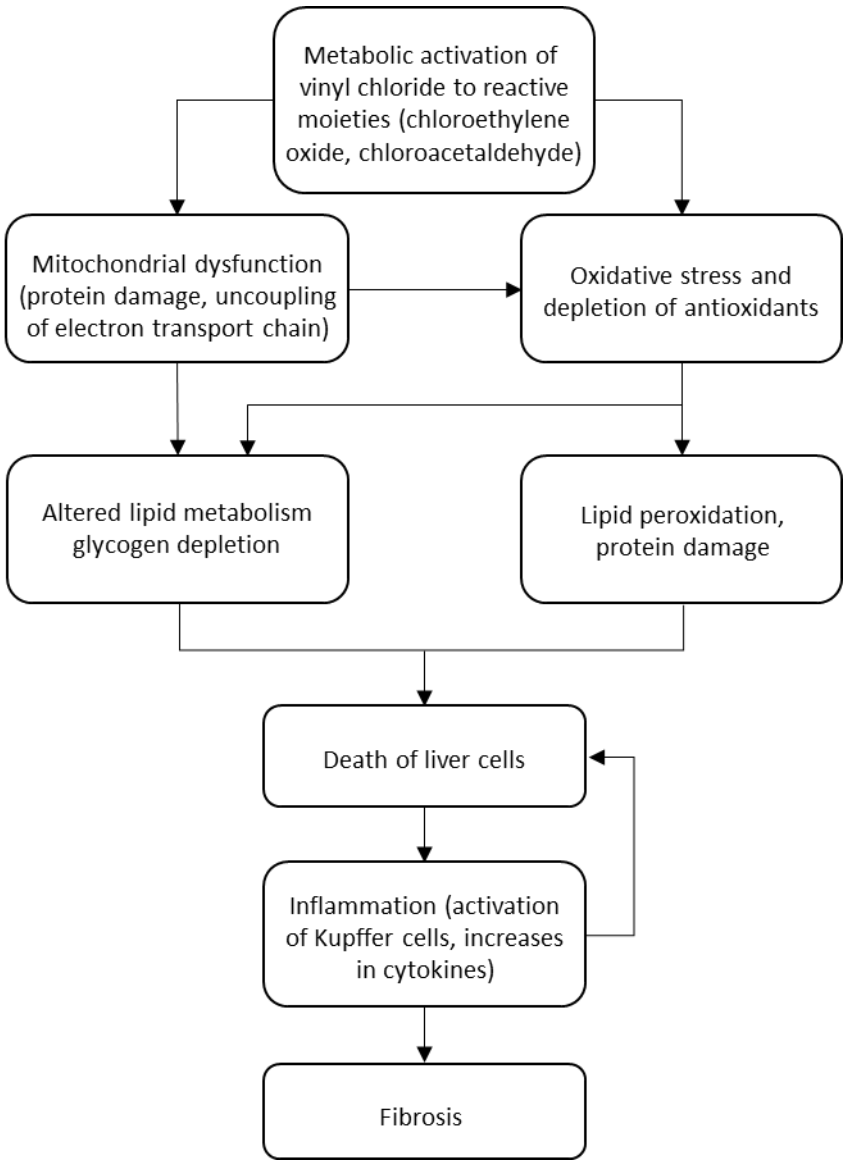
Popper et al. (1981) compared histopathological findings from sections of liver from mice and rats exposed by Maltoni and Lefemine (1975) with the liver biopsy material obtained from vinyl chloride workers. Hyperplasia and hypertrophy of hepatocytes and/or sinusoidal cells, with areas of sinusoidal dilation, were observed in both humans and rodents. The major difference between the species was the greater degree of fibrosis, seen as reticulin deposition and collagen formation, in the livers of humans. Also, inflammatory cells were present in the livers of humans but not rodents.

Chronic-duration exposure of rats to vinyl chloride in their feed for 149 weeks produced an increase in the incidence of several types of microscopic liver lesions in male and female rats (Til et al. 1983, 1991). Neoplastic and preneoplastic lesions in the liver included several types of foci of cellular alteration (i.e., clear-cell, basophilic, eosinophilic, or mixed), neoplastic nodules, hepatocellular carcinoma, and angiosarcoma. Other liver lesions associated with vinyl chloride exposure included liver-cell polymorphism and hepatic cysts (Til et al. 1983, 1991). Mottled livers with hemorrhagic patches were seen in rats gavaged with ≥ 3 mg/kg/day for 2 years (Knight and Gibbons 1987). Chronic-duration oral exposure of rats fed vinyl chloride daily during a 4-hour period for up to 2.7 years also resulted in areas of hepatocellular alteration at concentrations as low as 1.7 mg/kg/day (Feron et al. 1981). In this study, areas of necrosis were observed in the liver of female rats fed 5 mg/kg/day and male rats fed 14.1 mg/kg/day (Feron et al. 1981). At 1.7 mg vinyl chloride/kg/day, there was increased incidence of hepatic cysts and clear or basophilic foci in female rats with male rats exhibiting the same foci (Til et al. 1983, 1991).

Mechanisms. The mechanisms of vinyl chloride liver toxicity were described by Rusyn et al. (2021) (Figure 2-4). Vinyl chloride is metabolized to reactive intermediates including chloroethylene oxide and chloroacetaldehyde. These metabolites produce mitochondrial dysfunction by damaging proteins and

uncoupling of the electron transport chain, leading to oxidative stress, altered lipid metabolism, and glycogen depletion resulting in steatohepatitis. Oxidative stress leads to depletion of antioxidants, lipid peroxidation, and protein damage leading to hepatocellular death and inflammation. Pro-inflammatory signaling promotes remodeling of the extracellular matrix and fibrosis. Altered lipid metabolism resulting from mitochondrial dysfunction contributes to steatosis.

Figure 2-4. Key Characteristics of Hepatotoxicity Associated with Vinyl Chloride



Source: Rusyn et al. 2021

2.10 RENAL

Human Studies. A retrospective mortality study of workers exposed to contaminated drinking water (vinyl chloride, tetrachloroethylene, trichloroethylene, benzene) at Camp Lejeune in North Carolina did not show an increase in mortality from kidney disease (Bove et al. 2014). An ecological study evaluating residential exposure to contaminated groundwater reported an increased risk of decreased estimated glomerular filtration rate (GFR) and increased proteinuria in residents living near a PVC plant in Taiwan (Chen and Wu 2017). Groundwater was contaminated with vinyl chloride and other chlorinated solvents including trichloroethylene, 1,1-dichloroethylene, 1,1-dichloroethane, 1,2-dichloroethane, and *cis*-1,2-dichloroethene. No additional human studies were available regarding renal effects of vinyl chloride exposure.

Animal Studies. Acute-duration exposure of mice and rats to 300,000 ppm of vinyl chloride for 30 minutes resulted in kidney congestion (Mastromatteo et al. 1960). Degenerative changes were observed in the kidneys of one of five mice exposed to 100,000 or 200,000 ppm of vinyl chloride for 30 minutes (Mastromatteo et al. 1960). Relative kidney weight was increased by 20% in pregnant rats exposed to ≥100 ppm vinyl chloride 6 hours/day on GDs 6–19 (Thornton et al. 2002). Exposure of rats to 50,000 ppm for 8 hours/day for 19 consecutive days or 20,000 ppm for 8 hours/day, 5 days/week for 92 days produced no adverse effects on the kidneys (Lester et al. 1963); this study was not included in Table 2-1 or Figure 2-2 due to colony contamination. However, relative kidney weight was increased in male rats exposed to 2,918 ppm for 6 hours/day, 6 days/week, for 3 and 12 months or 105.6 ppm vinyl chloride for 6 hours/day, 6 days/week for 12 months after a 6-month observation period (Bi et al. 1985). Relative kidney weights were increased in male rats exposed to 500 ppm vinyl chloride for 5 hours/day, 5 days/week, for 10 months, although no histopathological changes in the kidney were noted (Sokal et al. 1980). No changes in kidney weights were reported when mice or immunized rabbits were exposed to 983 ppm vinyl chloride 6 hours/day, 5 days/week for 8 weeks (Sharma and Gehring 1979; Sharma et al. 1980). Urinalysis values were within normal limits in rats and rabbits exposed to 200 ppm vinyl chloride for up to 7 hours/day, 5 days/week, for 6 months (Torkelson et al. 1961). One year of exposure to 5,000 ppm vinyl chloride for 7 hours/day, 5 days/week produced an increase in the kidney-to-body-weight ratio (Feron et al. 1979a) and tubular nephrosis in rats (Feron and Kroes 1979).

Renal toxicity was observed in mice where vinyl chloride in aqueous solution (0, 1, or 200 mg/mL) was applied to the nasal cavity 5 days/week for up to 3 weeks (Hsu et al. 2019). Blood urea nitrogen (BUN) and creatinine levels were increased at both concentrations and glomerulosclerosis and tubular injury

were observed. Immunohistochemical analysis showed an increase in markers of fibrosis and autophagy. Fibrosis and autophagy were also observed in experiments using the HK-2 proximal tubular epithelial cell line (Hsu et al. 2019).

2.11 DERMAL

Human Studies. Vinyl chloride exists as a liquid when stored under pressure. However, when it is released from pressurized containers, it rapidly vaporizes to a gas. Thus, the adverse dermal effects observed after exposure to vinyl chloride are not unique to vinyl chloride but can be expected as a result of a rapidly evaporating liquid on the skin. The effects are due to tissue freezing rather than direct toxicity of vinyl chloride. A man who had liquid vinyl chloride sprayed on his hands developed second-degree burns. At first, the man reported that his hands felt numb. Within a short period, the hands had developed marked erythema and edema (Harris 1953). Dermatological symptoms (not further specified) were reported in residents seeking medical attention following derailment of a train carrying vinyl chloride (Shumate et al. 2017).

Case reports and occupational health studies indicated that exposure to vinyl chloride resulted in scleroderma-like skin changes on the hands of a small percentage of exposed workers (Freudiger et al. 1988; Lilis et al. 1975; Marsteller et al. 1975; Suciu et al. 1975; Veltman et al. 1975; Walker 1976). The skin changes were characterized by a thickening of the skin (Lilis et al. 1975; Markowitz et al. 1972; Ostlere et al. 1992; Preston et al. 1976; Veltman et al. 1975; Walker 1976), decreased elasticity (Lilis et al. 1975), and edema (Lilis et al. 1975; Suciu et al. 1975) and were almost exclusively observed in exposed individuals who also suffered from Raynaud's phenomenon. Skin biopsies revealed increased collagen bundles in the subepidermal layer of the skin (Harris and Adams 1967; Markowitz et al. 1972; Ostlere et al. 1992; Veltman et al. 1975). Biochemical analyses by Jayson et al. (1976) demonstrated that a high rate of collagen synthesis was taking place in the affected skin. The skin changes were most often confined to the hands and wrists, but Jayson et al. (1976) reported scleroderma-like skin changes on the hands, arms, chest, and face of one afflicted worker.

Animal Studies. Skin changes were observed in rats exposed to 30,000 ppm for 12 months (Viola 1970). The skin of the paws of the exposed rats showed areas of hyperkeratosis, thickening of the epidermis, edema, collagen dissociation, and fragmentation of the elastic reticulum. Interpretation of these results is limited by the absence of a statistical analysis and insufficient information on the treatment of control animals. Lester et al. (1963) reported that male rats exposed to 50,000 ppm vinyl chloride 8 hours/day for

19 days had thin coats and scaly tails, while females exposed to the same concentration showed no effects; this study was not included in Table 2-1 or Figure 2-2 due to colony contamination.

Daily administration of 30 mg/kg of vinyl chloride to rats by gavage for 2 years produced increased thickness, moisture content, and collagen content of the skin. Newly synthesized intermolecular and intramolecular collagen crosslinks were also significantly increased (Knight and Gibbons 1987).

2.12 OCULAR

Human Studies. Local burns on the conjunctiva and cornea were observed in a man who died after exposure to an unknown quantity of vinyl chloride escaping from an open valve (Danziger 1960). First responders to a train derailment and nearby refinery workers reported irritation, pain, or burning of eyes (Brinker et al. 2015; Wilken et al. 2015). Ocular symptoms (not further specified) were also reported in nearby residents seeking medical attention after the train derailment (Shumate et al. 2017).

Animal Studies. No adverse ocular effects were noted in guinea pigs exposed for 30 minutes to up to 400,000 ppm vinyl chloride in inhalation chambers (Mastromatteo et al. 1960).

2.13 ENDOCRINE

Human Studies. A study of workers exposed to vinyl chloride in PVC manufacturing plants reported that most workers who presented with scleroderma were shown to have thyroid insufficiency detected by reduced iodine uptake (Suciu et al. 1975).

Animal Studies. No histopathological effects on the adrenals were reported in guinea pigs exposed to 400,000 ppm for 30 minutes (Mastromatteo et al. 1960). No changes in adrenal weights were reported when immunized rabbits were exposed up to 983 ppm vinyl chloride 6 hours/day, 5 days/week for 8 weeks (Sharma et al. 1980). Rats exposed to 30,000 ppm vinyl chloride 4 hours/day, 5 days/week for 12 months were found to have colloid goiter and markedly increased numbers of perifollicular cells (Viola 1970).

2.14 IMMUNOLOGICAL

Human Studies. The potential association between vinyl chloride exposure and immunological toxicity was evaluated in five cross-sectional studies, three case-control studies (Table 2-4), and many occupational health studies, case reports, and case series. Male workers exposed to vinyl chloride for an average of 8 years, with concentrations ranging from 1 to 300 ppm during sampling periods, were found to have significantly increased percentages of lymphocytes compared to controls (Fucic et al. 1995, 1998). Additionally, 75 out of these 100 workers showed disturbances of mitotic activity in their lymphocytes. A statistically significant increase in circulating immune complexes was observed in vinyl chloride workers when compared to the levels in unexposed workers (Bogdanikowa and Zawilska 1984; Saad et al. 2017). The increase in circulating immune complexes was greatest in women and in those with duties involving exposure to relatively higher levels of vinyl chloride. Compared to controls, IgG levels were significantly increased in women exposed to the high levels of vinyl chloride in the same study (Bogdanikowa and Zawilska 1984). Serum immunoglobulins (IgA, IgG, and IgM) and other inflammatory markers (i.e., ceruloplasmin, orosomucoid) were elevated in highly exposed male vinyl chloride workers when compared to a similar worker population exposed to lower concentrations (Bencko et al. 1988) or an unexposed residential population (Wagnerova et al. 1988). Proinflammatory cytokine levels (tumor necrosis factor-α, interleukin-1β, interleukin-6, and interleukin-8) were increased in the serum of vinyl chloride-exposed workers with steatohepatitis when compared with healthy control workers (Cave et al. 2010).

