Toxicological Profile for Vinyl Chloride

Draft for Public Comment

January 2023

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

CS274127-A

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FOREWORD

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

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

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

Each profile includes the following:

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

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

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

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public. ATSDR plans to revise these documents in response to public comments and as additional data become available. Therefore, we encourage comments that will make the toxicological profile series of the greatest use.

Electronic comments may be submitted via: www.regulations.gov. Follow the on-line instructions for submitting comments.

Written comments may also be sent to:

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The toxicological profiles are developed under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980, as amended (CERCLA or Superfund). CERCLA section 104(i)(1) directs the Administrator of ATSDR to "…effectuate and implement the health related authorities" of the statute. This includes the preparation of toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL) and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list. In addition, ATSDR has the authority to prepare toxicological profiles for substances not found at sites on the NPL, in an effort to "…establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" under CERCLA Section 104(i)(1)(B), to respond to requests for consultation under section 104(i)(4), and as otherwise necessary to support the site-specific response actions conducted by ATSDR.

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

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VERSION HISTORY

Date	Description
January 2023	Draft for public comment toxicological profile released
July 2006	Final toxicological profile released
September 1997	Final toxicological profile released
April 1993	Final toxicological profile released
August 1989	Final toxicological profile released

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

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

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CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

Vinyl chloride is a volatile compound used almost exclusively by the plastics industry to produce polyvinyl chloride (PVC) and several copolymers in the United States. The majority of the vinyl chloride produced at manufacturing facilities is converted to PVC and vinyl chloride derived copolymers on-site. Nearly all vinyl chloride shipped to facilities off-site is also converted to PVC or PVC copolymers. In many cases, vinyl chloride is transported by pipeline directly to the plant producing the polymer. The physical form of vinyl chloride is a neat liquid (99.9% minimum purity) stored or transported under pressure.

Anthropogenic sources are responsible for all of the vinyl chloride found in the environment. Most of the vinyl chloride released to the environment eventually escapes to the atmosphere. Vinyl chloride has been detected in the ambient air in the vicinity of vinyl chloride and PVC manufacturing plants, hazardous waste sites, and hydro fracking flowback pits. The compound has leached into groundwater from spills, landfills, and industrial sources; it can also enter groundwater after being produced by the bacterial degradation of trichloroethylene, tetrachloroethylene, and 1,1,1-trichloroethane.

When released to the atmosphere, vinyl chloride is expected to be removed by reaction with photochemically generated hydroxyl radicals (half-life of 1–2 days). When released to water, volatilization is expected to be the primary environmental fate process. In waters containing photosensitizers, such as humic materials, sensitized photodegradation may also be important. Vinyl chloride released to soil either volatilizes rapidly from soil surfaces or leaches readily through soil, ultimately entering groundwater.

Segments of the general population living in the vicinity of emission sources (e.g., plastic manufacturing facilities) may be exposed to vinyl chloride by inhalation of contaminated air. Community members living on or near hazardous waste sites may experience long-term exposure to low levels of vinyl chloride as it has been found in many National Priority List (NPL) sites identified by the U.S. Environmental Protection Agency (EPA). The majority of the general population is not expected to be exposed to vinyl chloride through ingestion of drinking water, due to its volatility and restrictions on its release to potable water as an indirect drinking water additive. Workers, particularly employees at vinyl chloride and PVC manufacturing facilities, are exposed to vinyl chloride mainly by inhalation, although minor absorption

through the skin is possible. Workers involved in the handling and processing of PVC resins are exposed to lower levels of vinyl chloride than employees at vinyl chloride and PVC manufacturing facilities since fabricated products contain only trace quantities of vinyl chloride present as residual monomer. Since the early 1970s, improvements in manufacturing facilities, engineering controls, and workplace practices have substantially reduced workplace exposures in the United States and most other industrialized countries that manufacture vinyl chloride and produce or fabricate PVC products. The 1974 ban on use of vinyl chloride in U.S. consumer products resulted in a reduction in possible exposures in the general population (IARC 2012).

1.2 SUMMARY OF HEALTH EFFECTS

Information on the toxicity of vinyl chloride comes primarily from a large database of occupational worker studies and inhalation studies in animals, with similar effects being exhibited in all species tested. Chronic oral studies of vinyl chloride in animals focus primarily on carcinogenicity; however, two studies reported noncancer effects in the liver.

As shown in Figures 1-1 and 1-2, the most sensitive effects appear to be liver damage and carcinogenicity, exacerbated immune response, and delayed fetal ossification. Neurological effects are also commonly reported in humans and animals, although they generally occur at higher inhalation concentrations. A systematic review of the noncancer endpoints resulted in the following hazard identification conclusions:

- Hepatic effects are a presumed health effect for humans.
- Neurological effects are a presumed health effect for humans.
- Immunological effects are a suspected health effect for humans.
- Developmental effects are a suspected health effect for humans.

A systematic review was also performed for insulin resistance. The hazard identification conclusion was that insulin resistance was not classifiable due to an insufficient level of evidence in both human and animal studies.

Figure 1-1. Health Effects Found in Humans and Animals Following Inhalation Exposure to Vinyl Chloride

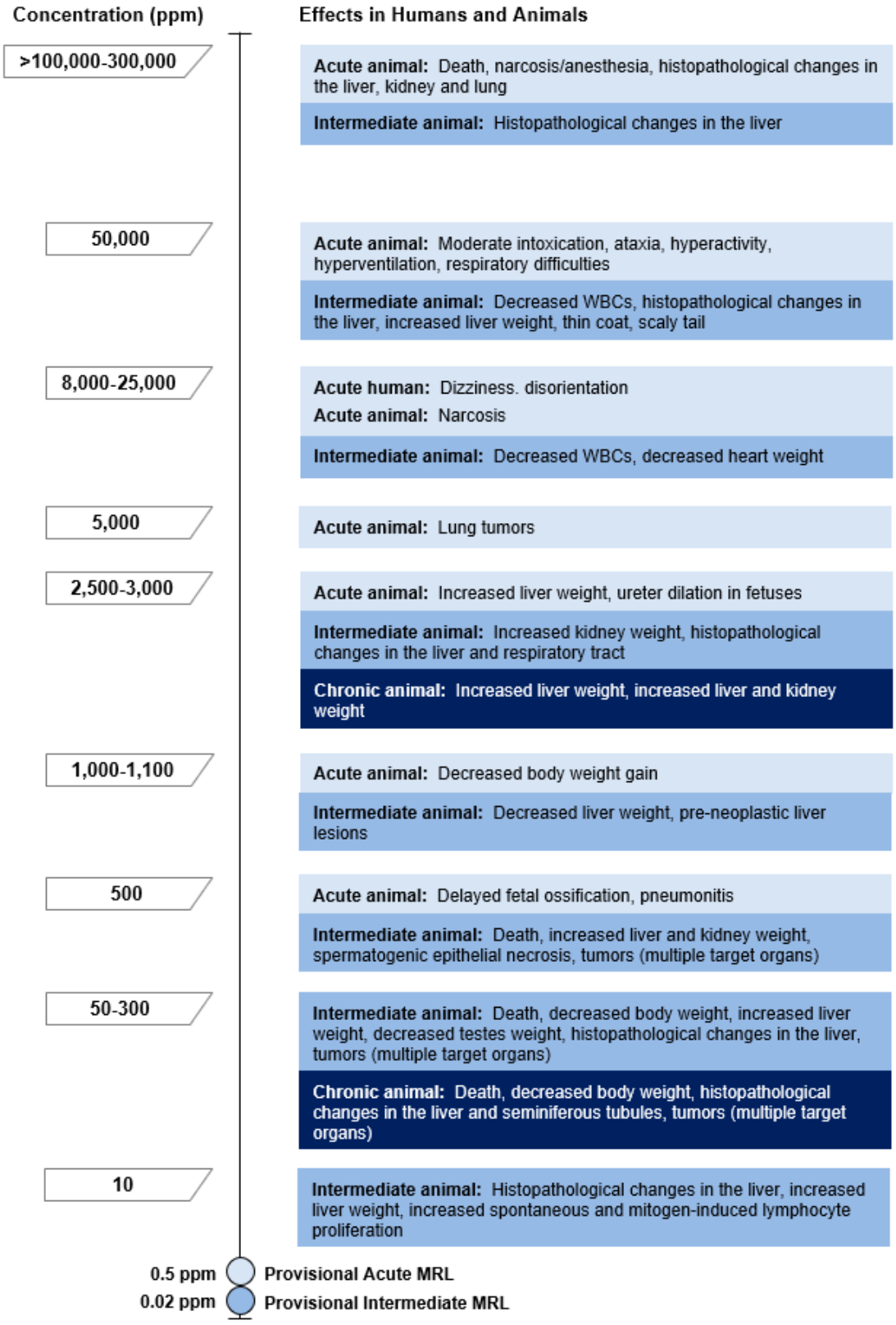
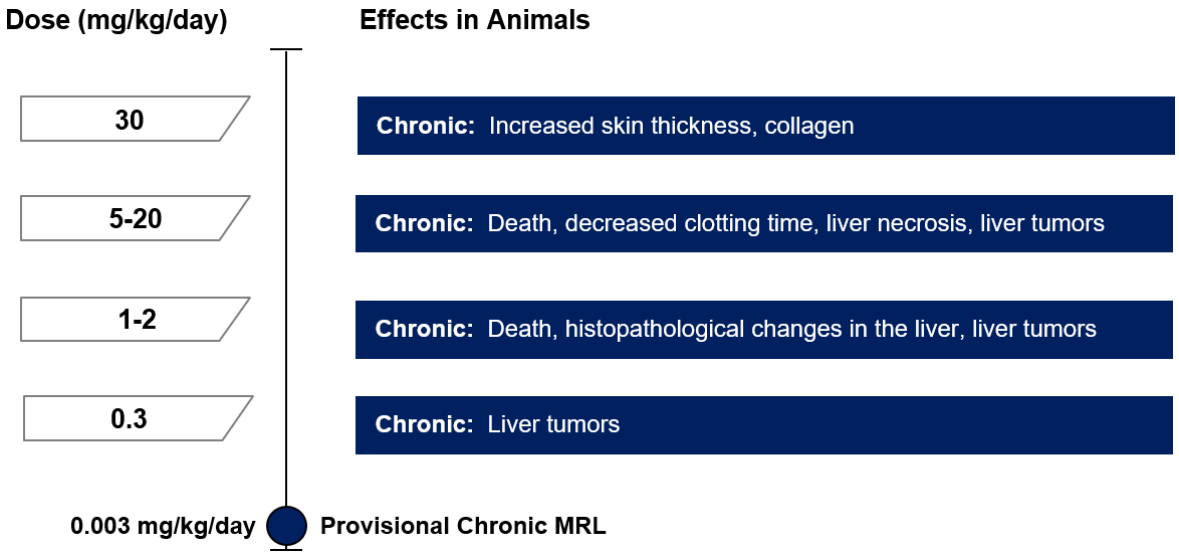


Figure 1-2. Health Effects Found in Animals Following Oral Exposure to Vinyl Chloride



Hepatic Effects. Results from numerous inhalation and oral animal studies support the identification of the liver as a presumed target in humans. Occupational studies have identified a consistent group of liver effects resulting from vinyl chloride exposure, including hypertrophy, hyperplasia of hepatocytes and sinusoidal cells, sinusoidal dilation, focal cellular degeneration, steatohepatitis, portal fibrosis, and cirrhosis (Berk et al. 1975; Cave et al. 2010; Du and Wang 1998; Falk et al. 1974; Fedeli et al. 2019a; Gedigke et al. 1975; Ho et al. 1991; Hsiao et al. 2004; Hsieh et al. 2007; Jones and Smith 1982; Lilis et al. 1975; Liss et al. 1985; Maroni et al. 2003; Marsteller et al. 1975; Mastrangelo et al. 2004; Mundt et al. 2017; NIOSH 1977; Popper and Thomas 1975; Suciu et al. 1975; Tamburro et al. 1984; Vihko et al. 1984; Ward et al. 2001; Zhu et al. 2005a). Plasma metabolomics analysis in vinyl chloride workers showed alterations in lipid and amino acid metabolites, which may contribute to the observed liver toxicity (Guardiola et al. 2016). Animal inhalation studies demonstrate that the severity of effects increased with increasing concentration, ranging from cellular hypertrophy and sinusoidal compression, to vacuolization, hepatic hyperplasia, fibrosis, and necrosis (Lester et al. 1963; Sokal et al. 1980; Thornton et al. 2002; Torkelson et al. 1961; Wisniewska-Knypl et al. 1980). Centrilobular hypertrophy, steatosis (fatty liver) and steatohepatitis (inflammation) resulted from intermediate-duration (15–364 days) inhalation exposures of 10, 50, and 100 ppm, respectively (Sokal et al. 1980; Thornton et al. 2002; Wisniewska-Knypl et al. 1980). Mice fed a high-fat diet (not included in Levels of Significant Exposure, LSE Tables) experienced enhanced liver damage, neutrophil infiltration, apoptosis, and oxidative and endoplasmic reticulum stress in the liver compared to mice fed a normal or low-fat diet (Chen et al. 2019; Fujiwara 2018; Lang et al. 2018, 2020; Liang et al. 2018; Wahlang et al. 2020). Chronic oral exposure of rats to 1.7 mg/kg/day resulted in liver cell polymorphisms and development of hepatic cysts (Til et al. 1983, 1991). In addition to noncancer effects, the liver was sensitive to tumor development. For intermediate- and chronic-duration (>365 days) inhalation and chronic-duration oral exposures, the development of liver angiosarcoma resulted from exposures as low as 50 ppm and 0.3 mg/kg/day, respectively (Drew et al. 1983; Holmberg et al. 1976; Hong et al. 1981; Maltoni et al. 1981).

Immune Effects. Workers exposed to high concentrations of vinyl chloride in air experienced Raynaud's phenomenon (decreased blood flow to the fingers), acroosteolysis (resorption of the distal bony phalanges), joint and muscle pain, enhanced collagen deposition, stiffness of the hands, and scleroderma-like skin changes and these effects may have an immunologic basis. The immunologic findings in workers with these conditions include an increase in circulating immune complexes, cryoglobulinemia (precipitation of abnormal proteins in the blood) (Bogdanikowa and Zawilska 1984; Grainger et al. 1980; Saad et al. 2017), increased incidence of B-cell proliferation (Ward 1976), hyperimmunoglobulinemia

(Ward 1976), and complement activation (Grainger et al. 1980; Saad et al. 2017; Ward 1976). Serum immunoglobulins (IgA, IgG, and IgM) and other inflammatory markers (i.e., ceruloplasmin, orsomucoid) were elevated in highly exposed male vinyl chloride workers (Bencko et al. 1988; Bogdanikowa and Zawilska 1984), and 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 (liver inflammation with fat accumulation) (Cave et al. 2010). There is evidence of a structurally altered IgG and it has been proposed that vinyl chloride (or a metabolite) binds to IgG (Grainger et al. 1980). Immunological effects are not well studied in animals; however, reported findings included increased spleen weight in rats (Sokal et al. 1980) and an increase in spontaneous and mitogen-stimulated lymphocyte proliferation in mice (Sharma and Gehring 1979).

Neurological Effects. Inhalation-related neurological effects in humans include dizziness, drowsiness and fatigue, headache, euphoria, irritability, nervousness, sleep disturbances, nausea, visual and hearing disturbances and loss of consciousness (Ho et al. 1991; Langauer-Lewowicka et al. 1983; Lilis et al. 1975; Marsteller et al. 1975; NIOSH 1977; Spirtas et al. 1975; Suciu et al. 1975; Veltman et al. 1975; Walker 1976). Signs of pyramidal and cerebellar disturbances have also been observed (not specified; Langauer-Lewowicka et al. 1983). Dizziness has been reported by volunteers acutely exposed to 8,000 ppm, while nausea and subsequent headache resulted from exposures of 20,000 to 25,000 ppm (Lester et al. 1963; Patty et al. 1930). Peripheral neurological effects have been reported, including paresthesia, tingling or warmth in the extremities, numbness or pain in the fingers, and depressed reflexes (Lilis et al. 1975; NIOSH 1977; Perticoni et al. 1986; Sakabe 1975; Spirtas et al. 1975; Suciu et al. 1975; Veltman et al. 1975; Walker 1976). Effects in animals from acute-duration (≤14 days) inhalation exposures include ataxia, decreased coordination, twitching, tremors, and unconsciousness (Hehir et al. 1981; Jaeger et al. 1974; Lester et al. 1963; Mastromatteo et al. 1960; Patty et al. 1930).

Developmental Effects. Early studies examining parental employment and/or residential proximity to vinyl chloride facilities and birth defects reported links to fetal loss and birth defects of the central nervous system (Infante et al. 1976a, 1976b; NIOSH 1977); however, 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 vinyl chloride concentration and 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). Developmental effects were observed in animal studies using the inhalation

route. Gestational exposures of 2,500 ppm resulted in ureter dilatation in rat offspring, while delayed ossification was observed following 500 ppm exposures in mice (John et al. 1977, 1981). No adverse effects were noted in an inhalation embryo-fetal developmental study in rats exposed to vinyl chloride at concentrations up to 1,100 ppm (Thornton et al. 2002).