Table 2-4. Results of Epidemiological Studies Evaluating Exposure to Vinyl Chloride and Immunological Effects

Reference, study type, and population	Exposure or biomarker	Outcome evaluated	Result[a]
Saad et al. 2017 Cross-sectional, 20 workers (Egypt)	Exposed versus unexposed (15 healthy controls)	Circulating immune complexes, complement factors C3 and C4	↑
Cave et al. 2010 Case-control, 16 male, non-obese, highly exposed workers with steatohepatitis, 26 healthy worker controls, and 11 unexposed, healthy volunteers (Kentucky, United States)	11,319 ppm-years, estimated mean cumulative, long-term exposure (mean 18.9 years)	TNF-α, IL-1β, IL-6, and IL-8	↑

Table 2-4. Results of Epidemiological Studies Evaluating Exposure to Vinyl Chloride and Immunological Effects

Reference, study type, and population	Exposure or biomarker	Outcome evaluated	Result[a]
Fucic et al. 1998 Cross-sectional, 121 male VCM workers, 60 unexposed controls (Croatia)	300±100 ppm (18.9 years duration)	Absolute and relative[b] lymphocyte counts	↑
Fucic et al. 1995 Cross-sectional, 100 male VCM workers, 100 unexposed controls (Croatia)	1 ppm (up to 300 ppm for short periods)	Percent lymphocytes	↑
Bencko et al. 1988 Cross-sectional, 59 male VCM workers exposed to >4 ppm compared to 98 male VCM workers exposed <4ppm (Czech Republic)	>4 ppm	Serum IgG, IgA, IgM, ceruloplasmin, orosomucoid	↑
Wagnerova et al. 1988 Cross-sectional, 110 VCM workers (59 smokers and 51 nonsmokers), 55 age-matched residential controls (Czechoslovakia)	Exposed versus unexposed	Serum IgA, IgG, IgM, lysozyme, orosomucoid, α_2-macroglobulin, ceruloplasmin	↑
		Transferrin, α_1-antitrypsin	↔
Black et al. 1983, 1986 Case-control, 44 workers with "vinyl chloride disease"[c], 30 asymptomatic worker controls, 200 unexposed controls (United Kingdom)	Exposed versus unexposed	HLA-DR5 antigen; severity of disease correlated with HLA-DR3 and HLA-B8 antigens	↑
		Antinuclear, anticentromere, anti-Scl-70 and collagen antibodies	↓
Bogdanikowa and Zawilska 1984 Cross-sectional, 136 vinyl chloride workers, 41 unexposed controls (Poland)	Exposed versus unexposed	Circulating immune complexes, IgG concentration	↑

Table 2-4. Results of Epidemiological Studies Evaluating Exposure to Vinyl Chloride and Immunological Effects

Reference, study type, and population	Exposure or biomarker	Outcome evaluated	Result[a]
Grainger et al. 1980 Case-control, 53 workers with definite or possible "vinyl chloride disease"[c], 35 asymptomatic worker controls, (location not specified)	Exposed versus unexposed	Circulating immune complexes, cryoglobulinemia, C3 complement activation, altered IgG structure	↑

[a]Up and down arrows were based on statistically significant results only.
[b]Relative to the white blood cell count.
[c]Symptoms of "vinyl chloride disease" include Reynaud's phenomenon, scleroderma-like lesions, dyspnea, arthralgia, and myalgia, as well as radiological evidence of acroosteolysis.

↑ = association with increase; ↓ = association with decrease; ↔ = no association; HLA = human lymphocytic antigen; Ig = immunoglobulin; IL-1β = interleukin-1β; IL-6 = interleukin-6; IL-8 = interleukin-8; TNF-α = tumor necrosis factor-α; VCM = vinyl chloride monomer

Studies of workers who developed "vinyl chloride disease," a syndrome consisting of Raynaud's phenomenon, acroosteolysis, joint and muscle pain, enhanced collagen deposition, stiffness of the hands, and scleroderma-like skin changes, indicate that this disease may have an immunologic basis. Sera obtained from patients with varying degrees of severity of symptoms of vinyl chloride disease demonstrate a close correlation between the disease severity and the frequency of the immunologic abnormality (Grainger et al. 1980; Langauer-Lewowicka et al. 1976; Ward 1976), although these symptoms have also been reported without immunological findings (Black et al. 1986; Ostlere et al. 1992). The most frequent immunologic finding in workers with vinyl chloride disease is an increase in circulating immune complexes or cryoglobulinemia. In workers with the most severe clinical signs, there also are an increased incidence of B-cell proliferation, hyperimmunoglobulinemia (Ward 1976), cryoglobulinemia (Grainger et al. 1980), and complement activation (Grainger et al. 1980; Ward 1976). Evidence of a structurally altered IgG is sometimes observed, and it has been proposed that vinyl chloride (or a metabolite) binds to IgG (Grainger et al. 1980).

Based on the similarity of vinyl chloride disease and systemic sclerosis, which may be a genetically linked autoimmune disease, Black et al. (1983, 1986) examined the human lymphocyte antigen (HLA) phenotypes of patients with vinyl chloride disease. Many autoimmune diseases show statistically significant associations with certain HLA alleles. These authors found that when compared to unexposed

controls or asymptomatic controls, workers with vinyl chloride disease were more likely to possess the HLA-DR5 allele. Furthermore, among those with the disease, the severity of the symptoms was significantly related to the possession of the HLA-DR3 and B8 alleles. These authors concluded that susceptibility was increased in the presence of HLA-DR5 or a gene in linkage disequilibrium with it. Progression was favored in those with the HLA-DR3 and B8 phenotypes. Immune system dysfunction has also been linked to a case of polymyositis (i.e., muscle fiber necrosis and atrophy) in an exposed worker where there was involvement of antibodies to histidyl-t-RNA synthetase (Jo-1) (Serratrice et al. 2001). Splenomegaly was reported in a number of case reports and occupational health studies (Ho et al. 1991; Marsteller et al. 1975; Popper and Thomas 1975; Suciu et al. 1975; Veltman et al. 1975).

Animal Studies. No histopathological changes were noted in the spleen or lymph nodes of guinea pigs exposed to 400,000 ppm vinyl chloride for 30 minutes (Mastromatteo et al. 1960). An increase in the relative spleen weight was observed in rats exposed to 50 ppm for 5 hours/day, 5 days/week for 10 months (Sokal et al. 1980). Although no dose response was evident, increased relative spleen weight was also reported by Bi et al. (1985) when rats were exposed to either 11.1 ppm for 6 hours/day, 6 days/week for 6 months or 2,918 ppm for 6 hours/day, 6 days/week for 3 months (Bi et al. 1985).

The immunologic effects of vinyl chloride were also examined in mice and rabbits (Sharma and Gehring 1979; Sharma et al. 1980). Rabbits were injected with a 1:1 mixture of tetanus toxoid and Freud's complete adjuvant in their footpad or an intradermal injection of tuberculin. Lymphocytes isolated from the spleens of mice and immunized rabbits exposed to concentrations as low as 10 ppm vinyl chloride 6 hours/day, 5 days/week for 4 weeks had increased spontaneous proliferation and in mice, mitogen-stimulated responses to phytohemagglutinin and pokeweed mitogen. This increase was not observed when lymphocytes from unexposed mice were cultured in the presence of vinyl chloride but was observed in the presence of the vinyl chloride metabolite, thiodiglycolic acid (Sharma and Gehring 1979; Sharma et al. 1980). Increased absolute and relative thymus weights were also seen in immunized rabbits exposed to 983 ppm (Sharma et al. 1980). Despite the increased immunoactivity in immunized rabbits exposed to vinyl chloride, the exposure did not affect antigen-induced immune responses (Sharma et al. 1980). A 2-fold increase in pulmonary interstitial macrophages was reported in male C57BL/6 mice exposed to 0.8 ppm vinyl chloride 6 hours/day, 5 day/week for 12 weeks; however, the levels of alveolar macrophages, circulating or bronchoalveolar lavage fluid (BALF) immune cells, cytokines or chemokines, endothelial progenitor cells, or platelet-immune cell aggregates were unaffected by exposure (Zelko et al. 2022).

Mechanisms. Vinyl chloride disease exhibits many of the characteristics of autoimmune diseases (Raynaud's phenomenon and scleroderma). B-cell proliferation, hyperimmunoglobulinemia, and complement activation, as well as increased circulating immune complexes or cryoglobulinemia, have been noted in affected workers indicating stimulation of immunological responses (Bogdanikowa and Zawilska 1984; Grainger et al. 1980; Ward 1976). Mechanisms for the vascular changes, such as those occurring with Raynaud's phenomenon, have been proposed by Grainger et al. (1980) and Ward (1976). According to these mechanisms, a reactive vinyl chloride intermediate metabolite, such as 2-chloroethylene oxide or 2-chloroacetaldehyde, binds to a protein such as IgG. The altered protein initiates an immune response, with deposition of immune products along the vascular endothelium. Circulating immune complexes are proposed to precipitate in response to low temperatures, and these precipitates are proposed to cause blockage of the small blood vessels. Scleroderma is an autoimmune disease of unknown etiology that involves a chronic hardening and contraction of the skin and connective tissues. It is characterized clinically by cutaneous and visceral fibrosis and can range from limited skin involvement to extensive cutaneous sclerosis with internal organ changes, including an enlarged and fibrotic spleen. Fetal cells may be involved in the pathogenesis of scleroderma. An increase in the number of microchimeric cells of fetal origin was reportedly associated with dermal fibrosis in mice injected with vinyl chloride (Christner et al. 2000).

2.15 NEUROLOGICAL

Human Studies. Epidemiology studies evaluating neurological effects of vinyl chloride exposure include two cohort studies, two volunteer studies, and three cross-sectional studies (Table 2-5). Other reports include three medical surveillance reports following a train derailment plus several occupational health studies and case reports, which often had no exposure measurements or comparison group (not tabulated).

Table 2-5. Results of Epidemiological Studies Evaluating Exposure to Vinyl Chloride and Neurological Effects

Reference, study type, and population	Exposure or biomarker	Outcome evaluated	Result[a]
Bove et al. 2014 Cohort (mortality), 8,964 Marine and Navy personnel stationed at Camp Lejeune (California, United States)	>500 µg/L-months (contaminated drinking water)	Amyotrophic lateral sclerosis	↔

Table 2-5. Results of Epidemiological Studies Evaluating Exposure to Vinyl Chloride and Neurological Effects

Reference, study type, and population	Exposure or biomarker	Outcome evaluated	Result[a]
Zhu et al. 2005a Cohort, 163 male and 75 female workers at a vinyl chloride polymerization plant (China)	>15,000 mg, mean cumulative exposure dose	Neurasthenia (not further defined)	↑
Perticoni et al. 1986 Cross-sectional, 64 male vinyl chloride workers (Italy)	Exposed versus unexposed (not quantified)	Peripheral neuropathy (denervation-related fasciculations and fibrillations and increased duration and amplitude of motor unit potentials)	↑
NIOSH 1977 Cross-sectional, 126 current and 71 former male workers with vinyl chloride exposure (United States)	Current or former workers with vinyl chloride exposure (exposure estimates not reported)	Headache, loss of consciousness, depressed reflexes	↑
Spirtas et al. 1975 Cross-sectional, 491 vinyl chloride and PVC workers	Exposure-response relationship observed (exposure estimates from job categories; low: 0–10 ppm, high: 20–30 ppm)	Headache, lightheadedness, dizziness, paresthesia, fatigue	↑
		Muscle weakness	↔
Lester et al. 1963 Volunteers, 3 men and 3 women	≥12,000 ppm for 5 minutes twice a day in periods separated by 6 hours on 3 consecutive days	Dizziness, headache, nausea	↑
Patty et al. 1930 Volunteers, 2 (gender not specified) (United States)	25,000 ppm for 3 minutes	Dizziness, disorientation, headache, burning sensation in feet	↑

[a]Up arrows were based on statistically significant results only.

↑ = association with increase; ↔ = no association

Neurological symptoms, including headache, dizziness, and lightheadedness were reported in first responders, refinery workers, and nearby residents following derailment of a train carrying vinyl chloride (Brinker et al. 2015; Shumate et al. 2017; Wilken et al. 2015). No abnormalities were observed by head CT scan or brain MRI evaluations of nearby residents seeking medical attention (Shumate et al. 2017).

Frequently reported central nervous system symptoms are consistent with the anesthetic properties of vinyl chloride. A man who had liquid vinyl chloride sprayed on his hands initially reported that his hands

felt numb (Harris 1953). The most commonly reported central nervous system effects are ataxia or dizziness (Ho et al. 1991; Langauer-Lewowicka et al. 1983; Lilis et al. 1975; Marsteller et al. 1975; Shumate et al. 2017; Spirtas et al. 1975; Suciu et al. 1975; Veltman et al. 1975), drowsiness or fatigue (Langauer-Lewowicka et al. 1983; Spirtas et al. 1975; Suciu et al. 1975; Walker 1976), loss of consciousness (NIOSH 1977), and/or headache (Brinker et al. 2015; Langauer-Lewowicka et al. 1983; Lilis et al. 1975; Marsteller et al. 1975; NIOSH 1977; Shumate et al. 2017; Spirtas et al. 1975; Suciu et al. 1975; Veltman et al. 1975; Wilken et al. 2015) and neurasthenia (i.e., lassitude, fatigue, headache, and irritability) (Zhu et al. 2005a). Other central nervous system effects that were reported by vinyl chloride workers include euphoria and irritability (Suciu et al. 1975), visual and/or hearing disturbances (Marsteller et al. 1975), nausea (Marsteller et al. 1975; Spirtas et al. 1975; Wilken et al. 2015), memory loss (Langauer-Lewowicka et al. 1983; Suciu et al. 1975), plus nervousness and sleep disturbances (Langauer-Lewowicka et al. 1983; Suciu et al. 1975). Central nervous system tests revealed pyramidal signs and cerebellar disturbances in some exposed subjects (Langauer-Lewowicka et al. 1983); however, reliable estimates of exposure levels producing these effects were not available.

Exposure of volunteers to known levels of vinyl chloride provided some indications of the levels of vinyl chloride associated with the effects noted above. Volunteers exposed to 25,000 ppm vinyl chloride for 3 minutes in a single-exposure study reported experiencing dizziness, disorientation, and burning sensations in the feet during exposure (Patty et al. 1930). Recovery from these effects was rapid upon termination of exposure, but the subjects later developed slight headaches, which lasted approximately 30 minutes. Exposure of volunteers to concentrations of vinyl chloride ranging from 4,000 to 20,000 ppm for 5 minutes twice a day in periods separated by 6 hours on 3 consecutive days was studied by Lester et al. (1963). No effects were noted at 4,000 ppm. However, at 12,000 ppm, two of six subjects reported feeling dizzy. The incidence of dizziness increased at higher concentrations. Nausea was experienced at higher concentrations, and recovery from all effects was rapid upon termination of exposure. Headaches developed following exposure to 20,000 ppm.

Indications of an exposure-related peripheral neuropathy were observed in a number of the occupational studies. A peripheral neuropathy, most severe in hands and feet, was diagnosed in 70% of the vinyl chloride workers examined in a study by Perticoni et al. (1986). The peripheral neuropathy was manifested as denervation-related fasciculations and fibrillations with increased duration and amplitude of motor unit potentials (indicating collateral sprouting). Similar effects were observed by Magnavita et al. (1986) in a case study of a vinyl chloride worker. Other peripheral nervous system symptoms were reported in occupational health studies of vinyl chloride workers. The symptom most frequently reported

was tingling (paresthesia) in the extremities (Lilis et al. 1975; Sakabe 1975; Spirtas et al. 1975; Suciu et al. 1975; Veltman et al. 1975; Walker 1976). Additional peripheral nervous system symptoms included numbness in the fingers (Lilis et al. 1975; Sakabe 1975), weakness (Langauer-Lewowicka et al. 1983; Suciu et al. 1975), depressed reflexes (NIOSH 1977), warmth in the extremities (Suciu et al. 1975), and pain in the fingers (Sakabe 1975). It is unclear whether some of these symptoms were associated with tissue anoxia due to vascular insufficiency, or whether they represent the direct toxic effects of vinyl chloride on peripheral nerves.