Cancer. 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 comes from the greater-than-expected incidences of liver angiosarcoma (details in Section 2.19), which is considered to be very rare in humans (25–30 cases/year in the United States) (Heath et al. 1975). The latency period for the development of hepatic angiosarcoma was 24–56 years in workers exposed prior to 1974 (Collins et al. 2014). Other liver tumors, including hepatocellular carcinoma and cholangiocellular carcinoma, have also been associated with occupational exposure to vinyl chloride (details in Section 2.19). The latency period for the development of hepatocellular carcinoma has been 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 exposure to 5–5,000 ppm vinyl chloride vapors resulted in significant incidence of mammary gland carcinomas, Zymbal's gland carcinomas, nephroblastoma, and liver angiosarcoma (Maltoni et al. 1981). Intermediate- (15–364 days) and chronic-duration (≥365 days) 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 (details in Section 2.19). With the exception of liver angiosarcomas, which have been observed in all species (including humans), there is little consistency in tumor types across species.

Chronic-duration oral administration of 1.7–5 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, and mammary gland carcinoma, as compared to the risk associated with exposure after 12 months of age (Drew et al. 1983; Maltoni and Cotti 1988; Maltoni et al. 1981). Due to the latency period for vinyl chloride-induced cancer, exposure of animals early in life may have increased the likelihood of developing tumors and affected the type of tumor that developed.

The Department of Health and Human Services has determined vinyl chloride to be a known human carcinogen (NTP 2016). The International Agency for Research on Cancer (IARC) has concluded that sufficient evidence for carcinogenicity in humans and animals exists and has placed vinyl chloride in carcinogenicity category 1 (i.e., carcinogenic to humans) (IARC 2012). Similarly, EPA concluded that vinyl chloride is a *known human carcinogen by the inhalation route of exposure*, based on human epidemiological data (EPA 2000). By analogy, vinyl chloride is considered a *known human carcinogen by the oral route* because of positive animal bioassay data as well as pharmacokinetic data allowing dose extrapolation across routes. By inference, EPA considers vinyl chloride *highly likely to be carcinogenic by the dermal route* because it acts systemically.

1.3 MINIMAL RISK LEVELS (MRLs)

The inhalation database was considered adequate for deriving acute- and intermediate-duration MRLs but inadequate for derivation of a chronic-duration MRL. As presented in Figure 1-3, the available inhalation data for vinyl chloride suggest that the liver, immune system, and the developing fetus are the most sensitive target of toxicity in laboratory animals.

The oral database was considered adequate for deriving a chronic-duration MRL. The oral database was inadequate for derivation of acute- or intermediate-duration MRLs. As presented in Figure 1-4, the available oral data for vinyl chloride suggest that the liver is the most sensitive target of toxicity in laboratory animals.

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

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

The liver and immune system are the most sensitive targets of vinyl chloride inhalation exposure.
Numbers in circles are the lowest LOAELs for all health effects in animals; numbers in triangles are the lowest LOAELs for all health effects in humans.

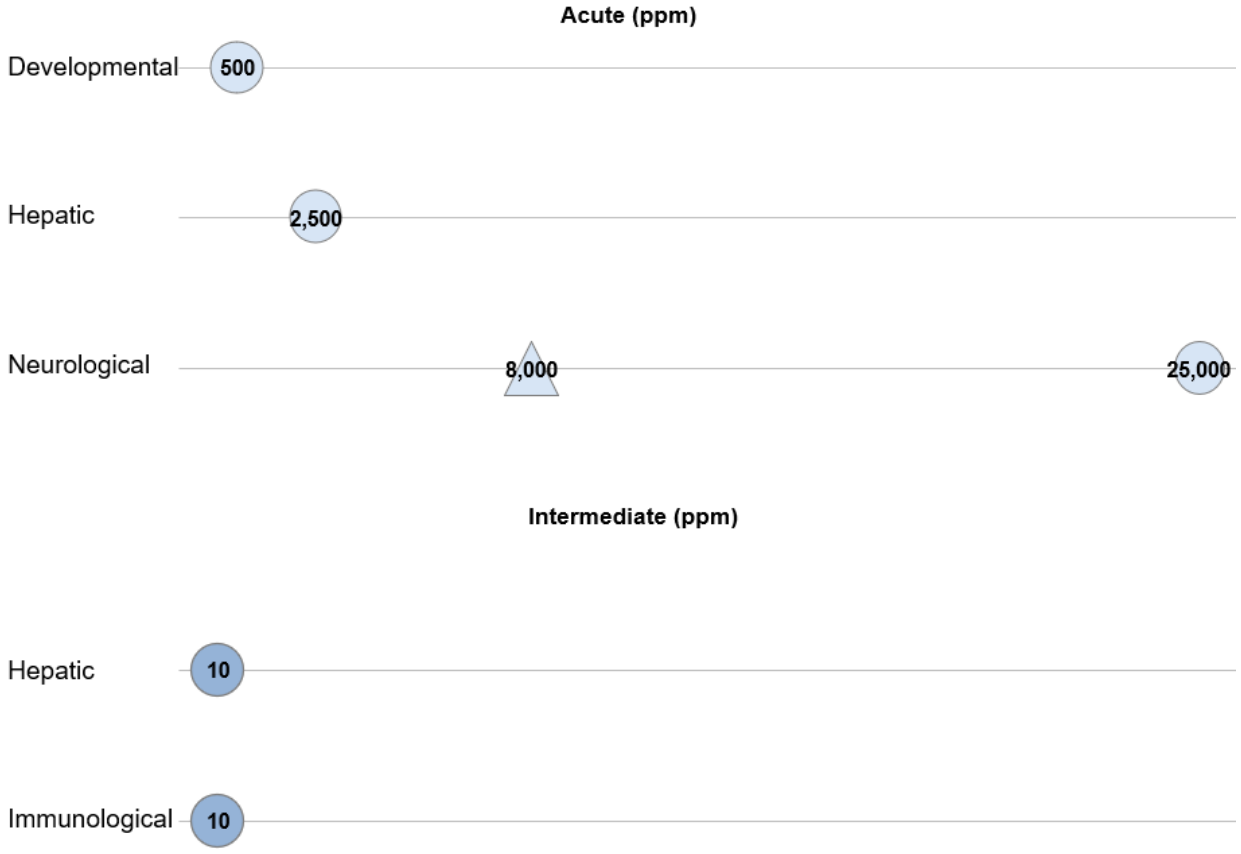


Figure 1-4. Summary of Sensitive Targets of Vinyl Chloride – Oral

The liver is the most sensitive target of vinyl chloride oral exposure.
Numbers in circles are the lowest LOAELs for all health effects in animals.
No reliable dose response data were available for humans.

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

Exposure duration	Provisional MRL	Critical effect	Point of departure/ human equivalent concentration	Uncertainty factor	Reference
Inhalation exposure (ppm)					
Acute	**0.5**	Delayed ossification	NOAEL: 50 ($NOAEL_{HEC}$: 15)	30	John et al. 1977, 1981
Intermediate	**0.02**	Increased incidence of centrilobular hypertrophy	$BMCL_{10}$: 2.05 ($BMCL_{10HEC}$: 0.5	30	Thornton et al. 2002
Chronic	Insufficient data for derivation of an MRL				
Oral exposure (mg/kg/day)					
Acute	Insufficient data for derivation of an MRL				
Intermediate	Insufficient data for derivation of an MRL				
Chronic	**0.003 (3 µg/kg/day)**	Liver cell polymorphism	NOAEL: 0.17 $NOAEL_{HED}$: 0.09	30	Til et al. 1983, 1991

[a]See Appendix A for additional information.

$BMCL_{10}$ = benchmark concentration lower confidence limit 10%; HEC = human equivalent concentration; HED = human equivalent dose; NOAEL = no-observed-adverse-effect level

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. LOAELs have been classified into "less serious" or "serious" effects. "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 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 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 inhalation studies.

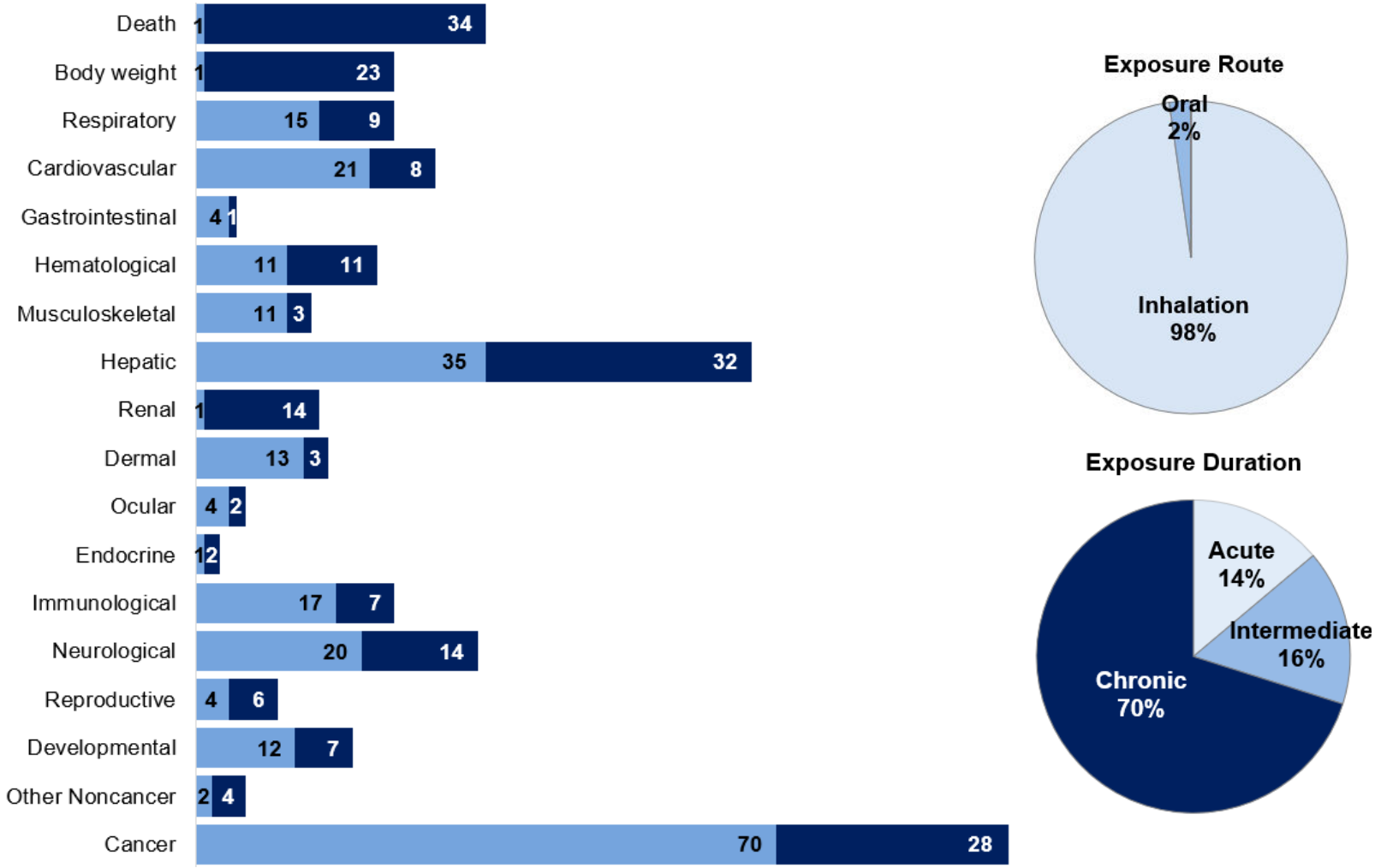
- **Developmental endpoints.** Developmental effects are a suspected health effect for humans based on strong evidence from acute inhalation exposures in mice and rabbits. The most sensitive developmental endpoint was delayed ossification in mice following prenatal inhalation exposure. Human data were 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

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
ACUTE EXPOSURE									
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	4,000	8,000		Dizziness
Lester et al. 1963									
2	Human 2 NS	3 minutes	25,000	CS	Neuro		25,000		Dizziness, disorientation
Patty et al. 1930									
3	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 Neuro	500 500			
Hehir et al. 1981									
4	Rat (Fischer-344) 85–92 M, 79–100 F	1 hour (WB)	0, 50, 500, 5,000, 50,000	CS, BW, GN, HP	Bd wt Neuro	50,000 50,000			
Hehir et al. 1981									
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
Jaeger et al. 1974									
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 dilatation
John et al. 1977, 1981									

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Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
7	Rat (Sherman) 2 NS	2 hours	50,000, 60,000, 70,000, 100,000, 150,000	LE, CS, GN, HP	Neuro		50,000		Moderate intoxication
Lester et al. 1963									
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
Mastromatteo et al. 1960									
9	Rat (NS) 10–30 NS	2 hours 1 time	146,625–205,275	LE, CS	Death			146,625	7/30 died
Prodan et al. 1975									
10	Rat (Holtzman) M	1, 5 days 6 hours/day	50,000	GN, HP	Hepatic	50,000			
Reynolds et al. 1975a									
11	Rat (NS) M	1 day 6 hours/day	50,000	BC, HP	Hepatic	50,000			
Reynolds et al. 1975b									
12	Rat (Sprague-Dawley) 25 F	GDs 6–19 4–6 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			
Thornton et al. 2002									

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Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
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
Hehir et al. 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
John et al. 1977, 1981									
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
Mastromatteo et al. 1960									
16	Mouse (NS) 20–90 NS	2 hours 1 time	87,975–195,500	LE, CS	Death			107,525	15/61 died
Prodan et al. 1975									

Table 2-1. Levels of Significant Exposure to Vinyl Chloride - Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
17	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
Mastromatteo et al. 1960									
18	Guinea pig (NS) 3–6, 18 NS	Up to 8 hours	0, 5000, 10,000, 25,000, 50,000, 100,000, 150000–250,000, 400,000	LE, CS, GN	Death			100,000	Death (incidence not reported)
					Neuro	10,000		25,000	Narcosis
Patty et al. 1930									
19	Guinea pigs (NS) 4–12 NS	2 hours 1 time	195,500–273,700	LE, CS	Death			224,825	1/6 died
Prodan et al. 1975									
20	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
John et al. 1977, 1981									
21	Rabbit (NS) 4 NS	2 hours 1 time	195,500–273,700	LE, CS, GN	Death			224,825	1/4 died
Prodan et al. 1975									

Table 2-1. Levels of Significant Exposure to Vinyl Chloride - Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
INTERMEDIATE EXPOSURE									
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 body weight 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
Bi et al. 1985									
23	Rat (Fischer-344) 112–224 F	6 months 5 days/week 6 hours/day	0, 100	LE, GN, HP	Cancer			100	CEL: hepatic hemangiosarcoma, hepatocellular carcinoma, neoplastic nodules, mammary fibroadenoma
Drew et al. 1983									
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
Froment et al. 1994									
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			
Hehir et al. 1981									

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Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
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
Hong et al. 1981									
27	Rat (Sherman) 15 M, 15 F	92 days 5 days/week 8 hours/day	0, 20,000	LE, BW, BC, GN, OW, HP	Hemato		20,000		Decreased white blood cells
					Hepatic		20,000		Moderate hepatocellular hypertrophy, fine to medium vacuoles, compression of sinusoids
					Renal	20,000			
Lester et al. 1963									
28	Rat (Sherman) 5 M, 5 F	19 days 8 hours/day	0, 50,000	CS, BW, BC, GN, OW, HP	Hemato		50,000		Decreased white blood cells
					Hepatic		50,000		Hepatocellular hypertrophy, large irregular vacuoles, compression of sinusoids, elevated relative liver weight
					Renal	50,000			
					Dermal	50,000 F			
							50,000 M		Thin coats, scaly tails
Lester et al. 1963									
29	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	500		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

Table 2-1. Levels of Significant Exposure to Vinyl Chloride - Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
					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
Sokal et al. 1980									
30	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] 10 M		Centrilobular hypertrophy in 6/30 F1 female rats, 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			
Thornton et al. 2002									
31	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			
Torkelson et al. 1961									

Table 2-1. Levels of Significant Exposure to Vinyl Chloride - Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
32	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
Wisniewska-Knypl et al. 1980									
33	Mouse (A/J) 70–72 M, 70 F	6 months 5 days/week 6 hours/day (WB)	0, 50, 200, 500	LE, GN, HP	Death			500 F 500 M	23/70 died 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
Adkins et al. 1986									
34	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			
Chen et al. 2019									
35	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 versus 780 days)
					Cancer			50	CEL: hemangiosarcoma of subcutis, peritoneum; mammary gland carcinoma
Drew et al. 1983									
36	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 versus 474 days)
					Cancer			50	CEL: hemangiosarcoma of skin, peritoneum; mammary gland carcinoma; lung carcinoma
Drew et al. 1983									

Table 2-1. Levels of Significant Exposure to Vinyl Chloride - Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
37	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
Hong et al. 1981									
38	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. 2018									
39	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			
Lang et al. 2020									
40	Mouse (C57BL/6J) 5–13 M	12 weeks 5 days/week 6 hours/day	0, 0.85	BW, BC, BI, HP	Bd wt	0.85			
					Cardio	0.85			
Liang et al. 2018									
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
Maltoni et al. 1981									

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Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
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
Schaffner 1978									
43	Mouse (CD-1) 12 M	2–8 weeks 5 days/week 6 hours/day	0, 10, 100, 1,000	CS, BW, BC, OW	Bd wt	1,000			
					Hemato	1,000			
					Hepatic		1,000		Decreased relative liver weight
					Renal	1,000			
					Immuno		10		Increased spontaneous lymphocyte proliferation
Sharma and Gehring 1979									
44	Mouse (CD-1) 1–7 M	5–6 months 5 days/week 5 hours/day	0, 2,500, 6,000	GN, HP	Resp		2,500		Proliferation and hypertrophy of bronchial epithelium; hypersecretion of mucin; hyperplasia of alveolar epithelium
Suzuki 1978, 1981									
45	Mouse (CD-1) 30–60 M	4 weeks 5 days/week 6 hours/day	0, 1, 10, 100, 300, 600	HP	Cancer			100	CEL: lung alveoli tumors
Suzuki 1983									
46	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, and nuclear condensation; at 1,433.6 ppm: steatosis, large lipid droplets, hepatic edema, cytoplasmic loosening, and hepatocyte nuclear fragmentation
Wang et al. 2019a									