Animal Studies. Acute-duration exposure to high levels of vinyl chloride in a number of species provides additional information on the central nervous system effects that are produced. Exposure to 10,000 ppm for 8 hours (Patty et al. 1930) was observed to be without effects in guinea pigs. Exposure to 25,000 ppm resulted in ataxia, which progressed to unconsciousness across the 8-hour exposure. As the concentration was increased, the latency before the animals became unconscious decreased. In a different study, Mastromatteo et al. (1960) observed the development of unconsciousness within 30 minutes at a vinyl chloride concentration of 100,000 ppm in guinea pigs. Mice experienced similar signs at approximately equivalent exposure levels. At 5,000 ppm, vinyl chloride was without effect during a 1-hour exposure. Exposure to 50,000 ppm produced ataxia and twitching (Hehir et al. 1981), and at 100,000 ppm for 30 minutes, unconsciousness was produced, proceeded by increased motor activity, incoordination, twitching, and tremors (Mastromatteo et al. 1960). Similar effects in rats were observed by Lester et al. (1963), Jaeger et al. (1974), and Mastromatteo et al. (1960). In contrast, in one rat study, exposure to 50,000 ppm for 1 hour was without effect (Hehir et al. 1981). No effects were noted in rats exposed to 500 ppm vinyl chloride for 2 weeks (1 hour/day, 5 days/week) or in rats exposed to 50 ppm for 20 weeks (1 hour/day, 5 days/week) (Hehir et al. 1981). In addition, tolerance developed to the intoxicating effects of exposure to 50,000 ppm vinyl chloride after five or six 8-hour exposures (Lester et al. 1963); this study was not included in Table 2-1 or Figure 2-2 due to colony contamination. No changes in brain weights were reported when immunized rabbits were exposed to 983 ppm vinyl chloride 6 hours/day, 5 days/week for 8 weeks (Sharma et al. 1980).

Chronic-duration exposure of rats to high levels of vinyl chloride produced damage to nervous tissue. Rats exposed to 30,000 ppm for 4 hours/day, 5 days/week for 12 months in a single-concentration study were soporific during the exposure periods (Viola 1970; Viola et al. 1971). Following 10 months of exposure, the rats had decreased responses to external stimuli and disturbed equilibrium. No animal studies were located that examined hearing damage after vinyl chloride exposure. Histopathological examination revealed diffuse degeneration of the brain gray and white matter. Cerebellar degeneration in

the Purkinje cell layer was pronounced. Peripheral nerve endings were surrounded and infiltrated with fibrous tissue (Viola 1970; Viola et al. 1971). Nonneoplastic lesions in the brain were not noted in rats exposed to 5,000 ppm for 7 hours/day, 5 days/week for 12 months in a single-concentration study by Feron and Kroes (1979).

Mechanisms. Peripheral nervous system symptoms such as paresthesia, numbness, weakness, warmth in the extremities, and pain in the fingers have been reported after vinyl chloride exposure (Langauer-Lewowicka et al. 1983; NIOSH 1977; Suciu et al. 1963, 1975). It is not known whether these effects represent direct adverse effects of vinyl chloride on peripheral nerves or whether they are associated with tissue anoxia due to vascular insufficiency.

2.16 REPRODUCTIVE

Human Studies. Occupational health studies of vinyl chloride workers suggest that sexual performance may be affected by vinyl chloride. However, these studies are limited by the lack of quantification of exposure levels and no comparison group. Sexual impotence was reported by 24% of the workers examined by Suciu et al. (1975). Approximately 20% of the workers examined by Veltman et al. (1975) complained of potency troubles. A loss of libido in 35% and impotence and decreased androgen secretion in 8% of workers exposed at least once to very high levels of vinyl chloride were also reported by Walker (1976).

In retrospective and prospective studies by Bao et al. (1988), increased incidence and severity of elevated blood pressure and edema during pregnancy (preeclampsia) were found in female workers exposed to vinyl chloride when compared to unexposed workers. Company records indicated that exposure levels ranged from 3.9 to 89.3 ppm during the retrospective study and from 0.2 to 130.7 ppm during the prospective study.

Animal Studies. A 2-generation reproductive toxicity study was conducted in rats exposed to vinyl chloride via inhalation (Thornton et al. 2002). Male and female Sprague-Dawley rats were exposed to 0, 10, 100, or 1,100 ppm vinyl chloride 6 hours/day for a 10-week premating period, a 3-week mating period, through GD 20, and from lactation day 4 through weaning (females only). No adverse effects were noted in reproductive capability over the two generations at any dose. No effects were seen in body weight, food consumption, ability to reproduce, gestation index or length, or pre- and postweaning developmental landmarks. Sperm counts, motility, and morphology were also unaffected by vinyl

chloride exposure. Changes in liver weights and/or histopathological alterations were seen in F0 and F1 generation male and female rats. For further information regarding the liver toxicity of vinyl chloride, refer to Section 2.9.

Exposure of rats to ≥105.6 ppm for 6 hours/day, 6 days/week for up to 12 months produced a significant increase in the incidence of damage to the seminiferous tubules and depletion of spermatocytes (Bi et al. 1985). At the 6-month interim sacrifice, a significant decrease in relative testicular weight was also observed at 105.6 ppm. Several methodological limitations have been identified for this study. Temperature and humidity conditions in the inhalation chambers were not maintained within the normal range. Inhalation chamber volume and air flow were also not held constant across dose groups.

A significant increase in damage to the spermatogenic epithelium and disorders of spermatogenesis were found with exposure to 500 ppm vinyl chloride for 5 hours/day, 5 days/week for 10 months (52% incidence versus 11% incidence in controls) (Sokal et al. 1980). These testicular effects were not observed in rats exposed to 20,000 ppm. The smaller number of animals in the 20,000-ppm group (17 versus 28 controls) may have contributed to the lack of statistical significance in this group. No significant change in testicular weight was found in rats exposed to 500 ppm for 7 hours/day, 5 days/week for 4.5 months, in dogs, rabbits, or guinea pigs exposed to 200 ppm for 7 hours/day, 5 days/week for 6 months (Torkelson et al. 1961), or in mice exposed to 0.85 ppm vinyl chloride 6 hours/day, 5 days/week for 12 weeks (Wahlang et al. 2020). No histopathological data on the testes of these animals were presented.

2.17 DEVELOPMENTAL

Human Studies. The potential association between vinyl chloride exposure and developmental toxicity was evaluated in one cohort study, one cross-sectional study, six case-control studies, and two ecological studies (Table 2-6). Although some early studies suggested that members of communities with nearby vinyl chloride polymerization facilities had significantly greater risk of fetal loss or birth defects (Infante 1976; Infante et al. 1976a, 1976b; NIOSH 1977), most studies failed to demonstrate a correlation between the developmental toxicity and either parental occupation or proximity to the facility (Bao et al. 1988; Edmonds et al. 1975, 1978; Rosenman et al. 1989; Theriault et al. 1983). Case-control studies evaluating exposure to multiple compounds in air and drinking water during pregnancy did not demonstrate an association between the vinyl chloride concentration and the risk of neural tube defects including spina

bifida (Ruckart et al. 2013; Swartz et al. 2015), oral clefts (Ruckart et al. 2013), or autism spectrum disorder (Talbott et al. 2015).

Table 2-6. Results of Epidemiological Studies Evaluating Exposure to Vinyl Chloride and Developmental Effects

Reference, study type, and population	Exposure or biomarker	Outcome evaluated	Result[a]
Swartz et al. 2015 Case-control, 1,108 cases of neural tube defects including spina bifida; 4,132 frequency matched controls (Texas, United States)	Ambient air concentration, 95th percentile $1.19x10^{-1}$ µg/m^3	Risk of neural tube defects (including spina bifida)	↔
Talbott et al. 2015 Case-control, 217 cases of autism spectrum disorder in children born between 2005 and 2009; 224 frequency matched controls and 5,007 controls from random sample of birth certificates (Pennsylvania, United States)	Ambient air concentration, 75th percentile $1.2x10^{-4}$ µg/m^3	Risk of autism spectrum disorder	↔
Ruckart et al. 2013 Case-control, 15 cases of neural tube defects (spina bifida and anencephaly), 24 cases of oral clefts (cleft lip and palate); 524 controls (North Carolina, United States)	Exposed versus unexposed comparison	Risk of neural tube defects	↔
	Mean high exposure group, ≥3 ppm in drinking water	Risk of oral clefts	↔
Rosenman et al. 1989 Case-control, cases of all birth defects (Plant A: 66, Plant B: 72), cases of CNS defects (Plant A: 31, Plant B: 29); controls (Plant A: 72, Plant B: 103) (New Jersey, United States)	Residential distance from two vinyl chloride polymerization facilities	Risk of birth defects, risk of CNS malformations	↔

Table 2-6. Results of Epidemiological Studies Evaluating Exposure to Vinyl Chloride and Developmental Effects

Reference, study type, and population	Exposure or biomarker	Outcome evaluated	Result[a]
Bao et al. 1988 Retrospective cohort, 236 female vinyl chloride workers, 239 unexposed controls; prospective cohort, 43 female vinyl chloride workers, 86 unexposed controls (China)	3.9–89.3 ppm (retrospective); 0.2–130.7 ppm (prospective)	Sex ratio, birth weight, birth height, perinatal mortality, incidence of congenital abnormalities	↔
Theriault et al. 1983 Case-control, 68 cases of birth defects, 68 matched controls (Canada)	Exposed (residence in a community with a PVC plant) versus unexposed (three comparison communities)	Risk of birth defects	↔
Edmonds et al. 1978 Case-control study, 46 infants with CNS birth defects (18 stillborn), 46 controls (West Virginia, United States)	Occupation at PVC plant; residential distance from the plant	Confirmed cases of anencephaly, spina bifida, hydrocephalus and other CNS malformation (1970–1974)	↔
Infante 1976 Ecological, three communities with PVC production facilities (Ohio, United States)	Residence in communities with PVC plant	Risk of CNS malformations (three communities combined)	↑
Infante et al. 1976a, 1976b; NIOSH 1977 Cross-sectional, 70 male workers (North Carolina, United States)	Exposed (VCM workers) versus unexposed (rubber workers	Fetal death (any conception not born alive; age-adjusted)	↑
Edmonds et al. 1975 Ecological, hospital birth registry study (Ohio, United States)	Distance from PVC polymerization plants	CNS malformations (anencephaly, spina bifida)	↔

[a]Up arrows were based on statistically significant results only.

↑ = association with increase; ↔ = no association; CNS = central nervous system; PVC = polyvinyl chloride; VCM = vinyl chloride monomer

The pregnancy outcome for wives of workers employed at a vinyl chloride polymerization facility was compared to the pregnancy outcome of wives of a control group made up of unexposed rubber workers

and PVC fabricators believed to be exposed to "very low" levels of vinyl chloride (Infante et al. 1976a, 1976b). Pregnancy outcomes were determined based on the responses given by fathers on a questionnaire. Infante et al. (1976a, 1976b) and NIOSH (1977) reported a significant excess of fetal loss in the group whose husbands had been exposed to vinyl chloride. The greatest difference occurred in wives of men under 30 years of age, where fetal loss was 5.3% for controls and 20.0% for exposed workers. However, this study has been severely criticized based on the way it was conducted and the method of statistical analysis used (Hatch et al. 1981; Stallones 1987). Evaluations by Hatch et al. (1981) and Stallones (1987) concluded that the study failed to demonstrate an association between parental exposure to vinyl chloride and increased fetal loss.

Additional work by Infante (1976) and Infante et al. (1976b) examined the occurrence of congenital malformations among populations exposed to emissions from PVC polymerization facilities. A statistically significant increase in birth defects was observed for three cities in which polymerization facilities were located when compared to statewide and countywide averages. The greatest increases were noted for malformations of the central nervous system, upper alimentary tract, and genital organs and in the incidence of club foot. However, this study has also been criticized based on the ecological study design (Hatch et al. 1981; Stallones 1987). These authors concluded that the study failed to demonstrate an association between exposure to emissions and the prevalence of birth defects. Furthermore, another study that examined the incidence of malformations in one of the cities studied by Infante (1976) concluded that, although the city had statistically increased incidences of congenital malformations, no correlation existed based on parental proximity to the polymerization plant or with parental employment at the plant (Edmonds et al. 1975). In fact, more parents of control infants worked at the plant or lived closer to the plant than parents of infants with central nervous system malformations.

Additional other studies also examined the prevalence of congenital malformations in populations exposed to emissions from polymerization facilities (Edmonds et al. 1978; Rosenman et al. 1989; Theriault et al. 1983). The incidence of central nervous system defects in a West Virginia County with a polymerization plant was compared to incidences in other regions in the United States with no known exposure to vinyl chloride (Edmonds et al. 1978). Although the rate of central nervous system defects in the West Virginia County exceeded that in control areas, no correlation was noted between the increased central nervous system defects and parental occupation or potential exposure based on proximity to the plant or prevailing wind patterns. Rosenman et al. (1989) suggested that the risk of central nervous system defects, but not overall birth defects, was correlated with the amount of emissions from individual polymerization facilities and with the distance of the residences of affected parents from the facilities;

however, the findings were not statistically significant, and the study was limited by the small sample size.

A significantly greater prevalence of birth defects was found in residents of a town with a polymerization facility than in three matched towns without potential for exposure to vinyl chloride (Theriault et al. 1983). The most commonly reported defects included those of the musculoskeletal, alimentary, urogenital, and central nervous systems. The incidences were observed to fluctuate with seasonal changes in emissions. However, no correlations were found between the presence of birth defects and the proximity of the residence to the plant or parental occupation. Other industrial emissions in the area evaluated could not be eliminated as potential contributors to the increased incidence of congenital malformations observed. Additional confounding factors such as nutritional status, smoking, and alcohol and other drug use were not adjusted for.

Pregnancy outcomes of mothers occupationally exposed to vinyl chloride for >1 year were compared to those of pregnant workers not exposed to vinyl chloride in retrospective and prospective studies (Bao et al. 1988). Company records indicated that exposure levels ranged from 3.9 to 89.3 ppm during the retrospective study and from 0.2 to 130.7 ppm during the prospective study. The study authors concluded that exposure to vinyl chloride did not correlate with changes in sex ratio, birth weight or body length, perinatal mortality, or the incidence of congenital abnormalities.

Ruckart et al. (2013) performed a case-control study to evaluate the relationship between exposure to solvents in contaminated drinking water during pregnancy and neural tube defects, oral clefts, and childhood hematopoietic cancers. The study included 524 controls, 15 cases of neural tube defects, 24 cases of oral clefts, and 13 cases of cancer. No significant association was seen between vinyl chloride exposure and these effects. The risk of spina bifida was evaluated in a case-control study using birth registry data and census tract-level estimates of ambient air concentrations of hazardous air pollutants (Swartz et al. 2015). Vinyl chloride concentrations were not associated with the risk of spina bifida in this study. Talbott et al. (2015) evaluated the relationship between modeled concentrations of air toxics and the risk of autism spectrum disorder. Cases of autism spectrum disorder were recruited from diagnostic and treatment centers and the control groups consisted of controls that were frequency matched by child's year of birth, sex, and race and controls from a random sample of birth certificates. The estimated vinyl chloride concentrations in air were not associated with increased risk of autism spectrum disorder.

Animal Studies. A number of inhalation studies examined the effects of vinyl chloride exposure on pregnancy outcome in animals. Results of these studies indicate that vinyl chloride produces adverse developmental effects at concentrations that are also toxic to maternal animals. John et al. (1977, 1981) exposed rats and rabbits to 0, 500, or 2,500 ppm and mice to 0, 50, or 500 ppm throughout the period of organogenesis. Separate control groups were used for each of the mice exposure concentrations. Mice were more sensitive to the effects of vinyl chloride than rats and rabbits. An increase in the mortality rate was observed in pregnant mice exposed to 500 ppm (John et al. 1977, 1981). Delayed ossification of skull and sternebrae and unfused sternebrae were noted in fetuses at 500 ppm. Crown-rump length was increased at 50 ppm but not at 500 ppm. The biological significance of this effect is unknown.

In rats (John et al. 1977, 1981), 500 ppm produced increased crown-rump length and vertebral lumbar spurs, but these findings were not increased at 2,500 ppm. The only effect observed at 2,500 ppm was an increased incidence of dilated ureters (fetal incidence of 27 versus 5% in controls).

In rabbits exposed to 500 ppm, fetal animals had delayed ossification of the sternebrae that was not observed in rabbits at 2,500 ppm. No conclusions may be drawn as to the dose response of these effects.

An embryo-fetal developmental toxicity study was conducted in rats exposed to vinyl chloride via inhalation (Thornton et al. 2002). Female Sprague-Dawley rats were exposed to 0, 10, 100, or 1,100 ppm vinyl chloride 6 hours/day on GDs 6–19. No adverse effects were noted in embryo-fetal developmental parameters including uterine implantation, fetal sex distribution, fetal body weight, and fetal malformations and variations. Maternal kidney weights were increased relative to total body weight at 100 ppm.

Exposure of rats to either 0 or 1,500 ppm of vinyl chloride during the first, second, or third trimester of pregnancy was examined (Ungvary et al. 1978). In maternal animals, an increased liver-to-body weight ratio was observed in those exposed during the first and second trimesters, but no histopathologic alterations were found. A significant increase in resorptions was observed in animals exposed during the first trimester of pregnancy. Two central nervous system malformations (microphthalmia and anophthalmia) were observed in exposed fetuses but not in controls, but the incidence of these malformations did not reach statistical significance. This study is limited in that only a single concentration of vinyl chloride was tested, precluding conclusions as to the dose-response relationship of the effects observed.

The effects of exposure of rats to vinyl chloride throughout gestation were examined by Mirkova et al. (1978) and Sal'nikova and Kotsovskaya (1980). An unspecified number of pregnant rats were exposed to 0, 1.9, or 13.9 ppm for 4 hours/day for the 21 days of gestation. Fetuses were examined for abnormalities just prior to the end of gestation, and offspring were examined at 6 months post-parturition (Sal'nikova and Kotsovskaya 1980). At 13.9 ppm, a decrease in maternal erythrocyte count was observed. Fetuses had an increased incidence of hemorrhages at 1.9 and 13.9 ppm and increased edema at 13.9 ppm. However, the affected organs were not specified. Rats examined at 6 months, following *in utero* exposure to 1.9 ppm, were found to have decreased hemoglobin and leukocytes and decreased organ weights (males: liver, kidneys, spleen; females: lung, liver). In addition to these effects, exposure to 13.9 ppm *in utero* resulted in an increased hexanol sleep time and a decreased ability of the rats to orient themselves.

Continuous exposure of an unspecified number of rats to 2.4 ppm of vinyl chloride throughout gestation resulted in decreased fetal weight and increased early postimplantation loss, hematomas, and hydrocephaly with intracerebral hematoma. Weanling rats had hepatotoxic effects including decreased bile secretion and decreased cholic acid content. No histological data on the livers of pups, information regarding maternal health, or statistical analyses of the data were presented (Mirkova et al. 1978). Both this study and the report by Sal'nikova and Kotsovskaya (1980) failed to provide information on the number of animals in each test group.

Vinyl chloride administration to pregnant mice by intraperitoneal injection on GD 6 produced a dose-related reduction in embryo survival 4 days after injection (percent survival was 96, 86, 67, and 55% at doses of 0, 200, 400, and 600 mg/kg, respectively). The incidences of morphological abnormalities were 6, 51, and 71% at doses of 200, 400, and 600 mg/kg, respectively. Neural tube defects were the primary abnormality observed (Quan et al. 2014). The mechanism for this effect appears to be related to inhibition of neural epithelial cell proliferation and induction of caspase 3-mediated apoptosis. The developmental toxicity of vinyl chloride was examined using a whole embryo culture system (Zhao et al. 1996). Vinyl chloride induced embryo growth retardation but was not shown to be teratogenic in the rat *in vitro* whole embryo culture system.

2.18 OTHER NONCANCER

Human Studies. Epidemiology studies evaluating exposure to vinyl chloride and insulin resistance are described in Table 2-7. A cross-sectional study of vinyl chloride workers in Taiwan demonstrated an

exposure-related decrease in the adiponectin/leptin ratio, which may be suggestive of increased insulin resistance (Lee et al. 2020). No change in serum concentrations of glucose, insulin, adiponectin, or leptin was observed. Vinyl chloride workers with steatohepatitis also demonstrated measures suggestive of insulin resistance (increased serum glucose, insulin, and adiponectin) when compared to healthy workers exposed to vinyl chloride and unexposed healthy volunteers (Cave et al. 2010). Plasma metabolomics analysis in vinyl chloride workers showed alterations in lipid and amino acid metabolites, which may contribute to the steatohepatitis (Guardiola et al. 2016).

Table 2-7. Results of Epidemiological Studies Evaluating Exposure to Vinyl Chloride and Insulin Resistance

Reference, study type, and population	Exposure or biomarker	Outcome evaluated	Result[a]
Cave et al. 2010 Case-control, 16 male, non-obese, highly exposed workers with steatohepatitis, 26 healthy worker controls, and 11 unexposed, healthy volunteers (Kentucky, United States)	11,913 ppm-years, estimated mean cumulative, long-term exposure (mean 18.9 years)	Serum glucose, insulin, adiponectin	↑
		Serum leptin	↔
Lee et al. 2020 Cross-sectional, 108 male and 5 female workers (Taiwan)	2,065 μg/m^3; mean of high-VCM group	Adiponectin/leptin ratio	↓
		Serum glucose, insulin, adiponectin, leptin	↔

[a]Up and down arrows were based on statistically significant results only.

↑ = association with increase, ↓ = association with decrease, ↔ = no association; VCM = vinyl chloride monomer

Animal Studies. In C57BL/6J mice exposed to 0.85 ppm vinyl, 5 days/week, 6 hours/day for 12 weeks, no treatment-related effects were observed on fasting blood glucose levels or glycogen storage (Wahlang et al. 2020). In other studies, normal findings were observed in tests of oral glucose tolerance (Chen et al. 2019; Lang et al. 2018) and insulin or pyruvate tolerance (Lang et al. 2018). Zelko et al. (2022) reported no effect on blood glucose or insulin in C57BL/6 mice exposed to 0.8 ppm vinyl, 5 days/week, 6 hours/day for 12 weeks, but did show a 2-fold decrease in glucose tolerance following intraperitoneal injection of glucose.

2.19 CANCER

Overview. The development of cancer in humans as a result of vinyl chloride exposure was demonstrated in a number of studies of workers in the vinyl chloride production industry. The strongest evidence comes from the greater-than-expected incidences of liver angiosarcoma, a tumor type that is considered to be very rare in humans (25–30 cases/year in the United States). The latency period for the development of hepatic angiosarcoma in workers exposed prior to 1974 ranges between 24 and 56 years (Collins et al. 2014; Mundt et al. 2017). Other liver tumors, including hepatocellular carcinoma and cholangiocarcinoma (commonly referred to as colangiocarcinoma), were also associated with occupational exposure to vinyl chloride. The latency period for the development of hepatocellular carcinoma is estimated to range from 32 to 67 years (Mundt et al. 2017).

Studies in several animal species support the conclusion that vinyl chloride is carcinogenic. In rats, chronic-duration exposure to 5–5,000 ppm vinyl chloride vapors resulted in significantly increased incidence of mammary gland carcinomas, Zymbal's gland carcinomas, nephroblastoma, and liver angiosarcoma compared to controls. Intermediate- and chronic-duration exposures of 50–2,500 ppm vinyl chloride resulted in significant incidence of liver angiosarcoma, carcinoma, and angioma, lung adenoma, mammary gland carcinoma, adipose tissue hemangiosarcoma, and hemangiosarcoma of the subcutis and peritoneum in mice. With the exception of liver angiosarcomas, which were observed in all species (including humans), there is little consistency in tumor types across species. Chronic-duration oral administration of 2–6 mg/kg/day of vinyl chloride resulted in the development of neoplastic liver nodules, hepatocellular carcinoma, and lung and liver angiosarcoma in rats (Feron et al. 1981; Til et al. 1983, 1991).

Studies in rats, mice, and hamsters provide evidence that exposure early in life increases the risk of hemangiosarcoma in liver, skin, and spleen, stomach angiosarcoma, as well as mammary gland carcinoma, when compared to the risk associated with exposure after 12 months of age (Drew et al. 1983; Maltoni et al. 1981). Due to the latency period for vinyl chloride-induced cancer, exposure of animals during gestation and/or early in life may have increased the likelihood of developing tumors and affected the type of tumor that develops.

Human Studies. Bosetti et al. (2003) pooled the analyses of worker cohorts from 56 vinyl chloride plants in North America and Europe. The pooled analysis, which included over 22,000 workers, showed an elevated risk of liver cancer mortality. While differences between the North American and European

cohorts were observed for soft tissue sarcoma and brain cancer, no significant excess in mortality from these cancers was seen in the pooled data. Deaths from lung and laryngeal cancer were lower than expected, and no excess mortality from lymphoid and hematopoietic system cancers was observed. Boffetta et al. (2003) performed a meta-analysis including the multicenter cohort studies from North America and Europe as well as six smaller studies from the former Soviet Union, France, Canada, Germany, China, and Taiwan. The meta-analysis confirmed the elevated risk of liver cancer mortality among vinyl chloride workers. It also reported excess mortality from multiple types of liver cancer including angiosarcoma, hepatocellular carcinoma, and other liver tumors with unspecified histopathology. Boffetta et al. (2003) also reported a possible increase in the risk for soft-tissue sarcoma, especially in North American workers; however, misclassification of the diagnosed cause of death may have contributed to this result (i.e., angiosarcoma of the liver classified as a soft tissue sarcoma). A meta-analysis that included three occupational cohorts and 12,816 participants reported an association between cumulative exposure to vinyl chloride and increased mortality from liver angiosarcoma and soft tissue sarcoma (Edwards et al. 2021). Similar to the pooled results from Bosetti et al. (2003), Boffetta et al. (2003) reported that no increase was observed in mortality from lung or brain cancers. A strong association was not observed between vinyl chloride exposure and lymphatic/hematopoietic system cancers; however, this negative conclusion was considered premature due to the heterogeneity of the study results (Boffetta et al. 2003).

Epidemiology studies evaluating the risk of selected types of cancer associated with vinyl chloride exposure are presented in Table 2-8 (ecological studies and case reports are not tabulated). The most compelling evidence for the carcinogenic potential of vinyl chloride in humans comes from many reports of greater-than-expected incidences of angiosarcoma of the liver in workers occupationally exposed to vinyl chloride (Table 2-8).

Approximately 30 years after the introduction of vinyl chloride for use in the industrial production of PVC, it became apparent that workers exposed to high levels of vinyl chloride had an unusually high incidence of angiosarcoma of the liver. Investigators identified an increased likelihood of developing hepatic angiosarcoma among those exposed to the highest levels of vinyl chloride and those exposed to vinyl chloride for the longest duration (Fortwengler et al. 1999; Fox and Collier 1977; Infante et al. 1976b; Jones et al. 1988; Mundt et al. 2017; Rinsky et al. 1988; Weber et al. 1981; Wong et al. 1991; Wu et al. 1989). Mundt et al. (2017) demonstrated a strong association between mortality from angiosarcoma of the liver and exposure to cumulative vinyl chloride concentrations of ≥865 ppm-years. An increase in

hepatobiliary cancer mortality was observed in workers exposed to vinyl chloride for ≥16 years (Carreón et al. 2014).

Angiosarcoma of the liver was not found in residents living in the vicinity of vinyl chloride sites unless they were also exposed to high concentrations of vinyl chloride in the workplace (Elliott and Kleinschmidt 1997). Lewis et al. (2003) reported the occurrence of angiosarcoma of the liver in retirees from a PVC production plant in Louisville, Kentucky. This incidence increase is reported primarily for those workers employed prior to 1960, suggesting that those exposed to the highest concentrations of vinyl chloride remain at risk for developing cancer for the remainder of their lives. The reported latency period for workers diagnosed prior to 1975 was 12–28 years, while those diagnosed after 1975 showed a latency of 27–47 years. Examination of >73,000 death certificates of North American workers employed between 1940 and 2008 showed a mean latency for death from angiosarcoma of the liver of 37 years (range of 24–56 years) (Collins et al. 2014). Workers with the first exposure occurring after 1974 did not develop angiosarcoma of the liver (Collins et al. 2014). The median latency for angiosarcoma deaths in vinyl chloride workers from 35 facilities in the United States was 36 years (ranging from 14 to 56 years) (Mundt et al. 2017). Plasma metabolomics analysis of vinyl chloride workers who developed angiosarcoma showed upregulation of taurocholate, bradykinin, and fibrin degradation product 2 (Guardiola et al. 2021).