Table 2-1. Levels of Significant Exposure to Vinyl Chloride - Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
47	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			
Wahlang et al. 2020									
48	Mouse (C57BL/6) 25 M	12 weeks 5 days/week 6 hours/day	0, 0.85	BW, BC, HE, IX	Bd wt	0.8			
					Hemato	0.8			
					Immuno	0.8			
					Other noncancer		0.8		Impaired glucose tolerance
Zelko et al. 2022									
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 versus 463 days)
					Cancer			200	CEL: liver hemangiosarcoma; skin hemangiosarcoma, spleen hemangiosarcoma; mammary gland carcinoma
Drew et al. 1983									
50	Hamster (Golden Syrian) 30–62 M	30 weeks 5 days/week 4 hours/day	0, 50, 250, 500, 2,500, 6,000, 10,000	BW, GN, HP	Cancer			500	CEL: liver angiosarcoma
Maltoni et al. 1981									
51	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			
Torkelson et al. 1961									

Table 2-1. Levels of Significant Exposure to Vinyl Chloride - Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
CHRONIC EXPOSURE									
52	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
					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
Bi et al. 1985									
53	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 versus 703 days)
					Cancer			100	CEL: hepatic hemangiosarcoma, hepatocellular carcinoma, neoplastic nodules; mammary gland fibroadenoma and adenocarcinoma
Drew et al. 1983									
54	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
Holmberg et al. 1976									
55	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
Lee et al. 1978									

Table 2-1. Levels of Significant Exposure to Vinyl Chloride - Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
56	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
Maltoni et al. 1981									
57	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 versus 780 days)
					Cancer			50	CEL: hemangiosarcoma of peritoneum, subcutis; 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 versus 474 days)
					Cancer			50	CEL: lung; hemangiosarcoma of peritoneum, subcutis; mammary gland carcinoma
Drew et al. 1983									
59	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
Lee et al. 1977a, 1978									

Table 2-1. Levels of Significant Exposure to Vinyl Chloride - Inhalation

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (ppm)	Parameters monitored	Endpoint	NOAEL (ppm)	Less serious LOAEL (ppm)	Serious LOAEL (ppm)	Effects
60	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 versus 463 days)
					Cancer			200	CEL: liver hemangiosarcoma; skin carcinoma, hemangiosarcoma; spleen hemangiosarcoma; mammary gland carcinoma; stomach adenoma

Drew et al. 1983

[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 a provisional 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 a provisional MRL of 0.5 ppm.
[c]Used to derive a provisional 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; 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

Figure 2-2. Levels of Significant Exposure to Vinyl Chloride – Inhalation

Acute (≤14 days)

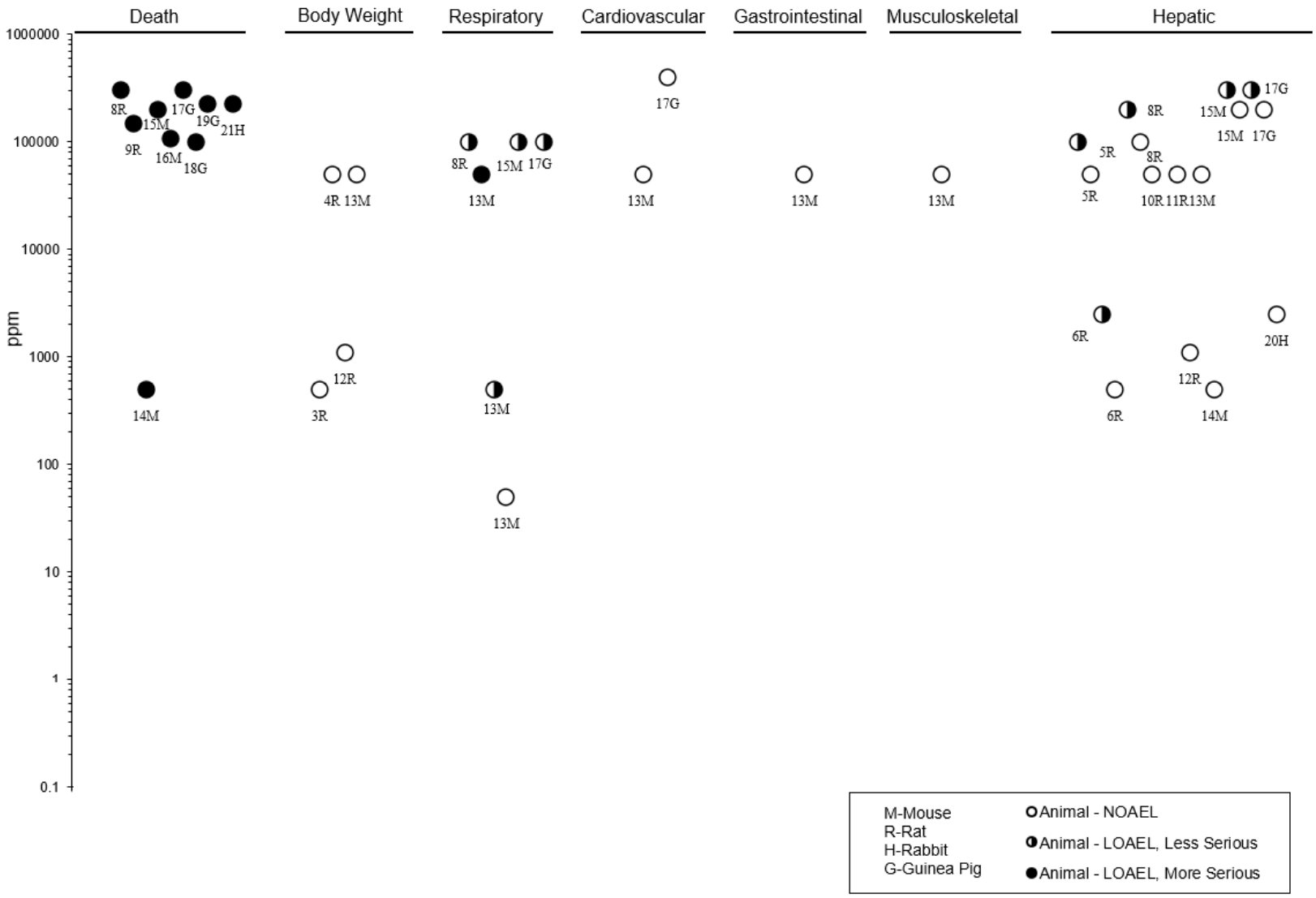
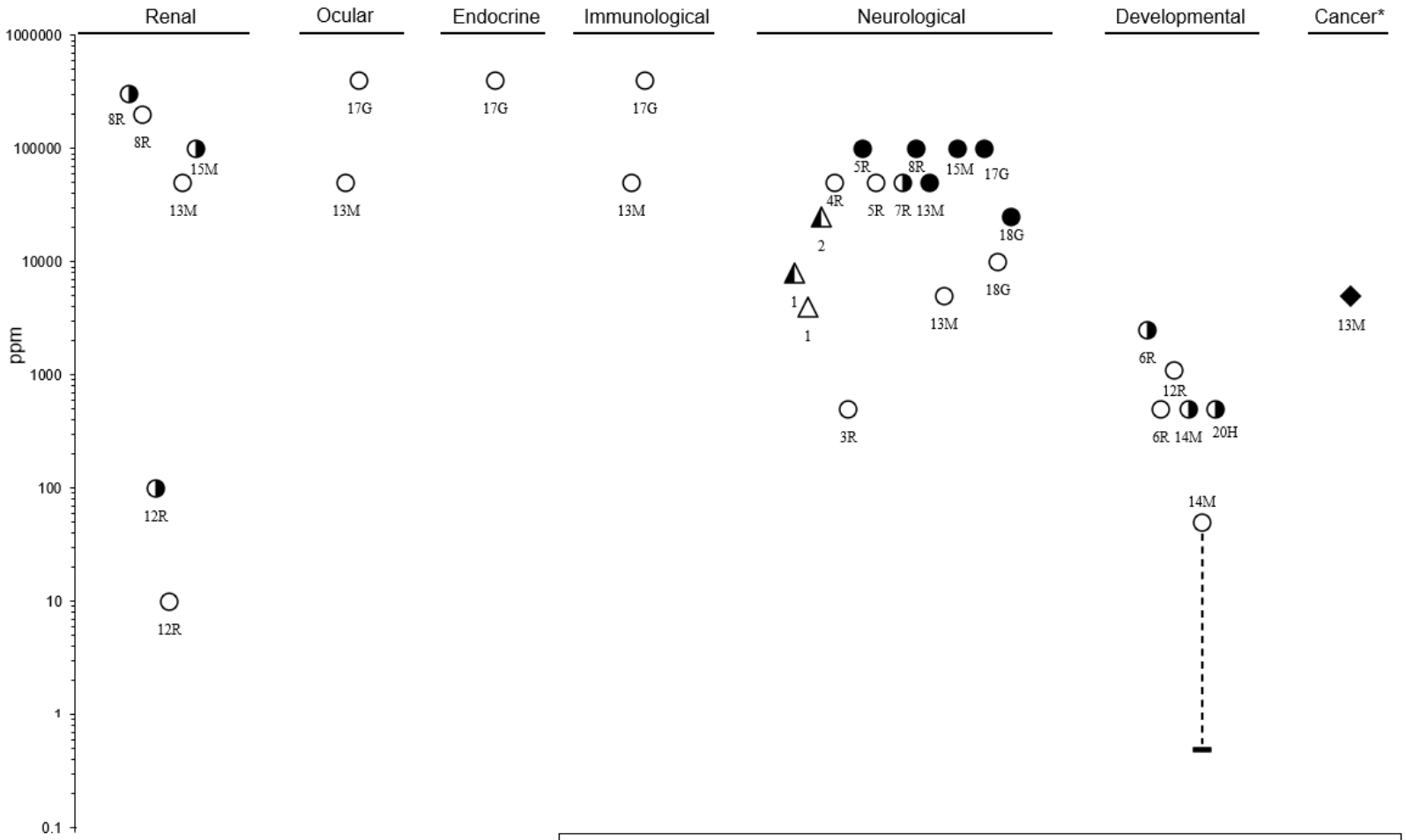


Figure 2-2. Levels of Significant Exposure to Vinyl Chloride – Inhalation

Acute (≤14 days)



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

M-Mouse
R-Rat
H-Rabbit
G-Guinea Pig

△Human - NOAEL
▲Human - LOAEL, Less Serious
●Animal - LOAEL, More Serious
▬Minimal Risk Level for effects other than cancer

○Animal - NOAEL
◑Animal - LOAEL, Less Serious
◆Animal - Cancer Effect Level

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

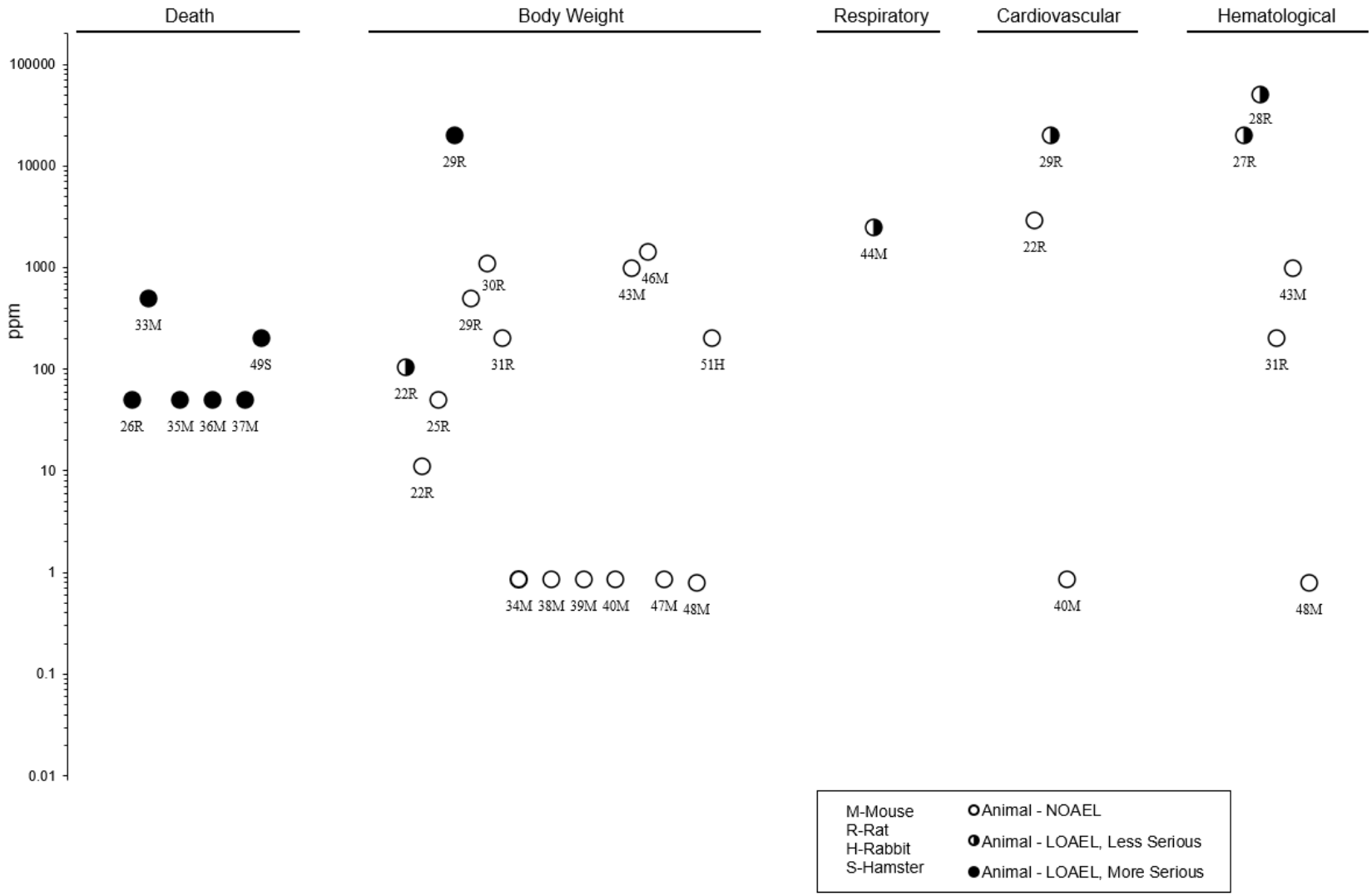


Figure 2-2. Levels of Significant Exposure to Vinyl Chloride – Inhalation
Intermediate (15-364 days)