Table 2-8. Summary of Epidemiological Studies Evaluating Possible Associations between Vinyl Chloride Exposure and Risk of Selected Cancer Types

Cancer type	Association[a]	No association[b]
Liver and biliary (angiosarcoma, hepatocellular carcinoma, cholangiocarcinoma)	Scarselli et al. 2022[c] Guardiola et al. 2021[d] Fedeli et al. 2019a[c] Mundt et al. 2017[c] Carreón et al. 2014[c] Collins et al. 2014[c] Hsieh et al. 2011[c] Gennaro et al. 2008[c] Mastrangelo et al. 2004[d] Lewis et al. 2003[c] Maroni et al. 2003[c] Wong et al. 2002a[c], 2003a[d] Ward et al. 2001[c] Cheng et al. 1999a[e] Fortwengler et al. 1999[c] Du and Wang 1998[d] Elliott and Kleinschmidt 1997[f,g] Laplanche et al. 1992[c]	Marsh et al. 2021[c,h] Marsh et al. 2007a[c,h] Marsh et al. 2007b[c,h]

Table 2-8. Summary of Epidemiological Studies Evaluating Possible Associations between Vinyl Chloride Exposure and Risk of Selected Cancer Types

Cancer type	Association[a]	No association[b]
	Simonato et al. 1991[c] Wong et al. 1991[c] Pirastu et al. 1990[c] Teta et al. 1990[c] Wu et al. 1989[c] Jones et al. 1988[c] Rinsky et al. 1988[c] Forman et al. 1985[d] Theriault and Allard 1981[c] Weber et al. 1981[c] Fox and Collier 1977[c] Byren et al. 1976[c] Infante et al. 1976b[c] Waxweiler et al. 1976[c] Monson et al. 1975[c]	
Brain and central nervous system	Rodrigues et al. 2020[d] Wong et al. 1991[c,i] Cooper 1981[c,i] Waxweiler et al. 1976[c,i] Monson et al. 1975[c]	Mundt et al. 2017[c] Pan et al. 2005[d] Lewis and Rempala 2003[d] Lewis et al. 2003[c] Lewis 2001[c] Ward et al. 2001[c] Mundt et al. 2000[c] Simonato et al. 1991[c] Wu et al. 1989[c,i] Jones et al. 1988[c] Thomas et al. 1987[d] Fox and Collier 1977[c] Byren et al. 1976[c] Tabershaw and Gaffey 1974[c,i]
Lung and respiratory tract (large-cell undifferentiated carcinoma or adenocarcinoma)	Girardi et al. 2022[c] Gennaro et al. 2008[c] Mastrangelo et al. 2003[d] Belli et al. 1987[c] Heldaas et al. 1984[c] Infante et al. 1976b[c] Waxweiler et al. 1976[c] Monson et al. 1975[c]	Mundt et al. 2017[c] Hsieh et al. 2011[c] Scelo et al. 2004[d] Wong et al. 2002a[c] Wong et al. 1991[c] Ward et al. 2001[c] Mundt et al. 2000[c] Cheng et al. 1999a[e] Du and Wang 1998[d] Simonato et al. 1991[c] Hagmar et al. 1990[c] Wu et al. 1989[c] Jones et al. 1988[c] Cooper 1981[c] Buffler et al. 1979[c] Fox and Collier 1977[c]
Connective and other soft tissues (including soft tissue sarcoma)	Mundt et al. 2017[c] Mundt et al. 2000[c]	Ward et al. 2001[c]

Table 2-8. Summary of Epidemiological Studies Evaluating Possible Associations between Vinyl Chloride Exposure and Risk of Selected Cancer Types

Cancer type	Association[a]	No association[b]
Lymphatic/hematopoietic system (including leukemias, myelomas and lymphomas)	Poynter et al. 2017[e] Hsieh et al. 2011[c] Wong et al. 2002a[c] Du and Wang 1998[d] Rinsky et al. 1988[c] Smulevich et al. 1988[c] Weber et al. 1981[c] Monson et al. 1975[c]	Mundt et al. 2017[c] Bove et al. 2014[c] Carreón et al. 2014[c] Ruckart et al. 2013[d] Ward et al. 2001[c] Mundt et al. 2000[c] Cheng et al. 1999a[e] Infante et al. 1976b[c] Jones et al. 1988[c] Wong et al. 1991[c]

[a]Significant association between exposure and cancer incidence or mortality.
[b]No significant association between exposure and cancer incidence or mortality.
[c]Cohort studies.
[d]Case-control studies.
[e]Cross-sectional study.
[f]Ecological studies.
[g]Association was reported for exposed workers, but not residents living near sites.
[h]Exposure to vinyl chloride was relatively low (<2 ppm-year).
[i]Studies based on workers from the same cohort from a Chemical Manufacturers Association (CMA) study (Wong and Whorton 1993).

Histopathological examination of liver tissue from humans with hepatic angiosarcoma led to the hypothesis that angiosarcoma develops as a result of hyperplastic changes in sinusoidal cells. In liver parenchyma, areas of transition to angiosarcoma contained greatly increased numbers of sinusoidal cells with greatly expanded sinusoidal spaces. Hepatic cells were replaced by fibrous tissue-forming trabeculae. These areas also showed infiltration of angiosarcoma cells. In fully developed angiosarcoma, multiple areas with nodules of angiosarcoma cells were noted, the centers of which exhibited hemorrhagic necrosis (Popper et al. 1981). Case reports suggest that vinyl chloride can also produce malignant hemangiopericytomas (Hozo et al. 1997, 2000) and epithelioid hemangioendotheliomas (Gelin et al. 1989) in the liver (both are vascular tumors similar to angiosarcomas), and adrenal epithelioidangiosarcoma (Criscuolo et al. 2014).

Other liver tumors, including hepatocellular carcinoma and cholangiocellular carcinoma, have also been associated with occupational exposure to vinyl chloride (Cheng et al. 1999a; Du and Wang 1998; Fedeli et al. 2019a; Hsieh et al. 2011; Lelbach 1996; Mundt et al. 2017; Saurin et al. 1997; Ward et al. 2001; Weihrauch et al. 2000; Wong et al. 2002a, 2003a). The latency period for the development of hepatocellular carcinoma was estimated to range from 32 to 67 years in a study of vinyl chloride workers

in the United States (Mundt et al. 2017). The risk of developing liver cancer was elevated in those with a history of Hepatitis B viral infection (Du and Wang 1998; Wong et al. 2003a).

Mastrangelo et al. (2004) evaluated the possible interaction between alcohol consumption, hepatitis infection, and hepatocellular carcinoma in a large cohort of vinyl chloride workers. Vinyl chloride was suggested to be an independent risk factor for hepatocellular carcinoma with a synergistic interaction described for alcohol consumption and an additive interaction for hepatitis infection. Sequential development of hepatocellular carcinoma followed by later development of angiosarcoma of the liver was demonstrated in the case report of a worker exposed to high concentrations of vinyl chloride (4,100 ppm-years) (Guido et al. 2016). Mortality from liver cancer was not elevated by vinyl chloride in a study of workers exposed to low concentrations of vinyl chloride (<2 ppm-years) (Marsh et al. 2007a, 2007b, 2021). An ecological study in Texas associated exposure to vinyl chloride in polluted ambient air and the incidence of hepatocellular carcinoma (Cicalese et al. 2017); however, several letters to the editor from the vinyl industry described significant methodological limitations of this study (Gennissen et al. 2018; Krock 2018; Marsh and Towle 2018). Therefore, Cicalese et al. (2017) was not included in Table 2-8. An ecological study, funded by the vinyl industry, did not report an association between Texas county-level ambient air concentrations of vinyl chloride and liver cancer incidence or mortality (Towle et al. 2021).

Other tumor types have statistically significant increases in mortality rates among vinyl chloride workers, in at least some studies. They include cancer of the brain and central nervous system, the lung and respiratory tract, connective and other soft tissues, plus the lymphatic/hematopoietic system (Table 2-8). In general, follow-up mortality studies at polymer production plants indicate that liver cancer mortality remained elevated while brain cancer mortality was markedly reduced when recent studies are compared to the earlier studies. Increased brain cancer incidence was not associated with vinyl chloride exposure in these later studies (Lewis 2001; Lewis and Rempala 2003; Lewis et al. 2003; Mundt et al. 2000, 2017; Ward et al. 2001). A recent case-control study of brain and other CNS cancers in semiconductor workers showed an association between cumulative vinyl chloride exposure (1965–1999) and cancer risk (Rodrigues et al. 2020).

An association between respiratory tract cancer and vinyl chloride exposure has not been consistently observed (Table 2-8). Although smoking history was not considered in these studies, Waxweiler et al. (1976) noted that the types of respiratory tract cancer most frequently recorded were large-cell undifferentiated lung carcinoma or adenocarcinoma that are not usually associated with smoking but can

be influenced by the smoking status of the exposed individual. Increased risk of lung cancer was also associated with exposure to high concentrations of PVC dust particles (Girardi et al. 2022; Mastrangelo et al. 2003; Waxweiler et al. 1976).

A significant increase in cancers of connective and other soft tissues was observed in some, but not all follow up mortality studies (Table 2-8). A meta-analysis of five occupational exposure studies suggested a weak association between vinyl chloride exposure and pancreatic cancer (Ojajarvi et al. 2001). However, no association was observed between vinyl chloride exposure and mortality from pancreatic cancer in the updated mortality studies of vinyl chloride workers (Carreón et al. 2014; Fedeli et al. 2019a).

No consistent findings were noted regarding the association between cancers of the lymphatic/ hematopoietic system and exposure to vinyl chloride (i.e., both positive and negative findings were reported, and the conclusions of the pooled and meta-analysis differed) (Table 2-8; Boffetta et al. 2003; Bosetti et al. 2003).

An increased incidence of malignant melanoma among vinyl chloride workers has been reported (Heldaas et al. 1984, 1987), but the significance of this finding has been disputed (ten Berge 1987). A follow up to the original Heldaas et al. (1984, 1987) studies reported only one additional case of melanoma between 1985 and 1993, weakening the proposed association between vinyl chloride exposure and the development of malignant melanoma (Langard et al. 2000). Follow-up mortality studies have not demonstrated an association between vinyl chloride exposure and risk of melanoma (Mundt et al. 2017; Ward et al. 2001).

Few studies directly address the incidence of cancer in women occupationally exposed to vinyl chloride. One study found that women employed in the production of vinyl chloride and PVC had a significantly greater chance of developing leukemia or lymphomas (Smulevich et al. 1988). In the same study, the subgroup of women who were exposed to the highest levels of vinyl chloride had increased incidences of stomach cancer and the highest incidences of leukemia and lymphoma. In this study, there was no significant increase in any type of cancer in exposed males, irrespective of their level of exposure. Increased breast cancer risk was associated with exposure to vinyl chloride as a hazardous air pollutant in California (Garcia et al. 2015).

The human epidemiology data demonstrate a clear association between vinyl chloride exposure and liver cancer (i.e., angiosarcoma and hepatocellular carcinoma). Although other cancers have been previously reported for vinyl chloride workers (i.e., respiratory tract cancer, brain cancer, soft tissue cancers, lymphatic/hematopoietic system cancers, malignant melanoma), more recent follow-up studies and pooled and meta-analysis studies do not demonstrate a consistent association between vinyl chloride exposure and tumor formation in these organs or tissue-systems (Boffetta et al. 2003; Bosetti et al. 2003; Table 2-8).

Animal Studies. Studies in several animal species support the conclusion that vinyl chloride is carcinogenic. A large series of experiments was performed by Maltoni et al. (1981) using rats (Sprague-Dawley and Wistar), mice, and hamsters. In one group of studies, Maltoni et al. (1981) exposed Sprague-Dawley rats to vinyl chloride for 52 weeks at concentrations ranging from 1 to 30,000 ppm. Animals were examined at the time of their spontaneous death. Statistically significant increases were noted in the incidence of mammary gland carcinomas, Zymbal gland carcinomas, nephroblastoma, and liver angiosarcoma. Exposure of Swiss mice to 50 ppm vinyl chloride for 4 hours/day, 5 days/week for 30 weeks also appeared to increase the incidence of liver angiosarcoma and angioma (Maltoni et al. 1981). Maltoni et al. (1981) also reported that decreasing the duration of exposure decreased the incidence of vinyl chloride-related tumors (nephroblastomas, liver angiosarcomas, Zymbal gland carcinomas, and to some extent, neuroblastomas).

Some variation in the target organs that developed tumors was observed when different species were exposed to vinyl chloride (Maltoni et al. 1981). Whereas angiosarcomas of the liver were reported to occur in rats, mice, and hamsters, mammary gland carcinomas were found only in rats and mice. Zymbal gland carcinomas, neuroblastomas, and nephroblastomas were found only in rats; lung tumors were found only in mice; and melanomas, acoustical duct epithelial tumors, plus leukemias were found only in hamsters.

Other inhalation experiments support the carcinogenicity of vinyl chloride. Rats and mice exposed to 0, 50, 250, or 1,000 ppm for 6 hours/day, 5 days/week for 6 months (Hong et al. 1981) or up to 12 months (Lee et al. 1977a, 1978) had a significantly increased incidence of hemangiosarcoma of the liver at ≥250 ppm. In a 2-generation study in rats, pre-neoplastic liver lesions (i.e., foci of hepatocellular alteration, hepatocellular foci) were observed in F1 males at 100 ppm and F1 males and F1 females at 1,100 ppm (6 hours/day for 16–19 weeks) (Thornton et al. 2002). Increases in bronchio-alveolar adenoma of the lung and mammary gland tumors (adenocarcinomas, squamous and anaplastic cell

carcinomas) were also observed in mice at ≥50 ppm, (Lee et al. 1977a, 1978). Mice exposed to 50 or 500 ppm vinyl chloride for 6 hours/day, 5 days/week for 6 months or 1 year had an increased incidence of lung adenoma, as well as hemangiosarcoma of fat tissue in various organs (Holmberg et al. 1976). Only one liver hemangiosarcoma was noted.

Male rats exposed to concentrations as low as 105.6 ppm for 6 hours/day, 6 days/week, for 12 months had significantly increased incidence of cancer, including angiosarcoma of the liver and lung, when sacrificed at 18 months (Bi et al. 1985). Rats exposed to 30,000 ppm vinyl chloride 4 hours/day, 5 days/week, for 12 months had an increased incidence of epidermoid carcinoma of the skin, adenocarcinoma of the lungs, and osteochondroma in the bones (Viola et al. 1971), while rats exposed to 5,000 ppm for 52 weeks had primary tumors in the brain, lung, Zymbal gland, and nasal cavity (Feron and Kroes 1979). However, these studies (Feron and Kroes 1979; Viola et al. 1971) are limited by the absence of statistical analysis of the data. Female mice exposed to 50 ppm vinyl chloride for 6 months showed increased incidence of hemangiosarcoma of the subcutis, peritoneum, and skin, as well as lung and mammary gland carcinomas (Drew et al. 1983).

In a preliminary study with a limited number of animals, alveogenic lung tumors developed in 26 of 27 mice exposed to 2,500 or 6,000 ppm for 5–6 months (Suzuki 1978). A concentration-related increase in the incidence of alveogenic tumors was observed in a study in which a larger number of mice were exposed to 0–600 ppm for 4 weeks and then observed for up to 40 weeks postexposure (Suzuki 1983). The lowest concentration at which multiple foci tumors were observed was 100 ppm (Suzuki 1983). A significant increase in the incidence of pulmonary adenomas was reported in mice exposed to 50 ppm, 6 hours/day, 5 days/week for 6 months (Adkins et al. 1986). An increase in bronchioalveolar adenoma was observed in a lifespan study of mice that were exposed once to 5,000 ppm for only 1 hour (Hehir et al. 1981).

Some data suggest that exposure of animals during gestation and/or early post-birth may increase the likelihood and the type of tumor that develops (Drew et al. 1983; Maltoni et al. 1981). Maltoni et al. (1981) evaluated the effect of vinyl chloride dosing on liver carcinogenicity in Sprague-Dawley rats. Rats were exposed to 0, 6,000, or 10,000 ppm vinyl chloride for 100 hours, beginning either at 1 day or at 13 weeks of age. The incidence of angiosarcoma of the liver in newborn rats exposed for only 5 weeks was higher than the incidence observed in rats exposed for 52 weeks beginning at 13 weeks. Hepatoma incidence was approximately 50% in newborn rats exposed for 5 weeks but did not occur in rats exposed for 52 weeks after maturity.

When hamsters, mice, and rats were exposed to vinyl chloride for periods of 6–24 months starting at various time-points after weaning, the incidence of tumors such as hemangiosarcoma of the liver, skin, and spleen, and angiosarcoma of the stomach was greater when animals were exposed for 12 months immediately after weaning than if animals had no exposures for 12 months and were then exposed for the subsequent 12 months (Drew et al. 1983). Maltoni and Cotti (1988) also exposed pregnant rats to 2,500 ppm vinyl chloride starting on GD 12 and continued to expose both maternal animals and offspring for a total of 76 weeks. Hepatocellular carcinoma, hepatic angiosarcoma, and neuroblastoma were increased in treated animals compared to controls. The incidence of hepatocarcinoma was reported to be much higher in offspring than in maternal animals. In contrast, the incidence and latency period of neuroblastomas and hepatic angiosarcomas was similar between offspring and their parents.

Mammary gland carcinoma was significantly increased when 2- or 8-month-old hamsters, but not 14- or 20-month-old hamsters, were exposed to 200 ppm vinyl chloride for 6 months (Drew et al. 1983). Fibroadenoma of the mammary gland was increased in female rats exposed to 100 ppm of vinyl chloride for 6 hours/day, 5 days/week, over 6–24 months (Drew et al. 1983). When pregnant rats were exposed to 6,000 ppm vinyl chloride from GD 12 through 18, the incidence of mammary gland carcinomas, Zymbal gland carcinomas, and forestomach epithelial tumors was reported to be greater in the transplacentally-exposed animals than in the maternal animals (Maltoni et al. 1981). At 10,000 ppm in this study, more nephroblastomas were observed in transplacentally exposed animals than the maternal animals (Maltoni et al. 1981); however, there was no unexposed control group.

Many of the tumors that were observed in the Drew et al. (1983) and Maltoni et al. (1981) studies were also observed in a study performed by Froment et al. (1994). In this study, Sprague-Dawley pups were exposed to 500 ppm vinyl chloride 8 hours/day, 6 days/week, on postpartum days 3–28. After weaning, 22 animals/gender were exposed for an additional 2 weeks, for a total exposure duration of 33 days. Rats were observed daily until death or development of tumors, and the surviving rats were sacrificed at 19 months. All livers from exposed animals that appeared normal at gross examination were found to contain multiple nodular hyperplastic foci of hepatocytes. Liver tumors that were found in exposed animals included angiosarcomas, hepatocellular carcinomas, and benign cholangiomas. Other tumors found included pulmonary angiosarcoma (probably metastatic), nephroblastoma, abdominal angiomyoma, leukemia, Zymbal gland carcinoma, pituitary adenoma, mammary carcinoma, and mammary fibroma. Tumor incidence was not reported in control animals. Only one concentration (500 ppm) of vinyl

chloride was used because the purpose of the study was to examine the genotoxic impact of vinyl chloride in the liver tumors produced by exposure.

Vinyl chloride induced preneoplastic foci in newborn rats, but not in mature rats (Laib et al. 1985). A study with newborn male or female Wistar rats exposed to 2,000 ppm vinyl chloride indicated that the induction of preneoplastic hepatocellular lesions in rats by vinyl chloride is restricted to an early stage in the life of the animals. The early life stage sensitivity to the induction of tumors in animals exposed to vinyl chloride appears to be related to the induction by vinyl chloride of hepatic adenosine-5'-triphosphatase (ATPase) deficient enzyme altered foci, which are putative precursors of hepatocellular carcinoma.

Five studies were located that examined the carcinogenic potential of vinyl chloride in animals when administered by the oral route. In two Wistar rat studies, vinyl chloride was added to the diet for up to 149 weeks by adding a PVC powder containing a high level of the monomer (Feron et al. 1981; Til et al. 1983, 1991). To limit volatilization of vinyl chloride from the diet, the rats were allowed access to the diet for only 4 hours/day. The actual intake of vinyl chloride in these reports was calculated by taking into consideration both the food consumption data and the rate of vinyl chloride evaporation. Statistically significant increases in angiosarcoma were observed in the 2.7-year study by Feron et al. (1981) at 5mg/kg/day in males and 14.1 mg/kg/day in females. In the same study, statistically significant increases in neoplastic nodules of the liver were also observed at a concentration of 5 mg/kg/day in males and as low as 1.7 mg/kg/day in females (Feron et al. 1981). In the 149-week study by Til et al. (1983, 1991), statistically significant increases in hepatocellular carcinoma were observed in males and hepatic neoplastic nodules in females at 1.7 mg/kg/day. A few animals exposed to 1.7 mg/kg/day in this study developed hepatic angiosarcoma. An increased incidence of Zymbal gland tumors was also observed in the study by Feron et al. (1981). Although the increase was not statistically significant, the tumors were considered to be treatment related based on the historical rarity of this type of tumor. Conversely, Til et al. (1983, 1991) did not observe any Zymbal tumors in rats fed ≤1.7 mg vinyl chloride/kg/day for 149 weeks. Wistar rats gavaged with 300 mg/kg/day developed liver tumors, predominantly angiosarcomas, within 60 days of exposure (Knight and Gibbons 1987). Liver tumors were also observed in rats exposed to a lower dose for a longer period of time (30 mg/kg/day for 2 years) (Knight and Gibbons 1987).

Two studies were located in which vinyl chloride was administered to Sprague-Dawley rats by gavage for 52 weeks. In one of these studies, a statistically significant increase in the incidence of hepatic

angiosarcomas was observed at doses as low as 16.65 mg/kg/day in females and 50 mg/kg/day in males. Zymbal gland tumors at 16.65 and 50 mg/kg/day, even though not statistically significant, were considered to be treatment related because of the rarity of this type of tumor (Maltoni et al. 1981). Lower doses of vinyl chloride were also tested in a similar study where hepatic angiosarcomas were observed at doses as low as 0.3 mg/kg/day and Zymbal gland tumors at 1 mg/kg/day. Although neither of these findings reached statistical significance, the tumors were considered to be treatment related because historically they rarely occurred in the rat colony (Maltoni et al. 1981).

Mechanisms of Cancer. The metabolism of vinyl chloride to its highly reactive metabolites, the observance of deoxyribonucleic acid (DNA) adduction in mechanistic studies, and the observed carcinogenicity resulting from a single, high level inhalation exposure in animals, suggest that the primary mechanism for vinyl chloride carcinogenicity involves direct interaction with DNA rather than secondary responses to cytotoxicity. 2-Chloroethylene oxide and 2-chloroacetaldehyde can both react with DNA nucleotide bases. 2-Chloroethylene oxide is the more potent mutagen and may be the ultimate carcinogenic metabolite of vinyl chloride (Chiang et al. 1997). The mutation profile for the DNA adducts formed by the reactive metabolites of vinyl chloride (2-chloroethylene oxide and 2-chloroacetaldehyde) includes the four cyclic etheno-adducts: 1,N^6-ethenoadenine, 3,N^4-ethenocytosine, 3,N^2-ethenoguanine, and 1,N^2-ethenoguanine (Akasaka et al. 1997; Chiang et al. 1997; Dosanjh et al. 1994; Guichard et al. 1996; Matsuda et al. 1995; Pandya and Moriya 1996; Zhang et al. 1995; Zielinski and Hergenhahn 2001). The role of etheno-adducts in the carcinogenesis of vinyl chloride was reviewed in several publications (Albertini et al. 2003; Barbin 1998, 2000; Dogliotti 2006; Guengerich and Ghodke 2021; Kielhorn et al. 2000; Laib 1986; Rioux and Delaney 2020; Whysner et al. 1996). These adducts lead to base-pair transitions during transcription and DNA crosslinks (Cullinan et al. 1997; Pandya and Moriya 1996; Singer 1996; Singer et al. 1987). Such mutations have resulted in the mutation of *ras* oncogenes such as those found in hepatic angiosarcoma tumors of workers exposed to high levels of vinyl chloride. In addition, mutations in the p53 tumor suppressor gene identified in vinyl chloride workers are associated with a variety of tumor types. Mutations of the p53 gene in vinyl chloride-exposed rats were similar to those reported in humans (Section 2.20).

The mechanisms for the clastogenic effects of vinyl chloride exposure were examined by Fucic et al. (1990a). Since chromatid and bichromatid breaks most frequently occurred in the terminal A, B, and C group chromosomes, these investigators suggested that vinyl chloride or its metabolites might interact with specific sites along chromosomes, thereby fragmenting the gene. This implies that the carcinogenicity induced by vinyl chloride can be explained in part by its nonrandom interaction with

particular genes. Epigenetic processes that may contribute to vinyl chloride induced cancer formation include aberrant DNA methylation (Chappell et al. 2016) and cell cycle deregulation (Pan et al. 2021).

Cancer Weight-of-Evidence Determination. The Department of Health and Human Services NTP classified vinyl chloride as "known to be a human carcinogen" (NTP 2021) and IARC concluded that there is sufficient evidence for carcinogenicity in humans and animals to classify vinyl chloride as a Category 1 carcinogen (carcinogenic to humans) (IARC 2012). The IARC Working Group (IARC 2012) concluded that vinyl chloride causes both liver angiosarcomas and hepatocellular carcinomas and found suggestive evidence for an increased risk of malignant neoplasia of soft and connective tissue. No association was found between vinyl chloride exposure and lung cancer, and the evidence for an increased risk for brain cancer, lymphatic and hematopoietic cancers, and melanoma was characterized as weak.

The EPA weight-of-evidence characterization for vinyl chloride classifies it as a *known human carcinogen by the inhalation route of exposure* based on human epidemiological data (EPA 2000). By analogy, vinyl chloride is *carcinogenic by the oral route* because of the positive animal bioassay results and the pharmacokinetic data that support extrapolation across exposure routes. Vinyl chloride is also considered *highly likely to be carcinogenic by the dermal route* because it is well absorbed and acts systemically (EPA 2000). However, the animal data suggest that dermal absorption of vinyl chloride gas is not likely to be significant (Hefner et al. 1975a). Because the epidemiological evidence does not provide sufficient exposure and incidence data to quantify risk based solely on the human data, the EPA cancer potency factors for inhalation and oral exposure were calculated based on animal data. An inhalation unit risk of 8.8×10^{-6} per $\mu g/m^3$ for continuous lifetime exposure initiated at birth was estimated (EPA 2000) based on the incidence of liver tumors in the rat inhalation study by Maltoni et al. (1981). An inhalation unit risk of 4.4×10^{-6} per $\mu g/m^3$ for continuous lifetime exposure during adulthood was also estimated by EPA (2000) based on the same study (Maltoni et al. 1981).

2.20 GENOTOXICITY

Vinyl chloride is mutagenic and clastogenic in both *in vitro* and *in vivo* test systems. Tables 2-9 and 2-10 list the key *in vitro* and *in vivo* genotoxicity studies, respectively, for vinyl chloride.

Table 2-9. Genotoxicity of Vinyl Chloride *In Vitro*

Species (test system)	Endpoint	Result		Reference
		With activation	Without activation	
Salmonella typhimurium	Reverse mutation	+	–	Rannug et al. 1974
		+	+	Bartsch et al. 1975, 1976
		+	+	Andrews et al. 1976
		+	+	Simmon et al. 1977
		Not tested	–	Elmore et al. 1976
		+	+	Poncelet et al. 1980
		+	+	de Meester et al. 1980
		+	+	Victorin and Stahlberg 1988
		+	Not tested	McCann et al. 1975
		+	+	Rannug et al. 1976
S. typhimurium TA100, TA1535	Base-pair substitution	+	+	du Pont 1992a, 1992b
		+	Not tested	Malaveille et al. 1975
Escherichia coli		Not applicable	+	Jacobsen et al. 1989
E. coli transfected with human plasmid DNA	DNA repair	Not applicable	+	Kowalczyk et al. 2006
E. coli transfected with plasmid DNA	Mutation and DNA repair	Not applicable	+	Maciejewska et al. 2010
Saccharomyces cerevisiae		Not tested	–	Shahin 1976
	Gene conversion	+	Not tested	Loprieno et al. 1976
Schizosaccharomyces pombe	Forward mutation	+	–	Loprieno et al. 1977
		+	Not tested	Loprieno et al. 1976
D7RAD yeast	Gene conversion	+	_	Eckardt et al. 1981
Chinese hamster ovary cells	Mutation	Not applicable	+	Huberman et al. 1975
		+	Not tested	Drevon et al. 1978
		+	–	du Pont 1992c
Chinese hamster lung cells	Chromosomal aberration	+	–	Asakura et al. 2008
Bacillus subtilis	Rec-repair	Not tested	–	Elmore et al. 1976
Rat liver microsomes	RNA alkylation	Not applicable	+	Laib and Bolt 1977
QT6 (avian cells)	Inhibition of DNA synthesis	Not applicable	+	Kandala et al. 1990
African green monkey fibroblast cell line (COS-7)	Mutation spectra after transfection with DNA adducts of vinyl chloride	Not applicable	+	Fernandes et al. 2005

Table 2-9. Genotoxicity of Vinyl Chloride *In Vitro*

Species (test system)	Endpoint	Result	Reference
Human plasmid DNA	Mutation	Not applicable +	Kowalczyk et al. 2006
Human lymphoblast	Micronuclei	Not applicable +	Feng et al. 2014

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

Table 2-10. Genotoxicity of Vinyl Chloride *In Vivo*

Species (exposure route)	Endpoint	Results	Reference
Mouse (inhalation)	Dominant lethal	–	Anderson et al. 1976
	Micronuclei	+	Richardson et al. 1983
Rat (inhalation)	Dominant lethal	–	Short et al. 1977
		–	Anderson et al. 1976
		–	Purchase et al. 1975
	Chromosomal aberration	+	Anderson and Richardson 1981
Hamster (inhalation or i.p. injection)	Chromosomal aberration	+	Fleig and Thiess 1978
Human lymphocytes from exposed workers	Sister chromatid exchange	–	Hansteen et al. 1978
		+	Fucic et al. 1990a
		+	Fucic et al. 1992
		+	Fucic et al. 1995
		+	Fucic et al. 1996a
		+	Fucic et al. 1996b
		+	Kucerova et al. 1979
		+	Sinués et al. 1991
		+	Zhao et al. 1994
	DNA damage	+	Awara et al. 1998
		+	Du et al. 1995
		+	Lei et al. 2004
		+	Kumar et al. 2013
		+	Zhu et al. 2005b
		+	Zhu et al. 2008
	Micronuclei	+	Feng et al. 2017
		+	Fucic et al. 1990a
		+	Garaj-Vrhovac et al. 1990
		+	Ji et al. 2010
		+	Jiao et al. 2012
		+	Kumar et al. 2013
		+	Li et al. 2013
		+	Qiu et al. 2008

Table 2-10. Genotoxicity of Vinyl Chloride *In Vivo*

Species (exposure route)	Endpoint	Results	Reference
		+	Qiu et al. 2011a
		+	Qiu et al. 2011b
		+	Sinués et al. 1991
		+	Vaglenov et al. 1999
		+	Wang et al. 2010a
		+	Wang et al. 2011
		+	Wang et al. 2013a
		+	Wang et al. 2013b
		+	Wen-Bin et al. 2009
		+	Wu et al. 2013
		+	Zheng et al. 2017
	Chromosomal aberration	–	Picciano et al. 1977
		+	Anderson et al. 1980, 1981
		+	Anderson 1999
		+	Becker et al. 2001
		+	Ducatman et al. 1975
		+	Fleig and Thiess 1978
		+	Fucic et al. 1990a, 1990b
		+	Fucic et al. 1992
		+	Fucic et al. 1995
		+	Fucic et al. 1996a
		+	Fucic et al. 1996b
		+	Funes-Cravioto et al. 1975
		+	Garaj-Vrhovac et al. 1990
		+	Hansteen et al. 1978
		+	Heath et al. 1977
		+	Hrivnak et al. 1990
		+	Hüttner et al. 1998
		+	Hüttner et al. 1999
		+	Hüttner and Nikolova 1998
		+	Kucerova et al. 1979
		+	Kumar et al. 2013
		+	Purchase et al. 1978
		+	Vaglenov et al. 1999