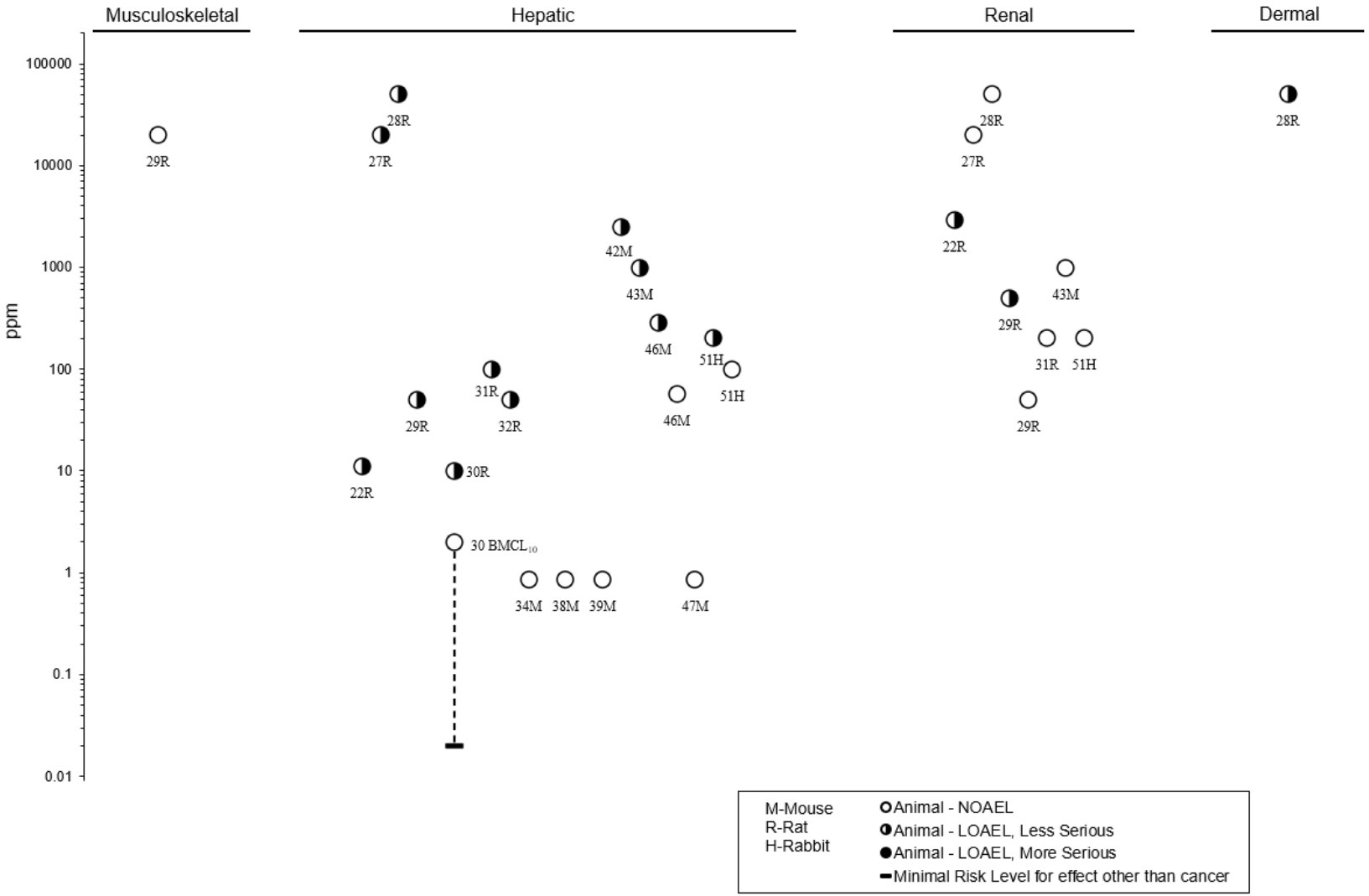
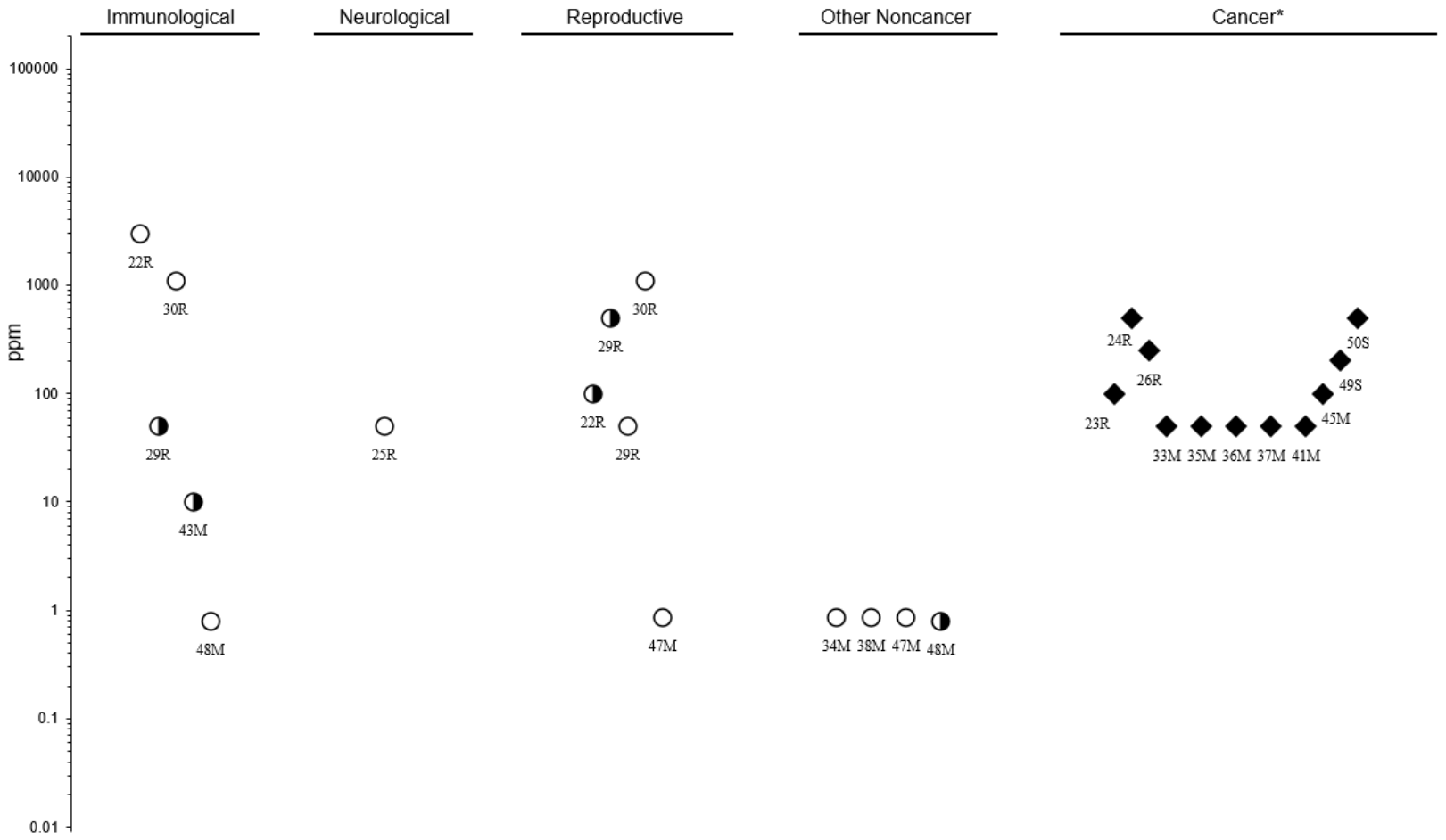


Figure 2-2. Levels of Significant Exposure to Vinyl Chloride – Inhalation
Intermediate (15-364 days)



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

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

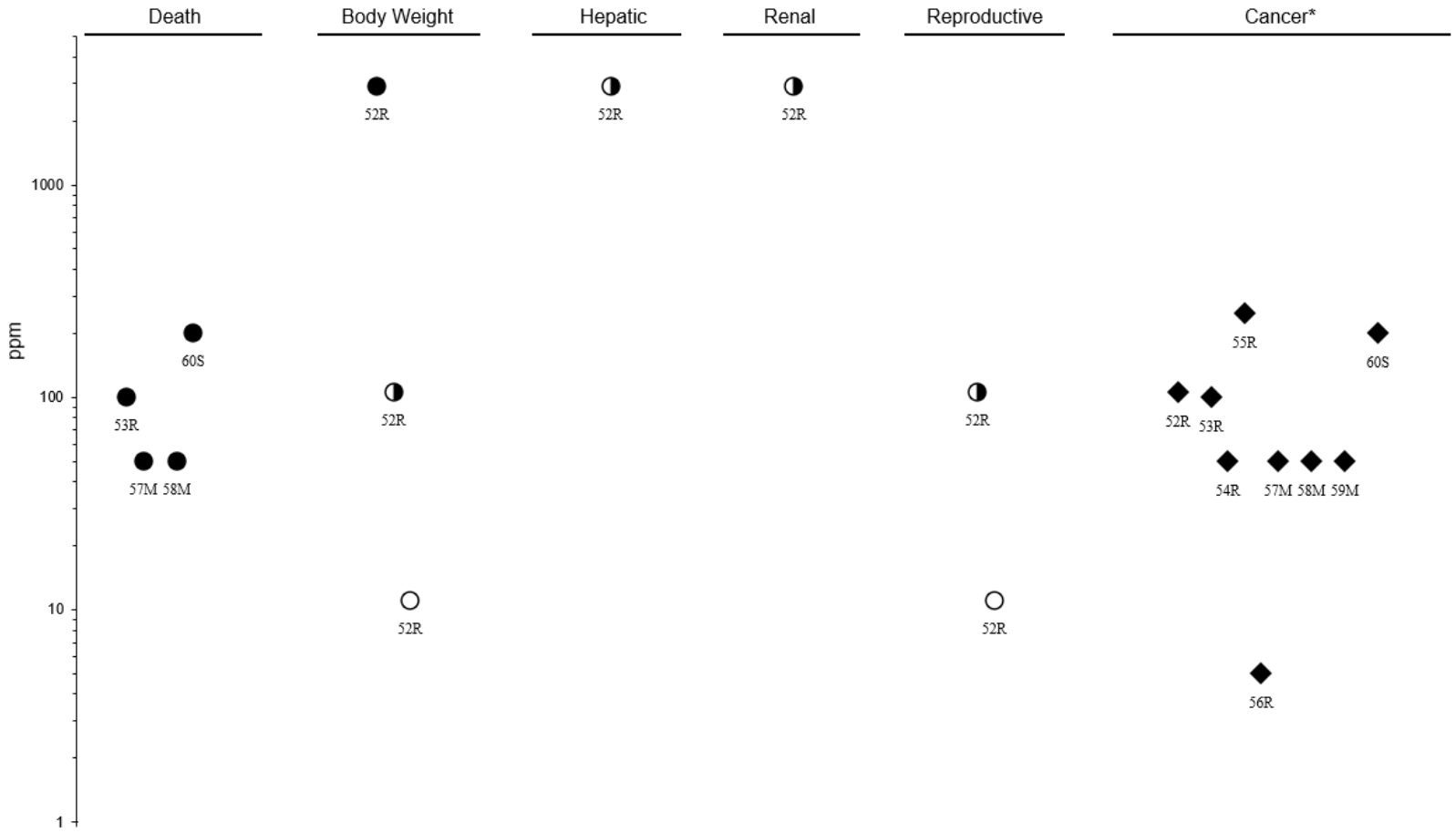


Table 2-2. Levels of Significant Exposure to Vinyl Chloride - Oral

Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
CHRONIC EXPOSURE									
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 14.1 M	7/60 females dead at 80 weeks 8/60 males dead at 80 weeks
					Resp			5	Breathing difficulties at 18 months
					Hemato	5	14.1		6–8% statistically significant decrease in clotting time
					Hepatic		1.7	5 F 14.1 M	LOAEL: cellular alteration SLOAEL: extensive necrosis
					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
Feron et al. 1981									
2	Rat (Wistar) 8–9 NS	2 years 1 time/day (GO)	0, 3, 30, 300	LE, BI, GN	Dermal		30		Increased skin thickness, collagen
Knight and Gibbons 1987									
3	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
Maltoni et al. 1981									

Table 2-2. Levels of Significant Exposure to Vinyl Chloride - Oral

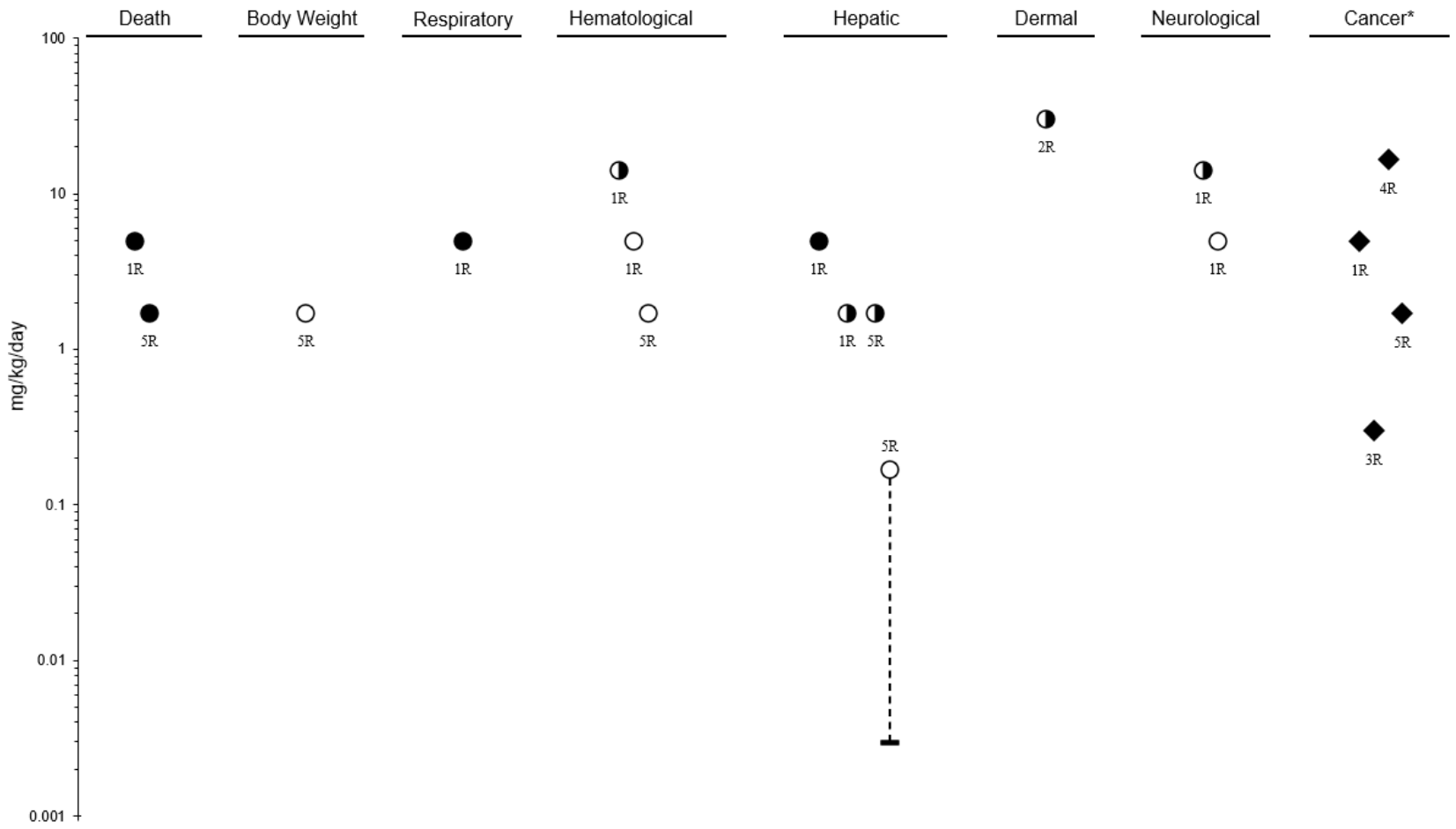
Figure key[a]	Species (strain) No./group	Exposure parameters	Doses (mg/kg/day)	Parameters monitored	Endpoint	NOAEL (mg/kg/day)	Less serious LOAEL (mg/kg/day)	Serious LOAEL (mg/kg/day)	Effects
4	Rat (Sprague-Dawley) 40 M, 40 F	52 weeks 5 times/week (GO)	0, 3.33, 16.65, 50	BW, GN, HP	Cancer			16.65 F	CEL: liver angiosarcoma
Maltoni et al. 1981									
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
Til et al. 1983, 1991									

[a]The number corresponds to entries in Figure 2-3.
[b]Used to derive a provisional 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; SLOAEL = serious lowest-observed-adverse-effect level; UR = urinalysis

Figure 2-3. Levels of Significant Exposure to Vinyl Chloride – Oral

Chronic (≥365 days)



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

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; 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. 1979; 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. 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 concentration 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 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. 1979). 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 to 1,000 ppm vinyl chloride

6 hours/day, 5 days/week for 8 weeks (Sharma and Gehring 1979) or up to 1433.6 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). 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 function 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 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 high-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, extraventricular 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. Chronic 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). 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 1,000 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. 1979).

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	↔
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)	↑

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]
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	↔
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	↑

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]
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)	↑
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)	↔

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]
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 chloride exposure.
[c]Workers exposed to vinyl chloride and ethylene chloride.

↑ = 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 = lactic 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 exposure of animals to extremely high concentrations of vinyl chloride leads to hepatic damage. For example, acute 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), changes in metabolic enzyme activities (Du et al. 1979; Wisniewska-Knypl et al. 1980), proliferation of reticulocytes (Sokal et al. 1980), and an increased liver-to-body-weight ratio (Bi et al. 1985; Lester et al. 1963; Sokal et al. 1980; Thornton et al. 2002; Torkelson et al. 1961). Histopathological liver lesions in mice have included lipid droplets, eosinophilic changes, nuclear condensation, steatosis, hepatic edema, cytoplasmic loosening, and hepatocyte nuclear fragmentation (Wang et al. 2019a). Mice fed a high-fat diet experienced enhanced liver damage, neutrophil infiltration, apoptosis, and oxidative and endoplasmic reticulum stress compared to mice fed a normal or low-fat diet (Chen et al. 2019; Fujiwara 2018; Lang et al. 2018, 2020; Liang et al. 2018; 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 1,000 ppm vinyl chloride for 6 hours/day, 5 days/week for 8 weeks (Sharma and Gehring

1979). 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).

Mice exposed to 2,500 ppm vinyl chloride 5 hours/day, 5 days/week for up to 6 months showed histopathological changes in the liver that included hyperplasia of hepatocytes and activated sinusoidal cells (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). Liver effects were observed in a 2-generation reproductive toxicity study where rats were exposed to $\geq$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.

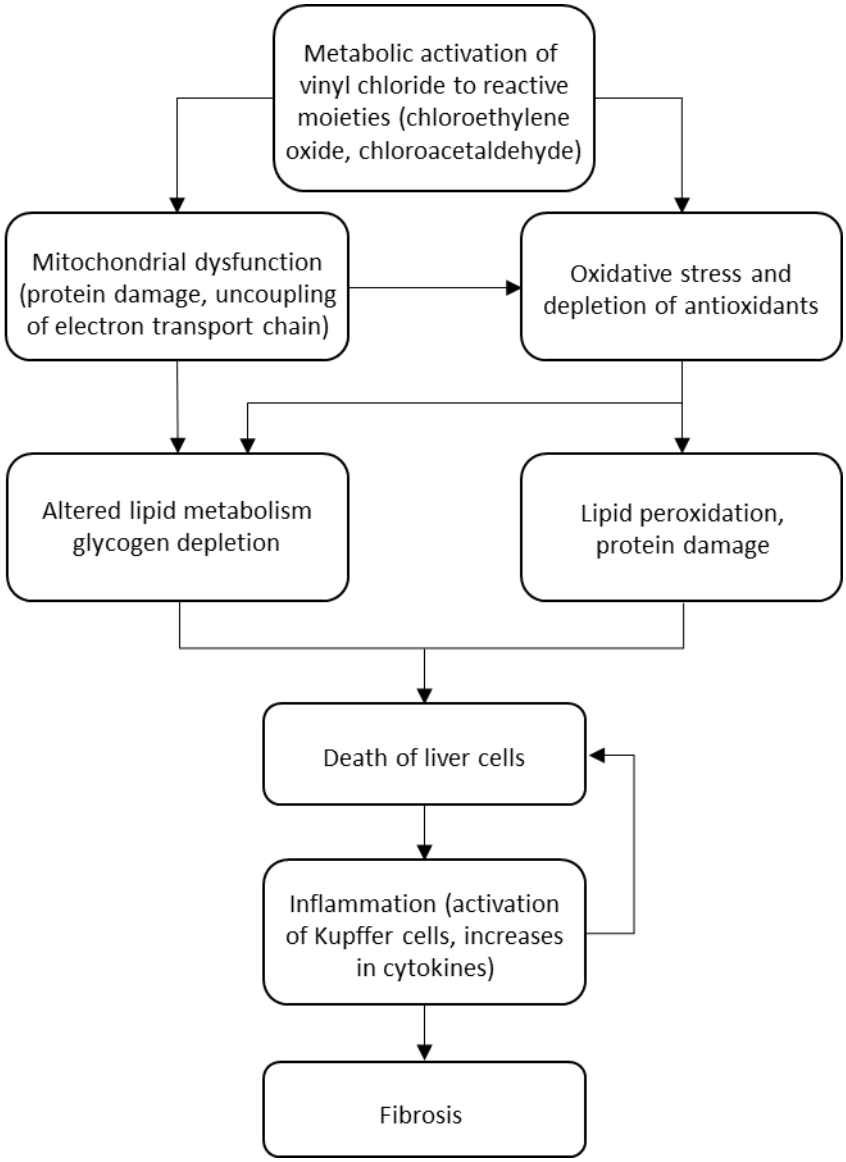
The NOAELs for liver effects in a number of species following a 6-month exposure to vinyl chloride indicated that mice and rats were the most sensitive (NOAEL of 50 ppm), rabbits were the next most sensitive (NOAEL of 100 ppm), and dogs and guinea pigs were the least sensitive (NOAEL of >200 ppm) (Torkelson 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 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). Chronic 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 was 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. Many of the same mechanisms (mitochondrial dysfunction, oxidative stress, altered lipid metabolism) have been noted in animal studies (Anders et al. 2016a, 2016b; Chen et al. 2019; Lang et al. 2018, 2020).

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 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). 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 were exposed to 1,000 ppm vinyl chloride 6 hours/day, 5 days/week for 8 weeks (Sharma and Gehring 1979). 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. 1979) 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 creatine 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.

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). 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, orsomucoid) were elevated in highly exposed male vinyl chloride workers when compared to a similar worker population exposed to lower concentrations (Bencko 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	↑
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, orsomucoid	↑

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]
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	↑
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; also 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 (Sharma and Gehring 1979). Lymphocytes isolated from the spleens of mice exposed to concentrations as low as 10 ppm vinyl chloride 6 hours/day, 5 days/week for 4 weeks had increased spontaneous and mitogen-stimulated responses to phytohemagglutin and pokeweed mitogen. This increase was not observed when lymphocytes from unexposed mice were cultured in the presence of vinyl chloride. 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	↔
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	≥8,000 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 8,000 ppm, one 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 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).

Chronic 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. 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 (anencephalus, 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 gender 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 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.

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 early in life may have increased the likelihood of developing tumors and affected the type of tumor that develops. Exposure of animals during development 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). Similar to the pooled results from Bosetti et al. (2003), 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 (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 (Byren et al. 1976; Collins et al. 2014; Creech and Johnson 1974; Fedeli et al. 2019a; Forman et al. 1985; Fox and Collier 1977; Infante et al. 1976b; Jones et al. 1988; Laplanche et al. 1992; Lee et al. 1996; Monson et al. 1975; Mundt et al. 2017; Pirastu et al. 1990; Rinsky et al. 1988; Simonato et al. 1991; Teta et al. 1990; Theriault and Allard 1981; Waxweiler et al. 1976; Weber et al. 1981; Wong et al. 1991; Wu et al. 1989).

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)	Guardiola et al. 2021 Fedeli et al. 2019a[c] Cicalese et al. 2017[d] 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[e] Lewis et al. 2003[c] Maroni et al. 2003[c] Wong et al. 2002a[c], 2003a[e] Ward et al. 2001[c] Cheng et al. 1999a[f] Fortwengler et al. 1999[c] Du and Wang 1998[e] Elliott and Kleinschmidt 1997[d,g] Laplanche et al. 1992[c]	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[e] 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[e] 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[e] Lewis and Rempala 2003[e] 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[e] 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)	Gennaro et al. 2008[c] Mastrangelo et al. 2003[e] Belli et al. 1987[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[e] Wong et al. 2002a[c] Wong et al. 1991[c] Ward et al. 2001[c] Mundt et al. 2000[c] Cheng et al. 1999a[f] Du and Wang 1998[e] 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]

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]
Connective and other soft tissues (including soft tissue sarcoma)	Mundt et al. 2017[c] Mundt et al. 2000[c]	Ward et al. 2001[c]
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[e] 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[e] Ward et al. 2001[c] Mundt et al. 2000[c] Cheng et al. 1999a[f] 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]Ecological studies.
[e]Case-control studies.
[f]Cross-sectional study.
[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 epitheliod hemagioendotheliomas (Gelin et al. 1989) in the liver (both are vascular tumors similar to angiosarcomas), and adrenal epitheliodangiosarcoma (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); however, an ecological study in Texas suggests an association between exposure to vinyl chloride in polluted ambient air and the incidence of hepatocellular carcinoma (Cicalese et al. 2017).

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 (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 development may increase the likelihood of developing tumors (Drew et al. 1983; Maltoni et al. 1981). Early life exposure may also affect the type of tumor that develops (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.

Four 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.

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; 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 2016) 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*

		Result		
Species (test system)	Endpoint	With activation	Without activation	Reference
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

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

Species (test system)	Endpoint	Result		Reference
		With activation	Without activation	
		+	+	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
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
		+	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

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

Species (exposure route)	Endpoint	Results	Reference
		+	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
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

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

Species (exposure route)	Endpoint	Results	Reference
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 revertants 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 revertants 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 thiodyglycolic 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 taken into account 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 (Chen et al. 1999).

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 postimplantation loss among the untreated females mated to the exposed males. These results indicate that no germinal mutations were produced by these acute 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.

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

3.1 TOXICOKINETICS

Human studies of vinyl chloride provide limited quantitative information on absorption, metabolism, and excretion. Vinyl chloride toxicokinetics have been studied in nonhuman primates (e.g., rhesus monkeys) and rodents, with most of the quantitative information derived from studies conducted in rats. An overview of these data is summarized below.

- Studies in humans and animals indicate that vinyl chloride is readily absorbed through the lungs following inhalation. Animal studies demonstrate that vinyl chloride is rapidly and almost completely absorbed from the gastrointestinal tract after oral exposure. A single study in monkeys suggests that dermal absorption of vinyl chloride gas is not likely to be significant.
- No human studies were identified that provided reliable information about the distribution of vinyl chloride in tissues other than blood.
- Animal studies indicate that the distribution of vinyl chloride is rapid and widespread; however, storage in the body is limited because of rapid metabolism and excretion. Metabolites of vinyl chloride can be found in the liver, kidney, spleen, skin, and brain, but tissue concentrations do not increase following repeated exposure.
- Vinyl chloride can cross the placenta after inhalation exposure in rat dams.
- Metabolism in humans and experimental animals occurs via the oxidation of vinyl chloride by CYP to form an epoxide intermediate, 2-chloroethylene oxide, which spontaneously rearranges to form 2-chloroacetaldehyde. Intermediates are detoxified primarily via glutathione conjugation and conjugates are excreted in urine as substituted cysteine derivatives.
- Metabolism follows Michaelis-Menten kinetics in rats, with enzyme saturation near 100 ppm in air or between 1 and 100 mg/kg/day for a single gavage dose.
- Vinyl chloride metabolites are excreted primarily in the urine following oral or inhalation exposure to low doses. At higher doses where metabolic saturation has been exceeded, vinyl chloride is exhaled as the parent compound.

3.1.1 Absorption

Inhalation absorption of vinyl chloride is rapid in humans. Five young adult male volunteers were exposed to vinyl chloride concentrations of 2.9, 5.1, 11.7, or 23.5 ppm by way of a gas mask for 6 hours (Krajewski et al. 1980). Retention was estimated by measuring the difference between inhaled and exhaled concentrations. An average retention of 42% was estimated. Although the results varied among

the individuals tested, the percentage retained was independent of the concentration inhaled. Since retention did not change with increasing vinyl chloride concentrations, it appears that saturation of the major pathway of overall metabolism did not occur in this exposure regimen.

Animal data demonstrate that the inhalation absorption of vinyl chloride occurs readily and rapidly. Physiologically based pharmacokinetic (PBPK) models developed to provide quantitative estimates of uptake are discussed in Section 3.1.5. Peak blood levels occurred at 30 minutes in rats exposed (head only) to 7,000 ppm (Withey 1976). On removal from the vinyl chloride-containing atmosphere, blood levels fell rapidly. After 2 hours, concentrations were barely detectable.

Several studies in rats indicate that vinyl chloride is rapidly and virtually completely absorbed from the gastrointestinal tract following oral exposure. Peak blood levels of vinyl chloride were observed within 10–20 minutes after gavage dosing of rats with vinyl chloride in an aqueous solution (single doses of 44–92 mg/kg) (Withey 1976). Peak blood levels varied from 6 to >40 µg/mL. Data from another study in which rats were administered single gavage doses of 0.05, 1, and 100 mg/kg vinyl chloride labelled with radioactive carbon (^{14}C-vinyl chloride) (in corn oil) suggested that absorption of vinyl chloride was nearly complete (Watanabe et al. 1976a).

The fraction of the administered dose recovered in the feces, roughly indicative of the proportion unabsorbed, ranged from 0.47 to 2.39%; total recovery ranged from 82.3 to 91.3%. Loss of radioactivity might be attributed either to experimental error or to incomplete sampling of the carcass. Fecal excretion was measured in rats fed 0, 1.8, 5.6, and 17.0 mg/kg/day of vinyl chloride monomer (from powdered PVC containing a high level of the monomer) (Feron et al. 1981). Fecal excretion accounted for 8, 10, and 17% of the vinyl chloride present in the low-, middle-, and high-dose groups, respectively. The investigators hypothesized that the vinyl chloride recovered from the feces was encapsulated by PVC, thereby not available to the rats for absorption, and that absorption of bioavailable vinyl chloride was virtually complete.

No studies were located regarding absorption in humans after dermal exposure to vinyl chloride. Animal data suggest that dermal absorption of vinyl chloride gas is not likely to be significant. Dermal absorption was measured in two rhesus monkeys that received full body (except head) exposure to vinyl chloride gas. It was estimated that 0.031 and 0.023% of the total available vinyl chloride was absorbed at 800 and 7,000 ppm, respectively, after a 2–2.5-hour exposure (Hefner et al. 1975a). The investigators concluded that, after short-term exposure to high concentrations, dermal absorption was far less

significant than inhalation absorption. No information is available regarding dermal absorption of vinyl chloride from liquid or solid media.

3.1.2 Distribution

Representative vinyl chloride partition coefficients for humans, rats, mice, and hamsters are provided in Table 3-1. These partition coefficients were obtained for use in PBPK models. They were estimated using a vial equilibration technique (U.S. Air Force 1990). Further details about how the values were obtained, including the number of experiments completed and whether the errors shown are standard deviations or standard errors, were not provided. In general, concentrations of vinyl chloride found in fat are higher than would be found in other tissues. Partition coefficients for vinyl chloride range from 10 to 20 (fat/air) and from 1 to 3 (muscle/air, blood/air, and liver/air). In animal studies, females have shown greater partitioning from air to fat than males.

Table 3-1. Vinyl Chloride Partition Coefficients

			Partition coefficient			
Species	Strain	Sex	Blood/air	Liver/air	Muscle/air	Fat/air
Rat	CDBR[a]	M	1.79±0.216	3.0±0.407	2.18±0.470	14.6±0.917
		F	2.12±0.437	1.66±0.429	1.28±0.245	19.2±0.96
	F-344[a]	M	1.60±0.328	1.99±1.96	2.06±0.703	11.8±0.811
		F	1.55±0.11	2.05±0.17	2.39±0.46	21.1±1.3
	Wistar[a]	M	2.10±0.313	2.69±0.555	2.72±0.575	10.2±1.61
		F	1.62±0.0664	1.48±0.28	1.06±0.221	22.3±0.542
	Sprague-Dawley[b]	M	2.4±0.5	–	–	–
Mouse	B6C3F1[a]	M	2.83±0.22	–	–	–
		F	2.56±0.14	–	–	–
	CD-1[a]	M	2.27±0.0725	–	–	–
		F	2.37±0.16	–	–	–
Hamster	Golden Syrian[a]	M	2.74±0.151	3.38±0.362	2.56±0.457	14.3±5.32
		F	2.21±0.47	1.31±0.28	1.96±0.28	21.10±2.01
Human[c]	NA	NR	1.16	–	–	–

[a]U.S. Air Force 1990; values determined using vial equilibration method.
[b]Barton et al. 1995.
[c]EPA 1987.

– = no data; F = female; M = male; NA = not applicable; NR = not reported

Tissue/blood partition coefficients in male Sprague-Dawley rats measured using a vial equilibration method were reported as 10±3 for fat/blood, 0.4±0.2 for muscle/blood, 0.7±0.3 for liver/blood, and 0.7±0.4 for kidney/blood (Barton et al. 1995).

Data from rat studies suggest that the distribution of inhaled vinyl chloride is rapid and widespread, but storage of vinyl chloride in the body is limited by rapid metabolism and excretion. In rats exposed to ^{14}C-vinyl chloride and pretreated with 6-nitro-1,2,3-benzothiadiazole to block metabolism of vinyl chloride by microsomal CYP oxidation pathways, the highest levels of radiolabel were located in the fat, with lesser amounts in the blood, liver, kidney, muscle, and spleen. When metabolism was not blocked, the highest levels of radiolabelled metabolites were located in the liver and kidney (Buchter et al. 1977).

Immediately after a 5-hour exposure to ^{14}C-vinyl chloride at 50 ppm, tissue levels of ^{14}C-activity, expressed as the percentage incorporated per gram of tissue, were highest in the kidney (2.13%) and liver (1.86%), with lower levels in the spleen (0.73%) and brain (0.17%) (Bolt et al. 1976a). Radioactivity in tissue was measured in rats 72 hours after exposure to 10 or 1,000 ppm ^{14}C-vinyl chloride for 6 hours. In order of decreasing concentration for rats exposed to 10 ppm, ^{14}C-labeled compounds (expressed as percentage present as nonvolatile metabolites), were measured in the liver (0.14), kidney (0.08), skin (0.07), lung (0.07), muscle (0.05), carcass (0.05), plasma (0.05), and fat (0.03). For rats exposed to 1,000 ppm, the tissue radiolabel percentages were: liver (0.15), skin (0.12), kidney (0.06), carcass (0.05), lung (0.05), muscle (0.04), fat (not detected), and plasma (not detected) (Watanabe et al. 1976b).

There was no difference in the routes or rate of excretion between repeated-dose versus single-dose exposure of rats to 5,000 ppm of ^{14}C-vinyl chloride (Watanabe et al. 1978a). The concentration of radiolabel detected in tissues 72 hours after exposure revealed no statistically significant difference between rats exposed once or repeatedly to vinyl chloride. Percentages of radioactivity after 72 hours measured in tissues are as follows (for single and repeated doses, respectively): liver (0.12 and 0.16), kidney (0.06 and 0.07), skin (0.05 and 0.08), carcass (0.03 and 0.04), and fat (not detected and not detected).

Placental transfer of vinyl chloride can occur rapidly in rats. Female rats exposed to approximately 0, 2,000, 7,000, or 13,000 ppm vinyl chloride for 2.5 hours on GD 18 showed high concentrations of vinyl chloride in maternal and fetal blood and amniotic fluid (Ungvary et al. 1978). Vinyl chloride concentrations in maternal blood were 19.02, 32.40, and 48.43 µg/mL, respectively, while fetal blood concentrations were 12.80, 22.67, and 30.52 µg/mL, respectively. Vinyl chloride concentrations in

amniotic fluid were 0, 4.27, 4.93, and 13.50 µg/mL at 2,000, 7,000, and 13,000 ppm vinyl chloride, respectively (Ungvary et al. 1978).

The level of ^{14}C-nonvolatile metabolites was measured in tissues of rats 72 hours after single gavage doses (0.05–100 mg/kg) of ^{14}C-vinyl chloride in corn oil (Watanabe et al. 1976a). The highest levels of radioactivity for each dose level occurred in the liver. These levels were 2–5 times higher than in the other tissues examined (skin, plasma, muscle, lung, fat, and carcass).