Table 2-10. Genotoxicity of Vinyl Chloride *In Vivo*

Species (exposure route)	Endpoint	Results	Reference
Rat (inhalation)	DNA alkylation	+	Bolt et al. 1986 (liver)
		+	Ciroussel et al. 1990 (liver, lungs brain)
		+	Eberle et al. 1989 (liver, lung)
		+	Green and Hathway 1978 (liver)
		+	Gwinner et al. 1983 (liver)
		+	Laib 1986 (liver)
		+	Singer et al. 1987 (liver)
Mouse (inhalation)	DNA alkylation	+	Osterman-Golkar et al. 1977
	DNA damage	+	Walles et al. 1988
Rat (inhalation)	DNA adduct	+	Bolt et al. 1986 (liver)
		+	Ciroussel et al. 1990 (liver, lungs brain)
		+	Eberle et al. 1989 (liver, lung)
		+	Fedtke et al. 1990 (liver, lung, kidney, brain, spleen)
		+	Morinello et al. 2002a, 2002b (liver, brain)
		+	Swenberg et al. 1992 (liver)
Rat (i.p. injection)	DNA damage	+	Qiu et al. 2019 (liver)

– = negative result; + = positive result; i.p. = intraperitoneal; DNA = deoxyribonucleic acid

Concentrations of vinyl chloride tested *in vitro* range from 0.275% (Shahin 1976) to 40% (du Pont 1992a). Shahin (1976) reported negative results for 0.275 and 0.55% vinyl chloride in *Saccharomyces cerevisiae*. In *Salmonella typhimurium*, a doubling of the number of revertant colonies was reported to occur at a concentration of about 5% vinyl chloride (Victorin and Stahlberg 1988). Vinyl chloride was found to be mutagenic in Chinese hamster ovary cells and yeast (Drevon et al. 1978; du Pont 1992c; Eckardt et al. 1981; Loprieno et al. 1976). A 5-hour exposure to 4,600 ppm vinyl chloride did not cause mutagenicity in the mammalian spot test (Peter and Ungvary 1980).

There is evidence that in *S. typhimurium*, *Escherichia coli*, and *Bacillus subtilis,* it is the oxidation of vinyl chloride to its reactive intermediates, 2-chloroethylene oxide and 2-chloroacetaldehyde, that leads to its mutagenicity (Bartsch et al. 1976, 1979; Hussain and Osterman-Golkar 1976; Jacobsen et al. 1989; Laumbach et al. 1977; McCann et al. 1975; Rannug et al. 1976). The S-9 fraction from surgically obtained human liver specimens was shown to metabolize vinyl chloride to electrophiles that were mutagenic to *S. typhimurium* TA1530 (Sabadie et al. 1980). Mutagenicity assays were performed by

exposing the plates containing *S. typhimurium* and 150 µL human S-9 fraction to a gaseous mixture of 20% vinyl chloride in air for 4 hours. The gaseous mixture was removed after the exposure, leaving a vinyl chloride concentration of $4x10^{-3}$ M in the aqueous phase of the plates. Incubation was continued for an additional 48 hours. When compared with the number of revertant colonies per plate resulting from identically prepared S-9 fractions from female strain BD IV rats, the human S-9 fractions mutations averaged 84% of those mediated by rat S-9. A 9-fold individual variation was observed among human S-9 samples.

The chloroacetaldehyde metabolite of vinyl chloride appears to be less genotoxic in yeast and Chinese hamster V79 cells than 2-chloroethylene oxide (Huberman et al. 1975; Loprieno et al. 1977) and has been shown to inhibit DNA synthesis in avian cells (Kandala et al. 1990). However, 2-chloroacetaldehyde can react directly with single-stranded DNA, producing DNA base changes and subsequent reversion when the DNA was inserted into *E. coli* via a phage technique (Jacobsen et al. 1989). Other studies found 2-chloroacetaldehyde to be mutagenic in human fibroblast cells using shuttle vectors (Matsuda et al. 1995).

Vinyl chloride produced chromosome aberrations in a gas exposure system using Chinese hamster lung cells (Asakura et al. 2008). DNA adducts of vinyl chloride were shown to be mutagenic following transfection into COS-7 mammalian cells (Fernandes et al. 2005). Chloroacetaldehyde, a metabolite of vinyl chloride, produced sequence specific mutations in the p53 gene region of human DNA (Kowalczyk et al. 2006). DNA repair kinetics, evaluated following transfection of human plasmid DNA into *E. coli*, were also sequence specific with rapid repair occurring in some locations and delayed repair occurring at mutation hotspots (Kowalczyk et al. 2006). Repair of chloroacetaldehyde-induced mutations in *E. coli* was shown to be mediated by the AlkB protein, which is produced as part of an adaptive response to alkylating agents in these bacteria (Maciejewska et al. 2010).

Genotoxicity studies of vinyl chloride in humans include assays evaluating micronuclei, chromosome aberrations, or DNA damage in cultured human lymphocytes of occupationally exposed workers. Studies completed through the mid-1980s generally found a statistically significant increase in the frequency of chromosomal aberrations, usually of the chromatid type (i.e., affecting only one of the two strands formed upon DNA replication), but also including some other chromosomal-type defects such as inversions, rings, and translocations, which affect the entire chromosome (Anderson 1999, 2000; Anderson et al. 1981; Fleig and Thiess 1978; Fucic et al. 1990a; Heath et al. 1977). Total chromosomal aberrations and chromatid type aberrations were increased in vinyl chloride workers with exposure durations of >8 years,

compared with workers exposed for a shorter time period and unexposed controls (Kumar et al. 2013). An increase in chromosomal aberrations was also observed following an accidental environmental exposure to vinyl chloride (Becker et al. 2001; Hüttner and Nikolova 1998; Hüttner et al. 1998, 1999). Micronuclei frequency was significantly increased in vinyl chloride workers compared to control workers (Feng et al. 2017; Fucic et al. 1990a; Garaj-Vrhovac et al. 1990; Ji et al. 2010; Jiao et al. 2012; Kumar et al. 2013; Sinués et al. 1991; Wang et al. 2010a, 2011, 2013a, 2013b; Wu et al. 2013; Zheng et al. 2017). The increase in micronuclei frequency was generally associated with cumulative exposure to vinyl chloride in the cited studies. Female workers were shown to be more susceptible to the increase in micronuclei frequency than male workers (Wang et al. 2013a). An increase in chromosome aberrations and micronuclei was correlated with both the air concentration of vinyl chloride and the excretion of thiodiglycolic acid in the urine of exposed workers at a plastic plant (Vaglenov et al. 1999).

Increased sister chromatid exchanges were reported in occupationally exposed workers (Fucic et al. 1990a, 1992, 1995; Kucerova et al. 1979; Sinués et al. 1991; Zhao et al. 1996). Sister chromatid exchange frequencies were significantly increased compared to those of the controls at 0.003–7.3 ppm vinyl chloride (Sinués et al. 1991). A positive correlation between frequency of chromosomal aberrations, length of exposure, and history of exposure to excursion levels (up to 2,000 ppm) was reported by Purchase et al. (1978) after examination of a cohort of 57 vinyl chloride workers, 19 on-site controls, and 5 off-site controls. The exposures for this cohort ranged from 1,000 ppm between 1945 and 1955 to 5 ppm in the years after 1975. These authors also reported an effect of vinyl chloride on chromosomal aberrations in the individuals who reported smoking. Smoking and the presence of an aldehyde dehydrogenase 2 genotype was associated with an increase in the frequency of sister chromatid exchange among vinyl chloride workers (Wong et al. 1998).

DNA single strand breaks were increased in lymphocytes from workers exposed to vinyl chloride concentrations >5 ppm (Kumar et al. 2013; Lei et al. 2004). A correlation was observed between the severity of DNA damage and the duration of exposure (Awara et al. 1998). The level of single-strand breaks was also significantly associated with levels of the urinary biomarker, thiodiglycolic acid (Lei et al. 2004). DNA single strand breaks present in human lymphocytes from exposed workers were quickly repaired following cessation of exposure (Du et al. 1995). Induction of single strand breaks in liver DNA was also observed in mice after inhalation of vinyl chloride (Walles et al. 1988).

The reversibility of chromosome damage was reported for several worker populations following cessation or reduction of exposure to vinyl chloride. The increase of chromosome aberrations observed in workers

exposed to 50 ppm returned to normal within 42 months after exposure levels were reduced to <5 ppm (Anderson et al. 1980). Another study demonstrated a statistically significant increase in aberrations in workers exposed to vinyl chloride concentrations of approximately 25 ppm. Following a reduction in exposure to 1 ppm, vinyl chloride chromosomal aberrations returned to control values (Hansteen et al. 1978). A 9-year follow-up study of an occupationally exposed population demonstrated a decrease in chromosome aberrations and sister chromatid exchange frequencies over time, corresponding to a decrease in vinyl chloride air concentrations at the plant (Fucic et al. 1996a, 1996b).

The reversibility of clastogenic effects was not observed in a study of 12 current and 3 retired plastics industry workers who had been exposed to vinyl chloride while employed for periods of 1.5–35 years (Fucic et al. 1992). Sister chromatid exchange frequencies were significantly higher in the workers exposed to concentrations up to 2,000 ppm than in the controls. These findings showed no significant decrease in sister chromatid exchange frequencies in the participants following periods of 8 days to 10 years after exposure (Fucic et al. 1992).

Other papers on human subjects focused on specific mechanisms involved in producing the clastogenic effects of vinyl chloride. A cohort of 67 workers exposed to approximately 5 ppm for an average of 15 years was reported to have a nonrandom distribution of chromatid and bichromatid DNA strand breaks (Fucic et al. 1990b). The most frequently affected areas of the genome were the terminal segments of the A, B, and C group chromosomes, suggesting that vinyl chloride or its metabolites interact more frequently with specific sites along the chromosome than would be expected. The study authors presented no correlation with particular fragile sites (gene sequences more prone to breakage than normal) or oncogene locations known to occur at these terminal segments. The implication is that the carcinogenicity of vinyl chloride could be at least partially explained by its nonrandom interaction with particular genes. The workers were also periodically exposed to vinyl chloride concentrations as high as 2,000 ppm for short periods. No specific information was given as to the frequency or duration of the high vinyl chloride concentration events.

Male workers (n=20) employed for 2–14 years at a vinyl chloride polymerization plant and exposed to concentrations of vinyl chloride of 1 ppm (with occasional peaks of 300 ppm) underwent cytogenetic testing (Fucic et al. 1995). The test results were compared to those from 20 unexposed male controls. The exposed individuals had higher percentages of chromosome aberrations, primarily chromatid breaks than the controls. Sister chromatid exchange frequencies were also increased in the exposed workers (4–22 per cell) compared to controls (4–7 per cell). Significant changes in mitotic activity were noted among

exposed workers; values for second mitosis events were lower than controls and values for a third mitosis event were higher than controls (Fucic et al. 1995, 1997). Chromosome aberrations were not increased in workers exposed to <5 ppm vinyl chloride; however, the average exposure duration for this study was less than 1 year (Picciano et al. 1977).

Polymorphisms of genes involved in metabolism (CYP2E1, glutathione S-transferase pi 1 [GSTP1], aldehyde dehydrogenase 2 [ALDH2]), DNA repair (human 8-oxoguanine glycosylase 1 [hOGG1], O6-methylguanine-DNA methyltransferase [MGMT], X-ray repair cross complementing group 1 [XRCC1], xeroderma pigmentosum complement groups A, C, D, and E [XPA, XPC, XPD, XPF], thymine-DNA glycosylase [TDG], apurinic/apyrimidinic endonuclease 1 [APE1]), apoptosis (MDM2, BCL2), and cell cycle control (p53, p21) are associated with increased micronuclei and sister chromatid exchange frequency in vinyl chloride workers (Feng et al. 2017; Ji et al. 2010; Li et al. 2013; Qiu et al. 2008, 2011a; Wang et al. 2010a, 2010b, 2013b; Wen-Bin et al. 2009; Wong et al. 2003b). Increased micronuclei frequency was also associated with altered promoter methylation of MGMT in vinyl chloride-exposed workers (Wu et al. 2013). Qiu et al. (2011b) found an increase in p21 mRNA expression in workers exposed to vinyl chloride; however, there was no correlation with the frequency of micronuclei measured in these workers. Polymorphisms of CYP2E1, XRCC1, and XPD were also associated with susceptibility to DNA damage (single-strand breaks in lymphocyte DNA) of vinyl chloride-exposed workers (Zhu et al. 2005b, 2008). Genetic polymorphisms of the XRCC1 DNA repair gene were also associated with an increase in the retention of etheno-DNA adducts in lymphoblast cell lines derived from vinyl chloride workers (Li et al. 2006, 2009a). The occurrence of mutation biomarkers in serum was correlated with polymorphisms of the DNA repair genes XRCC1 (mutant p53) and excision repair cross complementation group 2 (ERCC2)/XPD (mutant p53 and ras-p21) in vinyl chloride workers (Li et al. 2006, 2009b). The presence of a polymorphism for CYP2E1 (variant c2 allele) was also associated with the occurrence of mutant p53 and ras-p21 serum biomarkers (Schindler et al. 2007). Polymorphisms of other genes involved in vinyl chloride metabolism (microsomal epoxide hydrolase [mEH], glutathione S-transferase mu 1 [GSTM1], glutathione S-transferase theta 1 [GSTT1]) were not associated with mutant p21 or p53 biomarkers in vinyl chloride workers (Li et al. 2005a, 2005b; Schindler et al. 2007).

Animal studies of rats and mice exposed via inhalation to vinyl chloride concentrated on identifying the direct effects of vinyl chloride and its metabolites on DNA. Vinyl chloride is metabolized by cytochrome P450 mixed function oxidases (CYP) to form an epoxide intermediate, 2-chloroethylene oxide, which spontaneously rearranges to form 2-chloroacetaldehyde (Section 3.1.3, Metabolism). Reactive

metabolites of vinyl chloride can be transported intercellularly from parenchymal cells to the nonparenchymal cells (Kuchenmeister et al. 1996). Many studies have characterized the mutation profile associated with DNA adducts formed by the reactive metabolites of vinyl chloride (Akasaka et al. 1997; Chiang et al. 1997; Dosanjh et al. 1994; Guichard et al. 1996; Matsuda et al. 1995; Pandya and Moriya 1996; Zhang et al. 1995; Zielinski and Hergenhahn 2001). The four primary mutagenic DNA adducts formed by the reactive metabolites of vinyl chloride are cyclic etheno-adducts that include 1,N^6-ethenoadenine, 3,N^4-ethenocytosine, N^2,3-ethenoguanine, and 1,N^2-ethenoguanine. These adducts can induce base-pair (i.e., purine-to-purine or pyrimidine-to-pyrimidine exchange) transitions during transcription (Cullinan et al. 1997; Oesch and Doerjer 1982; Pandya and Moriya 1996; Singer 1996; Singer et al. 1987). 1,N^6-Ethenoadenine adducts reduce the binding of topoisomerase I to DNA, affecting DNA replication and transcription (Pourquier et al. 1998). The adduct, 7-(2'-oxoethyl) guanine, is extensively formed in mammalian liver (Laib et al. 1981); however, it is quickly recognized and removed by DNA repair mechanisms. Etheno-adducts are less abundant, but more persistent because they are poorly repaired (Brandt-Rauf et al. 2000a; Whysner et al. 1996).