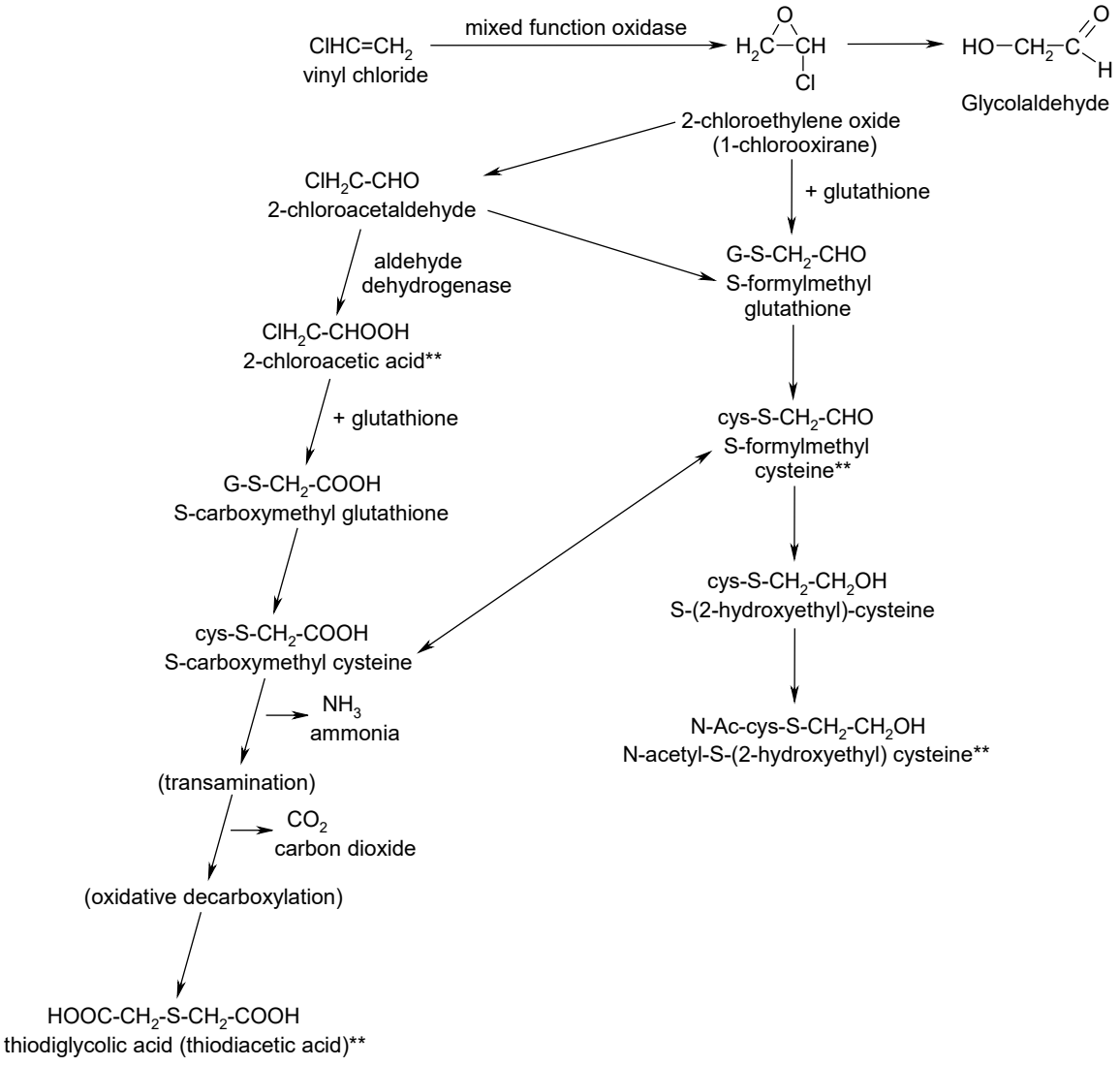
3.1.3 Metabolism

Vinyl chloride metabolism in humans is attributed to the CYP monooxygenases in the liver (Ivanetich et al. 1977; Sabadie et al. 1980; Salmon 1976). The proposed metabolic pathways for vinyl chloride are shown in Figure 3-1. Data obtained in rats indicate that metabolic pathways are consistent for both inhalation and oral exposure (Bartsch et al. 1976, 1979; Green and Hathway 1975, 1977; Hathway 1977; Watanabe and Gehring 1976; Watanabe et al. 1976a). Metabolism occurs via the oxidation of vinyl chloride by CYP to form an epoxide intermediate, 2-chloroethylene oxide, which spontaneously rearranges to form 2-chloroacetaldehyde (Guengerich et al. 1979, 1981; Gwinner et al. 1983; Laib 1982). 2-Chloroethylene oxide can also be detoxified by epoxide hydrolase to yield glycolaldehyde (IARC 2012). These intermediates are detoxified mainly through conjugation with glutathione catalyzed by glutathione *S*-transferase. The conjugated products are excreted in urine as substituted cysteine derivatives and include thiodiglycolic acid, *S*-formylmethylcysteine, and *N*-acetyl-*S*-(2-hydroxyethyl) cysteine (Bolt et al. 1980; Hefner et al. 1975b). Urinary metabolites identified in rats exposed by inhalation include polar compounds at low exposure concentrations (Hefner et al. 1975b; Watanabe et al. 1976b) and 2-chloroacetic acid at high exposure concentrations (Hefner et al. 1975b). Mitochondrial aldehyde dehydrogenase 2 (ALDH2) may also play a role in detoxifying 2-chloroacetaldehyde (Chen et al. 2019). Activation of ALDH2 with an agonist (Alda-1) was shown to attenuate liver injury and reduce oxidative stress in mice exposed to vinyl chloride (Chen et al. 2019).

Metabolism follows Michaelis-Menten kinetics in rats, with enzyme saturation near 100 ppm in air or between 1 and 100 mg/kg/day for a single gavage dose (Hefner et al. 1975b; Watanabe et al. 1976a). Metabolic saturation was not demonstrated in volunteers exposed to vinyl chloride at concentrations of 2.9, 5.1, 11.7, and 23.5 ppm for 6 hours (Krajewski et al. 1980).

Isolated rat liver cells converted ^{14}C-vinyl chloride into nonvolatile metabolites (Hultmark et al. 1979), indicating that the *in vitro* liver cell microsomal metabolism was NADPH-dependent and probably involved CYP. Pretreatment with 6-nitro-1,2,3-benzothiadiazole, an inhibitor of some microsomal CYP oxidation pathways, was sufficient to totally block the metabolism of vinyl chloride in rats exposed to 0.45 ppm in a closed system for 5 hours (Bolt et al. 1977). This observation suggests that metabolism of vinyl chloride proceeds primarily through a CYP pathway with likely production of an epoxide intermediate.

Figure 3-1. Proposed Metabolic Pathways for Vinyl Chloride*



**Excreted in urine.

Sources: Bolt et al. (1980); Hefner et al. (1975b); IARC (2012); Park et al. (1993); Plugge and Safe (1977)

Inhalation exposure of rats to high concentrations of vinyl chloride was associated with a reduction in the liver nonprotein sulfhydryl functional group concentration (Barton et al. 1995). A reduction in these functional groups is expected since there are limited amounts of liver glutathione and/or cysteine to conjugate the metabolites of vinyl chloride. (Bolt et al. 1976b; Hefner et al. 1975b; Jedrychowski et al. 1984; Watanabe et al. 1978b).

Saturation of metabolic pathways was observed in rats and monkeys that were exposed in a closed system to ^{14}C-vinyl chloride (Bolt et al. 1977; Buchter et al. 1980; Filser and Bolt 1979). In Wistar rats, metabolic saturation was determined to occur at approximately 250 ppm, and a metabolic rate (V_{max}) of 110 µmol/hour/kg was estimated (Bolt et al. 1977; Filser and Bolt 1979). Kinetic constants of 58 µmol/hour/kg for V_{max} and 1 µM for the K_m in male Sprague-Dawley rats were also reported (Barton et al. 1995). In an experiment using rhesus monkeys, metabolic saturation occurred at 200 ppm, with a V_{max} of 50 µmol/hour/kg (Buchter et al. 1980). The V_{max} of 50 µmol/hour/kg estimated using rhesus monkeys was suggested as a closer approximation of metabolism in humans than the value of 110 µmol/hour/kg estimated for rats by Filser and Bolt (1979).

Kinetic constants for vinyl chloride metabolism were derived from *in vitro* studies in rat liver microsomes (el Ghissassi et al. 1998). Metabolism followed Michaelis-Menton kinetics with a K_m of 7.42 µM and a V_{max} of 4,674 pmol/mg protein/minute. Inhibitor studies using chemical and immunological inhibitors demonstrate that vinyl chloride is metabolized primarily by CYP2E1.

Urinary metabolites identified from rats ingesting ^{14}C-vinyl chloride are consistent with the metabolic pathways postulated for inhalation exposure, in particular with the formation of 2-chloroethylene oxide and 2-chloroacetaldehyde. Metabolites identified include *N*-acetyl-*S*-(2-hydroxyethyl)cysteine, 2-chloroacetic acid, and thiodiglycolic acid (Green and Hathway 1975, 1977; Watanabe and Gehring 1976; Watanabe et al. 1976a). Metabolic saturation appears to occur with a single gavage dose of between 1 and 100 mg/kg/day (Watanabe et al. 1976a).

Several investigators observed the binding of nonvolatile metabolites of ^{14}C-vinyl chloride to liver macromolecules both *in vitro* and in rats exposed by inhalation (Guengerich and Watanabe 1979; Guengerich et al. 1979, 1981; Kappus et al. 1976; Watanabe et al. 1978a, 1978b). In single-exposure experiments at different concentrations, the extent of macromolecular binding increased proportionately to the amount of vinyl chloride metabolized and disproportionately to the exposure concentration (Watanabe et al. 1978b). The extent of macromolecular binding was increased by repeated exposure to

vinyl chloride (Watanabe et al. 1978a) and by pretreatment with phenobarbital (Guengerich and Watanabe 1979). Macromolecular binding was attributed to the reactive intermediate 2-chloroethylene oxide, which binds to DNA and RNA, and to its rearrangement product, 2-chloroacetaldehyde that can form an adduct with some amino acid side-chains, altering the protein conformation (Guengerich and Watanabe 1979; Guengerich et al. 1979, 1981; Kappus et al. 1976; Watanabe et al. 1978a, 1978b).

3.1.4 Excretion

Animal studies demonstrated that the primary route of vinyl chloride excretion is dose-dependent (Watanabe and Gehring 1976; Watanabe et al. 1976b, 1978a). Vinyl chloride metabolites are excreted primarily in the urine following oral and inhalation exposure at low doses or concentrations. At higher doses where metabolic saturation has been exceeded, vinyl chloride is exhaled as the parent compound. This was also demonstrated in humans exposed by inhalation, where exhalation of vinyl chloride was a minor pathway of elimination even at low concentrations (Krajewski et al. 1980).

Human data suggest that exhalation of unmetabolized vinyl chloride is not an important pathway of elimination at low exposure concentrations. The mean concentration in expired air for humans exposed for 6 hours to air containing 2.9–23.5 ppm ranged from 0.21 to 1.11 ppm, representing from 7.23 to 4.73% of the inhaled amounts, respectively (Krajewski et al. 1980). After dermal exposure in monkeys, most of the minimal vinyl chloride absorbed was excreted in exhaled air (Hefner et al. 1975a).

The mode of excretion of vinyl chloride and its metabolites following inhalation exposure of animals to different concentrations reflects the saturation of metabolic pathways. The cumulative excretion of radioactivity over a 72-hour postexposure period was measured in rats exposed to 10–1,000 ppm (Watanabe and Gehring 1976; Watanabe et al. 1976b) or 5,000 ppm (Watanabe et al. 1978a) ^{14}C-vinyl chloride for 6 hours. Radioactivity expired as carbon dioxide or vinyl chloride, excreted in the urine and feces, and retained in the carcass was expressed as a percentage of the total radioactivity recovered. The results suggest that metabolism was nearly complete at 10 ppm because <2% of the recovered radioactivity occurred as unchanged parent compound. The predominant route for excretion of radioactive metabolites was through the urine, accounting for about 70% of the recovered radioactivity. Metabolism appeared to become saturated at 1,000 ppm, since unchanged vinyl chloride increased to 12.3% and urinary radioactivity decreased to 56.3%.

Increasing vinyl chloride concentrations may have different effects for animals and humans. In rats exposed to 5,000 ppm for 6 hours, more than half of the recovered radioactivity appeared as unchanged vinyl chloride in expired air, and urinary excretion accounted for about 27% of the recovered activity (Watanabe et al. 1978a). Generally, there was little change in the proportion of recovered radioactivity excreted in the feces or exhaled as carbon dioxide. The percentage of the radioactivity retained in the carcass and tissues of rats appeared to be somewhat decreased at 5,000 ppm compared with 10 and 1,000 ppm, suggesting preferential retention of metabolites rather than unchanged vinyl chloride Watanabe and Gehring 1976; Watanabe et al. 1978a, 1976b). It should be noted that the trend for a greater percentage of vinyl chloride being exhaled at higher concentrations in animals is the opposite of what was observed in humans by Krajewski et al. (1980). In humans, a higher percentage of unmetabolized vinyl chloride was found in expired air at lower concentrations (Krajewski et al. 1980) than is seen in animals. However, it is possible that a reversal of this trend would occur in humans if concentrations were increased to those used in the animal studies or to concentrations closer to the K_m for human metabolism.

Pulmonary excretion of unaltered vinyl chloride in rats followed first-order kinetics regardless of exposure concentrations, with half-lives of 20.4, 22.4, and 30 minutes following 6-hour exposures at 10, 1,000, and 5,000 ppm, respectively (Watanabe et al. 1976b). After oral exposure, pulmonary excretion of vinyl chloride appeared to be monophasic at <1.0 mg/kg, with a half-life of about 55–58 minutes (Watanabe et al. 1976a). At 100 mg/kg, pulmonary excretion of vinyl chloride was biphasic, with half-lives of 14.4 and 40.8 minutes for the rapid and slower phases, respectively. Exhalation of unchanged vinyl chloride was generally complete within 3–4 hours; however, excretion of metabolites in urine continued for days (Green and Hathway 1975).

The urinary excretion of radioactivity was biphasic, with the second or slow phase accounting for <3% of the total urinary excretion (Cheng et al. 2001; Watanabe et al. 1976a). Estimated half-lives for the rapid (first-order) phase were 4.6, 4.1, and 4.5 hours at 10, 1,000, and 5,000 ppm, respectively (Cheng et al. 2001) and 4.5–4.6 hours for oral doses of 0.05–100 mg/kg (Watanabe et al. 1976a). Single oral doses of ^{14}C-vinyl chloride (0.05, 0.25, 1.0, 20, 100, and 450 mg/kg) were administered to rats, and the excretion of radioactivity was monitored over a 72-hour period (Green and Hathway 1975; Watanabe and Gehring 1976; Watanabe et al. 1976a). A striking increase in exhalation of unchanged vinyl chloride and compensatory decreases in urinary and fecal excretion of radioactivity and exhalation of carbon dioxide were observed at >20 mg/kg, suggesting that metabolic saturation had occurred at that dosage. At <1.0 mg/kg, the predominant route of elimination was urinary excretion of polar metabolites.

Urinary metabolites included *N*-acetyl-*S*-(2-hydroxyethyl)cysteine, thiodiglycolic acid, and possibly *S*-(2-hydroxyethyl)cysteine (Watanabe et al. 1976b). Identification of these metabolites of vinyl chloride in the urine indicates that vinyl chloride is transformed in the body to a reactive metabolite, which is then detoxified by reaction with glutathione (GSH, gamma-glutamylcysteinylglycine). Subsequently, the glutamic acid and glycine moieties of the tripeptide are cleaved, and the cysteine conjugate of the reactive metabolite of vinyl chloride is either acetylated or further oxidized and excreted. Thiodiglycolic acid is the major metabolite of vinyl chloride detected in the urine of exposed workers (Cheng et al. 2001). Urinary thiodiglycolic acid levels were correlated with vinyl chloride levels in air at concentrations >5 ppm; however, this correlation appears to be more variable at lower vinyl chloride concentrations in air (Chen et al. 2019).

Metabolites identified in the urine of orally treated rats were consistent with the formation of 2-chloroethylene oxide and 2-chloroacetaldehyde (Green and Hathway 1977; Watanabe et al. 1976a), as postulated for metabolism following inhalation exposure. The major metabolites were identified as thiodiglycolic acid, *N*-acetyl-*S*-(2-hydroxyethyl)cysteine, *N*-acetyl-*S*-(2-chloroethyl)cysteine, and *S*-(2-chloroethyl)cysteine (Green and Hathway 1977; Watanabe et al. 1976a). Minor metabolites included urea, glutamic acid, and 2-chloroacetic acid (Green and Hathway 1975).

Dermal exposure of high concentrations of vinyl chloride gas resulted in most excreted in expired air for the small fraction that was absorbed. Hefner et al. (1975a) reported that two rhesus monkeys received whole-body (except head) exposure to vinyl chloride gas (800 and 7,000 ppm) for 2–2.5 hours and most was excreted in expired air (Hefner et al. 1975a). The percentages of absorbed vinyl chloride that were exhaled were 0.028% at 700 ppm and 0.014% at 8,000 ppm (Hefner et al. 1975a).

The elimination of radioactivity following intraperitoneal administration of ^{14}C-vinyl chloride to rats resembles the pattern observed following inhalation or oral administration. Following an intraperitoneal dose of 0.25 mg/kg, exhalation of unchanged vinyl chloride, exhalation of carbon dioxide, and urinary and fecal excretion of radioactivity accounted for 43.2, 11.0, 43.1, and 1.8% of the administered dose, respectively (Green and Hathway 1975). At 450 mg/kg, exhaled vinyl chloride increased to 96.2% of the administered dose, carbon dioxide decreased to 0.7%, urinary radioactivity decreased to 2.6%, and fecal radioactivity decreased to 0.1%.

Doses administered intravenously were eliminated very rapidly and almost entirely by exhalation of unchanged vinyl chloride. Green and Hathway (1975) administered a 0.25-mg/kg intravenous dose of ^{14}C-vinyl chloride to rats and recovered 80% of the dose within 2 minutes and 99% within 1 hour as unchanged compound in expired air.

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

PBPK models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic endpoints.

PBPK models are available for vinyl chloride. These models predict the metabolism and distribution of vinyl chloride. The overall results and individual models are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations.

3.1.5.1 EPA (1987) Animal Models

EPA (1987) developed a PBPK model to estimate the metabolized dose of vinyl chloride when coupled to a multistage model to estimate cancer risk in animals. This PBPK model consists of four compartments: the liver, fat, highly perfused tissue, and poorly perfused tissue. All metabolism is assumed to occur in the liver by one saturable (reflecting Michaelis-Menten kinetics) first-order metabolism pathway.

The dose delivery provided by the vinyl chloride model developed by EPA (1987) was validated by the U.S. Air Force (1990) study and by additional vinyl chloride metabolism studies conducted in rats. At low concentrations, this model fit *in vivo* data in rats by Gehring et al. (1978) well, but at concentrations above 25 ppm, the model predicted a greater level of vinyl chloride metabolism than was observed.

3.1.5.2 U.S. Air Force (1990) Rat, Mouse, and Hamster Models

The U.S. Air Force (1990) modified the EPA (1987) model to improve the fit with actual data, particularly as it relates to glutathione depletion and doses above 25 ppm. In the first modification, both vinyl chloride and the epoxide metabolite were assumed to react with glutathione. This model had difficulty predicting glutathione depletion at high doses; for example, it predicted glutathione depletions higher than observed at 4,600–5,800 ppm vinyl chloride concentrations. The second alternative model assumed that only the product of the first-order metabolism reacted with glutathione. It also predicted glutathione depletions higher than observed at high exposure concentrations. To improve the model, the investigators suggested the addition of a low-affinity glutathione pathway.

Using vinyl chloride concentration data obtained from Wright-Patterson Air Force Base (AFB), the U.S. Air Force (1990) extended the first glutathione conjugation model, developed in rats, to different strains of rats, mice, and hamsters. Vinyl chloride gas uptake experiments were completed in which animals were exposed to various concentrations of vinyl chloride in closed chambers for up to 6 hours, and the disappearance of vinyl chloride was monitored. The glutathione content of the animals was also measured immediately after exposure. Using data from these studies with the physiologic parameters shown in Table 3-2, the investigators estimated metabolic parameters for vinyl chloride and the rate constant for the conjugation of vinyl chloride with glutathione (Table 3-3). Using the metabolic parameters determined from the gas uptake experiments, the model predictions showed good agreement with the actual data for all of the animal strains tested.

Table 3-2. Physiological Parameters Used to Estimate Parameters from Vinyl Chloride Gas Uptake Experiments[a]

Parameter	Rats	Mice	Hamsters
Ventilation rate (L/hour/body weight$^{0.74}$)	14	23–35[b]	13
Total cardiac output (L/hour/body weight$^{0.74}$)	14	23–35[b]	13
Blood flow to the liver (fraction of total cardiac output)	0.25	0.24	0.24
Blood flow to highly perfused tissue (fraction of total cardiac output)	0.51	0.52	0.52
Blood flow to fat (fraction of total cardiac output)	0.09[c]	0.05	0.09
Blood flow to poorly perfused tissue (fraction of total cardiac output)	0.15[c]	0.20	0.15
Volume of tissue (L/body weight)	0.04	0.04	0.04
Volume of highly perfused tissue (L/body weight)	0.05	0.05	0.05

Table 3-2. Physiological Parameters Used to Estimate Parameters from Vinyl Chloride Gas Uptake Experiments[a]

Parameter	Rats	Mice	Hamsters
Volume of fat tissue (L/body weight)	0.07–0.1[d]	0.04	0.07
Volume of poorly perfused tissue (L/body weight)	0.72–0.75[d]	0.78	0.75

[a]U.S. Air Force (1990); units of body weight were not provided.
[b]Ventilation rates and total cardiac outputs were 23 for male B6C3F1 mice, 25 for female B6C3F1 mice, 28 for female CD-1 mice, and 35 for male CD-1 mice.
[c]Male Wistar rats blood flow to fat = 0.08 and blood flow to slowly perfused tissue = 0.16.
[d]Female F-344 and female Wistar rats had volume of fat tissue = 0.07 and volume of slowly perfused tissue = 0.75; male F-344 and female Wistar rats had volume of fat tissue = 0.08 and volume of slowly perfused tissue = 0.74; male Wistar rats and male CDBR rats had volume of fat tissue = 0.1 and volume of slowly perfused tissue = 0.72.

Table 3-3. Estimates of Metabolic Parameters Obtained from Gas Uptake Experiments

Species	Strain	Sex	V_{max}/body weight$^{0.7}$ (mg/hour/body weight$^{0.7}$)	Kfc (body weight$^{0.3}$/ hour)	Kgsc (body weight$^{0.3}$/hour/µmol/L GSH)
Rat	CDBR	M	2.50	0.63	ND
		F	2.47	1.00	0.000241
	F-344	M	3.17	1.08	0.000249
		F	2.95	1.03	0.000227
	Wistar	M	3.11	0.45	0.000093
		F	2.97	1.55	0.00040
Mouse	B6C3F1	M	5.89	5.5	0.000827
		F	5.53	8.93	0.001670
	CD-1	M	6.99	5.1	0.000563
		F	5.54	6.62	0.000809
Hamster	Golden Syrian	M	4.94	1.67	0.000330
		F	4.76	2.06	ND

Source: U.S. Air Force 1990

F = female; GSH = glutathione; Kfc = first order of epoxide formation; Kgsc = rate constant for conjugation of vinyl chloride with glutathione; M = male; ND = not determined; V_{max} = maximum velocity of reaction

It does not appear that the investigators further validated the Wright-Patterson AFB model with data from studies other than those used to determine the metabolic parameters. This model was not used to estimate metabolized doses for humans because the investigators indicated that human data to estimate all of the required parameters were not available. They suggested that allometry may have to be used to estimate some of the parameters for humans.

3.1.5.3 Clewell et al. (1995) Human Models

Clewell et al. (1995) used PBPK modeling coupled with a linearized multistage model to predict human cancer risk. The model again had four compartments as described for the EPA (1987) study, and the same EPA physiologic parameters were used. Partition coefficients were from *in vitro* experiments and are shown in Table 3-1. Metabolism was modeled by two saturable pathways: one high affinity, low capacity (P4502E1), and one low affinity, high capacity (2C11/6 and 1A1/2). The metabolic parameters used were not provided, but they were estimated from the U.S. Air Force (1990) model. This model assumed that the metabolites (chloroethylene oxide and chloroacetaldehyde) were further degraded to carbon dioxide, reacted with glutathione, or reacted with DNA. The parameters (not stated) for the degradation reactions of chloroethylene oxide and chloroacetaldehyde were estimated from vinylidene chloride data (D'Souza and Andersen 1988) using appropriate allometric scaling.

Based on the Clewell et al. (1995) PBPK model and a linearized multistage model using liver angiosarcoma data from animal studies, the human risk estimates for lifetime exposure to 1 ppb vinyl chloride ranged from 1.1 to 15.7/million persons. Based on the incidence of liver angiosarcoma in human epidemiological studies, the risk estimates for lifetime exposure to 1 ppb vinyl chloride were 0.4–4.22/million persons. Clewell et al. (1995) indicated that the risk estimates in the occupational exposure range using PBPK modeling are about 30–50 times lower than estimates using external dose calculations based on the linearized multistage model.

Clewell et al. (2001) further refined the PBPK model for vinyl chloride. This model was applied by the EPA to develop quantitative toxicity values for vinyl chloride (i.e., reference dose [RfD], reference concentration [RfC], inhalation unit risk, oral slope factor) (EPA 2000). The model had four compartments and metabolism was modeled by two saturable pathways: one high affinity, low capacity (P4502E1), and one low affinity, high capacity (2C11/6 and 1A1/2). A description of glutathione kinetics was also included in the model. Cancer risk estimates in the occupational exposure range calculated using the PBPK model were consistent with risk estimates from epidemiological studies and were approximately 80-fold lower than cancer risk estimates from animal studies without PBPK modeling. The inhalation portion of the PBPK model is well documented with experimental inhalation data sufficient to ensure a high degree of confidence in the derived dose metrics. Less confidence is associated with the oral dose metrics due to the limited experimental data available (EPA 2000).

The Clewell et al. (2001) model was also applied to evaluate the potential impact of age- and gender-specific pharmacokinetic differences on the dosimetry of vinyl chloride (Clewell et al. 2004). The rate of metabolite production per volume of liver was estimated to rise rapidly from birth until about age 16 years, after which it remains relatively constant before rising again late in life. Other factors that may affect vinyl chloride toxicity at early life stages include the presence of fetal P450s and the level of glutathione transferase.

The PBPK model described in Clewell et al. (2001) and EPA (2000) was used to derive the chronic-duration oral MRL. For more information on ATSDR's use of the Clewell model, refer to Appendix A.

3.1.5.4 Reitz et al. (1996) Rat, Mouse, and Human Models

Reitz et al. (1996) also developed a PBPK model that coupled measures of delivered dose in rats to a linearized multistage model to predict the incidence of hepatic angiosarcoma in mice and humans. The model incorporated four compartments: fat, muscle, rapidly perfused tissues, and liver. Physiological parameters in the model were based on similar ones used in an earlier multispecies PBPK model developed for methylene chloride. Partition coefficients were estimated by vial equilibration techniques similar to those described in the U.S. Air Force (1990) study. Metabolic rate constants were obtained from *in vivo* gas uptake experiments performed at Wright-Patterson AFB.

Based on the PBPK-based procedure utilized by Reitz et al. (1996), the predicted human risk estimates ranged from about 200 cases of angiosarcoma per 100,000 (for workers employed 10 years at a plant where the time-weighted average [TWA] was 50 ppm) to almost 4,000 cases/100,000 in workers employed for 20 years in a plant where the TWA was 2,000 ppm. The predictions of human risk were compared with the data reported by Simonato et al. (1991). The predictions of angiosarcoma incidence in humans were almost an order of magnitude higher than actually observed in exposed human populations and were more than two orders of magnitude lower than risk estimations that did not utilize pharmacokinetic data.

3.1.5.5 Other Models

Yoon et al. (2007) evaluated the impact of assuming extrahepatic metabolism by CYP2E1 in PBPK models for vinyl chloride inhalation. The study concluded that predictions for the rat and human models were not significantly affected by the inclusion of extrahepatic metabolism by CYP2E1 in the kidney and lung. Chiu and White (2006) described the development of a simplified steady-state solution of a generic

PBPK model for volatile organic compounds. This steady-state analysis was shown to produce similar results to the full PBPK model reported in the EPA (2000) risk assessment for vinyl chloride. Mumtaz et al. (2012) developed a generic seven-compartment PBPK model, which added compartments for blood, kidney, and skin. A comparison of the results of this model to the Clewell et al. (2001) model showed that both models adequately predicted blood concentrations during, and immediately following, exposure.

3.1.6 Animal-to-Human Extrapolations

Limited information is available regarding the toxicokinetic differences between species. Toxicokinetic data in humans are limited (Krajewski et al. 1980; Sabadie et al. 1980). A primate study suggested that metabolism may saturate at lower concentrations in primates (>300–400 ppm) than in rats (Buchter et al. 1980).

PBPK models were also developed to predict the metabolism and distribution of vinyl chloride in laboratory animals and humans (Section 3.1.5). The most recent PBPK model for vinyl chloride (Clewell et al. 2001) was applied by EPA to develop quantitative toxicity values for vinyl chloride (RfD, RfC, inhalation unit risk, oral slope factor) (EPA 2000). The model has four compartments and metabolism was modeled by two saturable pathways: one high affinity, low capacity (P4502E1), and one low affinity, high capacity (2C11/6 and 1A1/2). A description of glutathione kinetics was also included in the model. Cancer risk estimates calculated using the PBPK model were consistent with risk estimates from epidemiological studies.

There appears to be a correlation of vinyl chloride toxicity between humans and animals with regard to respiratory, cardiovascular, hematological, hepatic, dermal, immunological, neurological, reproductive and cancer effects. Renal effects of vinyl chloride, including increased relative kidney weight and an increase in severity of tubular nephrosis, are reported in several rat studies (Bi et al. 1985; Feron and Kroes 1979; Feron et al. 1979). However, kidney toxicity was only observed in a single human study of exposure to multiple chlorinated solvents in drinking water (Chen and Wu 2017). Evidence for developmental effects of vinyl chloride has not been reliably demonstrated in epidemiology studies (Bao et al. 1988; Edmonds et al. 1975, 1978; Rosenman et al. 1989; Ruckart et al. 2013; Swartz et al. 2015; Talbott et al. 2015; Theriault et al. 1983), but did occur in studies of several animal species (John et al. 1977, 1981).

3.2 CHILDREN AND OTHER POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

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

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

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

Data suggest that fetuses, infants, and young children are susceptible to the toxic effects of vinyl chloride. Some epidemiologic studies (Infante et al. 1976a, 1976b; NIOSH 1977) suggested an association between fetal death and birth defects and parental vinyl chloride exposure. However, the design and analysis of these studies has been criticized (Hatch et al. 1981; Stallones 1987). Some inhalation studies with animals have suggested that vinyl chloride is a developmental toxicant (e.g., produces delayed ossification) at doses that also produce maternal toxicity (John et al. 1977, 1981; Mirkova et al. 1978; Sal'nikova and Kotsovskaya 1980; Ungvary et al. 1978). However, no adverse effects on embryo-fetal development were noted in a rat inhalation study (Thornton et al. 2002).

Vinyl chloride can cross the placenta and enter the blood of the fetus (Ungvary et al. 1978). Studies by Drew et al. (1983) and Maltoni et al. (1981) have shown that animals exposed by inhalation prior to adolescence or during pregnancy may have a greater death rate and increased likelihood of developing cancer than adult animals exposed for similar periods. This may relate to the length of the induction period of hepatic angiosarcoma rather than to an increased susceptibility of the young, *per se*. Lifetime cancer risk was also dependent on the age of the animals at the time of exposure to vinyl chloride. Refer to Section 2.19 for more details on studies addressing cancer and age of vinyl chloride exposure.

It is also possible that there are explanations for these findings. Cogliano and Parker (1992) suggested that in the multistage model of carcinogenesis, carcinogens that induce an initial transition early in the life of an animal would be more effective since there would be a longer period of time remaining in the lifespan for completion of the remaining transitions. Their empirical model of the effect of age at exposure on the development of cancer suggests that there is an age-sensitive period of exposure to vinyl chloride.

An age-related increase in DNA adduct formation was noted in an inhalation study of lactating rats and their 10-day-old pups exposed to 600 ppm of vinyl chloride, 4 hours/day for 5 days (Fedtke et al. 1990). Concentrations of two adducts found in livers of pups were 4-fold higher than those found in livers of dams; however, pups were exposed to contaminated breast milk in addition to air concentrations vinyl chloride. In another study, immature rats exposed to vinyl chloride formed 6 times more etheno-nucleosides compared with adults (Ciroussel et al. 1990). 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).

Taken together, the studies cited above suggest an early life stage sensitivity to vinyl chloride carcinogenicity (Cogliano et al. 1996). EPA has recommended an adjustment of the cancer risk estimates to account for early life-stage sensitivity to vinyl chloride (EPA 2000; Ginsberg 2003).

The toxicokinetic behavior of vinyl chloride in children is expected to be similar to that in adults (Clewell et al. 2004; EPA 2000; Gentry et al. 2003). Urinary metabolites of vinyl chloride and other volatile compounds have been measured in preterm infants in a neonatal intensive care unit (El-Metwally et al. 2018). An evaluation of pharmacokinetic differences across life stages suggests that the largest difference in pharmacokinetics occurs during the perinatal period (Gentry et al. 2003). The most important factor appears to be the potential for decreased clearance due to immature metabolic enzymes systems. For instance, clearance is hampered in the embryonic liver because CYP2E1 is not expressed but rapidly increases during the first 24 hours after birth. Between the developmental ages of 1 and 10 years, children's CYP2E1 protein levels and enzyme activity are comparable to adults (EPA 2000).

Young children appear to have the capacity of metabolizing vinyl chloride to reactive intermediates that form DNA adducts that lead to cancer. A PBPK model was applied to evaluate the potential impact of age- and gender-specific pharmacokinetic differences on the dosimetry of vinyl chloride (Clewell et al. 2004). The rate of metabolite production per volume of liver was estimated to rise rapidly from birth

until about age 16, after which it remains relatively constant before rising again late in life. The data on CYP2E1 levels in the developing organism suggests that early life stage sensitivity to vinyl chloride-induced cancer is not solely due to an increase in the production of reactive intermediates via this isozyme. Fetal CYP isoforms may play a role in metabolism of vinyl chloride to reactive intermediates in the fetus and neonate. Glutathione conjugation may also differ in the developing organism. DNA repair capacity and other pharmacodynamic factors may also be associated with an early life stage susceptibility to cancer.