The presence of etheno-nucleosides has been reported following inhalation exposure to vinyl chloride in rats (Bolt et al. 1986; Ciroussel et al. 1990; Eberle et al. 1989; Fedtke et al. 1990; Morinello et al. 2002a, 2002b; Swenberg et al. 1992). Immature rats exposed *in vivo* formed 6 times more of this nucleoside adduct, which correlated with the age-related sensitivity to carcinogenesis in these animals (Ciroussel et al. 1990). This age-related sensitivity to DNA adduct formation was also noted in an inhalation study of lactating rats and their 10-day-old pups exposed 4 hours/day, for 5 days to 600 ppm of vinyl chloride (Fedtke et al. 1990). Concentrations of two adducts found in the liver of the pups were 4-fold higher than those found in the liver of the dams. Increased alkylation of liver DNA and increased cell proliferation were reported by Laib et al. (1989) following exposure to 600 ppm vinyl chloride for 6 hours. Young rats were apparently more susceptible to the effects of vinyl chloride, but only three male adults and two female adults were used for comparison. In a similar study comparing three newborn rats to two adult rats, exposure to 2,000 ppm vinyl chloride 8 hours/day, 5 days/week for 10 weeks resulted in hepatocellular foci that were deficient in nucleoside-5-triphosphatase in newborns animals only (Laib et al. 1979). The concentration of ethenoguanine adducts was 2–3-fold greater in weanling rats as compared to adult rats exposed at the same dose for the time period (0, 10, 100, or 1,100 ppm, 6 hours/day for 5 days) (Morinello et al. 2002a). Rats exposed to 2,000 ppm vinyl chloride for 8 hours/day, 5 days/week, for 3 weeks beginning at 7 days of age demonstrated hepatocellular ATPase-deficient foci and alkylation of liver DNA (Gwinner et al. 1983). A study in rats exposed to 1,100 ppm vinyl chloride for 6 hours/day, 5 days/week for 1 or 4 weeks demonstrated that ethenoguanine adducts are not formed in the adult rat

brain (Morinello et al. 2002b). This differential induction of DNA adducts (brain versus liver) may relate to the direct effect of reactive intermediates at the site of metabolite generation.

The role of etheno-adducts in the carcinogenesis of vinyl chloride was reviewed by a number of researchers (Albertini et al. 2003; Barbin 1998, 1999, 2000; Gros et al. 2003; Kielhorn et al. 2000; Laib 1986; Mutlu et al. 2010, 2012; Nivard and Vogel 1999; Pottenger et al. 2014; Swenberg et al. 2011; Whysner et al. 1996). Both 2-chloroethylene oxide and 2-chloroacetaldehyde can react with DNA nucleotide bases; however, 2-chloroethylene oxide is a more potent mutagen and may be the ultimate carcinogenic metabolite of vinyl chloride (Chiang et al. 1997). Etheno-adducts mainly lead to base pair substitution mutations. Mutations in specific genes (i.e., *ras* oncogenes, p53 tumor suppressor gene) identified in vinyl chloride-induced liver tumors in rats and humans are discussed in further detail below. Exocyclic DNA adducts are excised from the DNA by glycosylase enzymes that contribute to genetic stability (Laval and Saparbaev 2001). The four primary cyclic adducts formed in DNA by the vinyl chloride metabolite, chloroacetaldehyde, are released by human glycosylase enzymes (Dosanjh et al. 1994; Singer and Hang 1999). The expression of the DNA repair enzyme N-methylpurine-DNA-glycosylase was shown to be deficient in nonparenchymal cells of the rat liver, the target cells for vinyl chloride-induced angiosarcomas (Holt et al. 2000; Swenberg et al. 1999). However, there were no differences observed in the formation of ethenoguanine adducts in hepatocytes and nonparenchymal cells immediately following vinyl chloride exposure (Morinello et al. 2002a). Together, these data suggest that cellular differences in DNA repair capacity may play a role in vinyl chloride-induced carcinogenesis. It is important to note that endogenously formed etheno-adducts are also present in humans and laboratory animals due to a reaction between DNA and lipid peroxidation by-products. The background incidence of etheno-adducts should be considered when evaluating exposure to chemicals like vinyl chloride (Albertini et al. 2003; Bartsch and Nair 2000; Gonzalez-Reche et al. 2002; Swenberg et al. 2000; Watson et al. 1999; Yang et al. 2000; Zielinski and Hergenhahn 2001). A stable isotope method using [$^{13}C_2$]-labeled vinyl chloride was used to determine the half-life of etheno-guanidine adducts following inhalation exposure in rats, which allowed for a distinction between endogenous and exogenous adducts (Mutlu et al. 2010, 2012; Swenberg et al. 2011).

Members of the *ras* gene family, including Ha-*ras*, Ki-*ras*, and N-*ras*, may be responsible for the control of cell proliferation and differentiation (Froment et al. 1994). DNA adducts formed by vinyl chloride metabolites can produce point mutations in these genes. Mutations of the Ki-*ras*-2 gene were found in hepatic angiosarcomas of workers exposed to high levels of vinyl chloride; this specific gene was shown to be activated by a GC-AT transition at codons 12 and 13 (Brandt-Rauf et al. 1995; Guido et al. 2016;

Marion et al. 1991; Weihrauch et al. 2002). Similar mutations of Ki-*ras*-2 were found in hepatocellular carcinomas of workers exposed to vinyl chloride (Weihrauch et al. 2001a, 2001b). Hypermethylation of the p16 gene was also associated with Ki-*ras*-2 mutation in hepatocellular carcinomas from exposed workers (Weihrauch et al. 2001b).

Mutation of the Ki-*ras*-2 gene results in the expression of a mutant p21 protein. This mutant oncoprotein was detected in serum samples taken from vinyl chloride workers with angiosarcoma of the liver (DeVivo et al. 1994; Marion 1998). Mutant p21 protein was also detected in the serum or plasma of exposed workers without liver tumors and a relationship between the frequency of the mutant protein in serum and the intensity of vinyl chloride exposure was demonstrated in several studies (Brandt-Rauf et al. 1995; DeVivo et al. 1994; Li et al. 1998; Luo et al. 1998, 2003; Marion 1998).

Rat liver tumors induced by exposure to 500 ppm vinyl chloride were examined for mutations of the Ha-*ras*, Ki-*ras*, and N-*ras* genes (Boivin-Angele et al. 2000; Froment et al. 1994; Marion and Boivin-Angele 1999). In contrast to the studies in humans, the Ki-*ras* gene mutation does not occur in rats or mice with angiosarcoma of the liver induced by vinyl chloride exposure. Rats with hepatocellular carcinoma demonstrated a AT–TA transversion of base 2 of codon 61 of the Ha-*ras* gene. However, this mutation was not detected in rodent angiosarcoma of the liver, suggesting that there might be cell-specific factors that affect the *ras* gene. Other mutations in codons 13 and 36 of the N-*ras* A gene were found in two out of five of the liver angiosarcomas examined (Froment et al. 1994).

The p53 tumor suppressor gene is mutated in a variety of human cancers (Staib et al. 2003; Trivers et al. 1995). A study was performed to examine the p53 tumor suppressor genes and the murine double min-2 (MDM2) proto-oncogenes from tumors of five vinyl chloride workers, four with angiosarcoma of the liver and one with hepatocellular carcinoma (Hollstein et al. 1994). The p53 tumor suppressor gene was being tested for mutation, while the MDM2 proto-oncogene was being tested for amplification. No amplification of the MDM2 gene was detected; however, adenosine-to-thymidine missense mutations were found in exons 5–8 (codons 249 and 255) of the p53 gene in two of the angiosarcoma cases. In another study, tumors (angiosarcoma of the liver) from three of six vinyl chloride workers also had adenosine-to-thymidine missense mutations in the p53 gene (codons 249, 255, and 179) (Trivers et al. 1995). Data from a study of angiosarcoma of the liver resulting from endogenous or unknown sources (i.e., no vinyl chloride exposure) indicated that p53 mutations were uncommon, providing support for the specificity of p53 mutations with vinyl chloride exposure in cases of angiosarcoma of the liver (Soini et al. 1995). The p53 gene mutation pattern in rat liver tumors (angiosarcoma and hepatocellular carcinoma)

was shown to be similar to that observed in human tumors from vinyl chloride-exposed workers (Barbin et al. 1997; Marion and Boivin-Angele 1999). In a different study, mutations of the p53 gene were found in hepatocellular carcinomas from workers exposed to vinyl chloride; however, no correlation with vinyl chloride exposure occurred and the mutation pattern was thought to reflect endogenous mechanisms (e.g., deamination of 5-methylcytosine) rather that chemical mutagenesis (Weihrauch et al. 2000). A p53 mutation at codon 179 was detected in myofibroblast-type cells isolated from a liver tumor in an exposed worker (Boivin et al. 1997). Ki-*ras* mutations were not observed in these cells. Vinyl chloride mutations of the p53 gene produce conformational effects in the expressed p53 protein that affect its function (Cheng et al. 1999a).

Mutant p53 protein and/or anti-p53 antibodies were detected in the serum and plasma of vinyl chloride-exposed workers (Luo et al. 1999; Marion 1998; Smith et al. 1998; Trivers et al. 1995). A relationship between the frequency of the mutant protein or p53 antibodies in serum/plasma and the vinyl chloride exposure concentration was demonstrated in these studies. Polymorphisms of the genes for vinyl chloride metabolism (CYP2E1) and DNA repair (x-ray cross-complementing group 1) are associated with a greater risk of p53 gene mutation and over-expression of p53 mutant protein (Li et al. 2003a; Wong et al. 2002b).

Rat studies suggest that gap junctional intercellular communication mediated by connexin 37 is disturbed in angiosarcoma of the liver; however, mutation of the connexin 37 gene is rare (Saito et al. 1997). The incidence of hypoxanthine-guanine-phosphoribosyl-transferase (HPRT) mutants was not consistently elevated in workers exposed to vinyl chloride (Hüttner and Holzapfel 1996; Liber et al. 1999). HPRT mutants were also not increased in humans accidentally exposed to vinyl chloride (Becker et al. 2001).

Vinyl chloride has not been shown to be positive for dominant lethal effects in rats exposed to up to 30,000 ppm, for 6 hours/day for 5 days (Anderson et al. 1976; Purchase et al. 1975; Short et al. 1977). The studies showed no evidence of pre- or post-implantation loss among the untreated females mated to the exposed males. These results indicate that no germinal mutations were produced by these acute-duration exposures. Vinyl chloride induces somatic and sex-linked recessive lethal mutations in *Drosophila* but does not induce dominant lethal mutations (Ballering et al. 1996; Giri 1995; Magnusson and Ramel 1978).

Vinyl chloride is mutagenic in *S. typhimurium* (Andrews et al. 1976; Bartsch et al. 1975, 1976; de Meester et al. 1980; Elmore et al. 1976; Malaveille et al. 1975; Poncelet et al. 1980; Simmon et al. 1977),

but only in strains reverted by base-pair substitution by alkylating agents rather than by frameshift mutations (Bartsch et al. 1976; du Pont 1992a, 1992b). Metabolic activation is necessary for any mutagenic activity in this system (Rannug et al. 1974) or for a maximal response (Simmon et al. 1977). In addition, vinyl chloride is mutagenic in the gaseous phase, but not when it is dissolved in water (Poncelet et al. 1980). The negative findings for vinyl chloride dissolved in water are most likely due to methodological problems associated with rapid evaporation and therefore do not reflect a lack of mutagenic potential.

Summary. There are substantial data on clastogenesis in humans exposed to vinyl chloride that indicate that this chemical acts as a potent genotoxicant (Anderson 2000; Anderson et al. 1980; Awara et al. 1998; Becker et al. 2001; Ducatman et al. 1975; Fucic et al. 1990a, 1990b, 1992, 1995; Funes-Cravioto et al. 1975; Hansteen et al. 1978; Hrivnak et al. 1990; Hüttner and Nikolova 1998; Hüttner et al. 1998, 1999; Kucerova et al. 1979; Marion et al. 1991; Purchase et al. 1978; Sinués et al. 1991; Wong et al. 1998; Zhao et al. 1996). Reversibility of chromosome damage has been reported for several populations of workers following a cessation or reduction of exposure to vinyl chloride (Anderson et al. 1980; Fucic et al. 1996a, 1996b; Hansteen et al. 1978). Findings in humans are supported by both animal studies and *in vitro* studies that show positive genotoxicity in a variety of microbial organisms, cultured cell lines, and isolated nucleic acid assays (Anderson and Richardson 1981; Andrews et al. 1976; Bartsch 1976; Bartsch et al. 1976; Bolt et al. 1986; Ciroussel et al. 1990; de Meester et al. 1980; Eberle et al. 1989; Froment et al. 1994; Green and Hathway 1978; Gwinner et al. 1983; Hansteen et al. 1978; Huberman et al. 1975; Jacobsen et al. 1989; Kandala et al. 1990; Laib and Bolt 1977; Laib et al. 1989; Loprieno et al. 1977; McCann et al. 1975; Osterman-Golkar et al. 1977; Poncelet et al. 1980; Rannug et al. 1974, 1976; Simmon et al. 1977; Singer et al. 1987; Victorin and Stahlberg 1988; Walles et al. 1988). The role that etheno-adducts play in the carcinogenesis of vinyl chloride has been extensively studied (Albertini et al. 2003, Barbin 1998, 1999, 2000; Kielhorn et al. 2000; Nivard and Vogel 1999; Whysner et al. 1996). Both 2-chloroethylene oxide and 2-chloroacetaldehyde can react with DNA nucleotide bases; however, 2-chloroethylene oxide is a more potent mutagen and may be the ultimate carcinogenic metabolite of vinyl chloride (Chiang et al. 1997). Etheno-adducts generate mainly base pair substitution mutations. Mutations in specific genes (i.e., *ras* oncogenes, p53 tumor suppressor gene) have been identified in vinyl chloride-induced liver tumors in rats and humans (Barbin et al. 1997; Brandt-Rauf et al. 1995; Hollstein et al. 1994; Marion and Boivin-Angele 1999; Marion et al. 1991; Trivers et al. 1995; Weihrauch et al. 2002). Immunological techniques were used to detect the presence of Asp13p21 (oncoprotein for mutation of the Ki-*ras* gene), p53 mutant protein, and p53 antibodies in the serum of exposed workers (Brandt-Rauf et al. 2000a, 2000b; Marion 1998). Statistical analyses suggest a relationship between vinyl chloride exposure

and the presence of these serum biomarkers; however, the predictive value of the biomarkers for development of cancer is not known.