Individuals with comorbidities (e.g., obesity and liver disease) and genetic polymorphisms of HLA-DR5, HLA-DR3, and B8 alleles are unusually susceptible to the effects of vinyl chloride. Lifestyle factors such as exposure to organochlorine pesticides, consuming high-calorie diets, ethanol or barbiturates, or taking Antabuse for alcoholism may make people have increased susceptibility to vinyl chloride effects. Irregular heart rhythms, impaired peripheral circulation, and systemic sclerosis (Section 3.3.2) may also increase susceptibility.

Mice fed a high-fat diet are more susceptible to liver injury induced by low concentrations of vinyl chloride. High-fat diet mice exposed to 0.85 ppm vinyl chloride for 12 weeks showed enhanced liver damage, neutrophil infiltration, non-parenchymal cell apoptosis, mitochondrial dysfunction, and oxidative and endoplasmic reticulum stress compared to mice fed a normal or low-fat diet (Chen et al. 2019; Fujiwara 2018; Lang et al. 2018, 2020; Liang et al. 2018; Wahlang et al. 2020). Mice injected with lipopolysaccharide or fed diets high in fat and exposed orally to 2-chloroethanol also experienced enhanced liver injury when compared to mice fed a normal or low-fat diet (Anders et al. 2016a, 2016b; Lang et al. 2019). This effect was attenuated by rapamycin, which protects against mitochondrial damage and subsequent oxidative stress (Lang et al. 2019). Mitochondrial ALDH2 may also play a role in detoxifying 2-chloroacetaldehyde (Chen et al. 2019). Activation of ALDH2 with an agonist (Alda-1) was shown to attenuate liver injury and reduce oxidative stress in high-fat diet mice exposed to vinyl chloride (Chen et al. 2019).

Vinyl chloride is metabolized in the liver in a multistep process. The prevalence of liver ultrasound abnormalities (not further defined) was associated with polymorphism of the CYP2E1 gene (c1c2/c2c2 genotype) (Zhu et al. 2005a). A genetic polymorphism of CYP2E1 (increase in CYP2E1 c2c2 genotype) was also associated with liver fibrosis, diagnosed by ultrasonography in 13 of 320 workers employed in five PVC manufacturing plants (Hsieh et al. 2007). No association was found between liver effects and genetic polymorphisms of glutathione transferase or aldehyde dehydrogenase in these studies.

Polymorphisms of genes involved in metabolism (CYP2E1, GSTP1, ALDH2), DNA repair (hOGG1, MGMT, XRCC1, XPA, XPC, XPD, XPF, TDG, APE1), apoptosis (MDM2, BCL2) and cell cycle control (p53, p21) have been associated with increased micronuclei, sister chromatid exchange frequency, DNA damage and retention of DNA adducts in vinyl chloride workers (Feng et al. 2017; Ji et al. 2010; Li et al. 2006, 2009a, 2013; Qiu et al. 2008, 2011a; Wang et al. 2010a, 2010b, 2013b; Wen-Bin et al. 2009; Wong et al. 2003b; Zhu et al. 2005b, 2008). The occurrence of the mutation biomarkers in serum was correlated with polymorphisms of the DNA repair genes XRCC1 (mutant p53), excision repair cross complementation group 2 (ERCC2)/XPD (mutant p53 and ras-p21) and ALDH2 and CYP2E1 in vinyl chloride workers (Li et al. 2003b, 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). The risk of developing liver cancer also appeared to be elevated in those with a history of Hepatitis B viral infection (Du and Wang 1998; Wong et al. 2003b).

Vinyl chloride workers with genetic polymorphisms of genes related to metabolism, DNA repair, and cell cycle control may be more susceptible to liver toxicity and liver cancer. A polymorphism of the CYP2E1 gene was associated with an increase in liver abnormalities evaluated by ultrasound (Hsieh et al. 2007; Zhu et al. 2005a). Genetic polymorphisms of several genes were associated with increased micronuclei frequency, DNA damage, retention of DNA adducts, and an increase in tumor biomarkers in serum (Ji et al. 2010; Li et al. 2006, 2009a; Qiu et al. 2008, 2011a; Schindler et al. 2007; Wang et al. 2010a, 2010b, 2013b; Wen-Bin et al. 2009; Zhu et al. 2005b, 2008). The risk of developing liver cancer also appears elevated in those with a history of Hepatitis B viral infection (Du and Wang 1998; Wong et al. 2003b). Work by Black et al. (1983, 1986) has shown that persons with the HLA allele, HLA-DR5, may have an increased likelihood of developing vinyl chloride disease, and those with the alleles, HLA-DR3 and B8, may have an increased severity of the disease.

Phenobarbital and Aroclor 1254 increase mixed function oxidase (MFO) activity and have been shown to greatly increase the hepatotoxicity of vinyl chloride (Conolly and Jaeger 1979; Conolly et al. 1978; Jaeger et al. 1974, 1977; Jedrychowski et al. 1985; Reynolds et al. 1975a, 1975b). The intermediary metabolites of vinyl chloride, 2-chloroethylene oxide and 2-chloroacetaldehyde, have been suggested to be responsible for some of the adverse effects produced by vinyl chloride. Thus, individuals taking barbiturates or who might be exposed to organochlorine pesticides that are known to induce microsomal enzymes (such as Aroclor 1254) would be expected to be at increased risk for developing vinyl chloride-induced hepatotoxicity.

Radike et al. (1981) demonstrated that ethanol-consuming rats exposed to vinyl chloride had an increased incidence of cancer and an earlier death rate than animals exposed to vinyl chloride in the absence of ethanol. Some persons consume the agent, Antabuse, to curb the desire for alcohol. In its role as a therapeutic agent, Antabuse blocks aldehyde dehydrogenase and causes a build-up of acetaldehyde, which is emetic, in the body when alcohol is consumed. If persons taking Antabuse are exposed to vinyl chloride, the alternative metabolic pathway for vinyl chloride metabolism will be blocked, causing more vinyl chloride to be metabolized to the toxic metabolite, 2-chloroethylene oxide. Thus, these persons may be at increased risk for hepatotoxicity, cancer, and death at an early age.

3.3 BIOMARKERS OF EXPOSURE AND EFFECT

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

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. Biomarkers of exposure to vinyl chloride are discussed in Section 3.3.1. The National Report on Human Exposure to Environmental Chemicals provides an ongoing assessment of the exposure of a generalizable sample of the U.S. population to environmental chemicals using biomonitoring (see http://www.cdc.gov/exposurereport/). If available, biomonitoring data for vinyl chloride from this report are discussed in Section 5.6, General Population Exposure.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that (depending on magnitude) can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effect caused by vinyl chloride are discussed in Section 3.3.2.

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

3.3.1 Biomarkers of Exposure

The only exposure biomarker specific to vinyl chloride is the measurement of this compound in expired air. Other exposure biomarkers are not specific to vinyl chloride exposure only. As such, there is limited utility in urine tests for thiodiglycolic acid and N-acetyl-S-(2-hydroxyethyl)-cysteine.

Vinyl chloride may be quantified in expired air following acute moderate-to-high exposures (Azari et al. 2016). The expiration of vinyl chloride follows first-order kinetics; therefore, this parameter can be directly correlated with exposure levels (Baretta et al. 1969). This measure provides the most direct evidence for vinyl chloride exposure. However, measurement of exposure by this technique is limited by the rapidity with which vinyl chloride is expired during breathing. The half-life of vinyl chloride in expired air is between 20 and 30 minutes following an inhalation exposure and is approximately 60 minutes following oral dosing (Watanabe and Gehring 1976; Watanabe et al. 1976b, 1978a, 1978b). Thus, testing must be initiated as soon as possible following termination of exposure. Measurement of vinyl chloride in expired air has limited utility for low-level exposures (<50 ppm) because of competition between absorptive uptake and rapid metabolism (Baretta et al. 1969). In addition, it provides no information on the duration of exposure.

Thiodiglycolic acid is a major urinary metabolite of vinyl chloride. Measurement of thiodiglycolic acid in urine can be used to monitor occupationally exposed workers (Cheng et al. 2001; Lee et al. 2020; Müller et al. 1979) and children living in the vicinity of industrial vinyl chloride-using facilities (Huang et al. 2016; Wang et al. 2019b). The validity of this biomarker for community health studies has been questioned in cases where exposure concentrations in air are generally low (<5 ppm) (Chen et al. 2018). The amount of thiodiglycolic acid in the urine varies according to individual metabolic idiosyncrasies because metabolism of vinyl chloride to thiodiglycolic acid is a saturable process. Therefore, when exposure exceeds a certain level, the excretion of vinyl chloride as thiodiglycolic acid will plateau (Watanabe and Gehring 1976). In addition, the rate of metabolism of vinyl chloride to thiodiglycolic acid

can be influenced by the presence of liver disease and by ethanol consumption as well as intakes of other substances such as barbiturates (Hefner et al. 1975b).

Similar to the measurement of vinyl chloride in expired air, the measurement of thiodiglycolic acid must take place shortly after exposure because of its rapid excretion. The half-life for excretion of thiodiglycolic acid following an acute exposure is between 4 and 5 hours (Watanabe and Gehring 1976; Watanabe et al. 1978a, 1978b). Cheng et al. (2001) suggested that urinary thiodiglycolic acid levels should not be measured at the end of a work shift but are best detected at the beginning of the following workday. Excretion of thiodiglycolic acid is not unique to vinyl chloride exposure. For example, thiodiglycolic acid can be excreted in the urine as the result of exposure to vinylidene chloride, ethylene oxide, or 2,2-dichloroethylether (Norpoth et al. 1986; Pettit 1986). Infants delivered prematurely can have high levels of urinary thiodiglycolic acid. A correlation was observed between the thiodiglycolic acid levels and the number of weeks that the infant was born prematurely. The origin of this thiodiglycolic acid in neonates is unknown, but is likely not associated with vinyl chloride exposure (Pettit 1986).

Boyle et al. (2016) suggest that urinary levels of N-acetyl-S-(2-hydroxyethyl)-cysteine may be a useful biomarker for combined exposure to vinyl chloride, ethylene oxide, and acrylonitrile. This compound is measured as a urinary biomarker for the listed volatile compounds in the National Health and Nutrition Examination Survey (NHANES) (Konkle et al. 2020).

3.3.2 Biomarkers of Effect

Biomarkers of effect for vinyl chloride include altered liver function, DNA adducts, and measures of genotoxicity including chromosomal aberrations, micronuclei, and DNA damage (i.e., strand breaks).

Liver function tests are sensitive indicators of the hepatic damage resulting from vinyl chloride exposure. These assays include the indocyanine clearance test, measurement of serum bile acids, and measurement of serum hyaluronic acid concentration (Berk et al. 1975; Liss et al. 1985; McClain et al. 2002; Vihko et al. 1984). In general, serum enzymes were found to be of limited value in monitoring the progression of vinyl chloride-induced hepatic changes (Berk et al. 1975; Liss et al. 1985; Vihko et al. 1984). This is likely due to the extent of hepatic damage produced by vinyl chloride and the late development of necrotic areas in the disease process (Popper et al. 1981). A study of hepatic ultrasound abnormalities suggests that functional and imaging tests may be useful biomarkers of liver toxicity in workers exposed

to vinyl chloride (Wang et al. 2008). Cave et al. (2010) suggested that an elevation of total cytokeratin 18 levels in serum may be indicative of liver cell necrosis (a known vinyl chloride effect).

The intermediary metabolites, 2-chloroethylene oxide and 2-chloroacetaldehyde, bind to macromolecules in the body. 2-Chloroethylene oxide is hypothesized to bind primarily to DNA and RNA, whereas 2-chloroacetaldehyde binds primarily to proteins (Bolt 1986; Guengerich and Watanabe 1979; Guengerich et al. 1979, 1981; Kappus et al. 1976; Watanabe et al. 1978a, 1978b). Several DNA adducts have been reported following vinyl chloride exposure (Mutlu et al. 2010, 2012; Pottenger et al. 2014; Swenberg et al. 2011; Yun et al. 2020). 7-(2-Oxoethyl)guanine (7-OEG) is the primary DNA adduct; however, it is not mutagenic (i.e., does not cause mispairing during replication) and would not be a biomarker of effect (Mutlu et al. 2010). N^2,3-Ethenoguanine is a mutagenic adduct and may be an important effect biomarker of vinyl chloride (Mutlu et al. 2010). Liquid chromatography-mass spectrometry (LCMS) and stable isotope methods have been used to detect DNA adducts in several tissues, including white blood cells and oral cells in humans (Yun et al. 2020) and liver, lung, and kidney in animals (Mutlu et al. 2010, 2012; Pottenger et al. 2014; Swenberg et al. 2011).

Ethenoguanine adducts may be quantified from urine following base excision repair and excretion where they can be measured using an LCMS method (Gonzalez-Reche et al. 2002). This method would also include the measurement of endogenously formed etheno-adducts; thus, it is critical to determine the background level of urinary adducts in a control population.

Chromosomal aberrations found in lymphocytes can be indicative of the genotoxic effects of vinyl chloride (Anderson 2000; Anderson et al. 1980; Ducatman et al. 1975; Fucic et al. 1990a, 1990b, 1992; Funes-Cravioto et al. 1975; Garaj-Vrhovac et al. 1990; Hansteen et al. 1978; Hrivnak et al. 1990; Kucerova et al. 1979; Purchase et al. 1978; Sinués et al. 1991). However, any of a number of genotoxic substances can produce chromosomal aberrations. de Jong et al. (1988) found that variability in the control population may obscure the observation of chromosomal aberrations in persons exposed to low levels of vinyl chloride. G-banding analysis appeared to provide a more sensitive indication of chromosomal alteration than sister chromatid exchanges (Zhao et al. 1996). DNA damage in lymphocytes can be directly assessed using a single-cell gel electrophoresis technique. The severity of the damage may correlate with the duration of exposure (Awara et al. 1998). The DNA adducts produced by the reactive intermediary metabolites of vinyl chloride, including 1,N^6-ethenoadenosine and 3,N^4-ethenocytidine, may be more specific indicators of vinyl chloride's genotoxic potential (Bolt 1986;

Guengerich and Watanabe 1979; Guengerich et al. 1979, 1981; Kappus et al. 1976; Watanabe et al. 1978a, 1978b).

The micronucleus assay, performed using peripheral lymphocytes of 32 vinyl chloride workers, was used to indicate the time elapsed since the last vinyl chloride exposure occurred (Fucic et al. 1994, 1997). The study showed a decrease in the frequency of micronuclei and mitotic activity in proportion to the length of the interval after the last vinyl chloride exposure. For the group with 10 years of employment, the percentage of micronuclei decreased from 12.82 when exposure occurred on the day of blood sampling to 3.16 when the last exposure occurred 90 days before blood sampling (Fucic et al. 1994). Similar changes were noted when the mean duration of employment was 5 years. However, this use of the micronucleus assay must take into account the total duration of exposure. Micronucleus frequency was shown to be several times higher in binucleated lymphocytes as compared to mononuclear lymphocytes in 25 workers exposed to vinyl chloride for an average of 10 years (Fucic et al. 2004). Zheng et al. (2019) suggested that reduced relative telomere length and gene expression of telomere associated proteins (i.e., shelterin complex) were associated with increased micronuclei and could be considered as potential biomarkers; however, these effects may be caused by many genotoxic compounds and are not specific to vinyl chloride.

3.4 INTERACTIONS WITH OTHER CHEMICALS

ATSDR (2007) prepared an interaction profile for chloroform, 1,1-dichloroethylene, trichloroethylene, and vinyl chloride. This report indicated that no direct data are available to characterize health hazards (and dose-response relationships) from mixtures containing all four components. In addition, PBPK/PD models have not yet been developed that would predict pertinent target doses of the components under mixture exposure scenarios. Toxicological data for the individual compounds suggest that sites of joint toxic action may include hepatic, renal, immunological, neurological, developmental effects, and cancer; however, no experimental data are available for mixtures (ATSDR 2007).

Studies have been performed to examine the effect of agents intended to alter the metabolism of vinyl chloride on its toxicity. For example, the effects of phenobarbital pretreatment on vinyl chloride-induced hepatotoxicity was examined by Jaeger et al. (1974, 1977), Jedrychowski et al. (1985), and Reynolds et al. (1975a, 1975b). Pretreatment of rats with phenobarbital for 7 days prior to a 4-hour vinyl chloride exposure produced an increase in microsomal CYP activity (Reynolds et al. 1975b) and enhanced hepatotoxicity (Jaeger et al. 1974, 1977; Jedrychowski et al. 1985; Reynolds et al. 1975a, 1975b). In the

absence of the phenobarbital pretreatment, a single exposure to approximately 50,000 ppm had no detectable adverse effect on the livers of exposed rats. However, following phenobarbital pretreatment, 50,000 ppm of vinyl chloride produced increased serum activity of hepatic enzymes (Jaeger et al. 1977; Jedrychowski et al. 1985), areas of hepatic necrosis (Reynolds et al. 1975a), or both (Jaeger et al. 1974; Reynolds et al. 1975b). Activation of ALDH2 with an agonist (Alda-1) was shown to attenuate liver injury and reduce oxidative stress in high-fat diet mice exposed to vinyl chloride (Chen et al. 2019).

Another agent known to increase CYP activity, Aroclor 1254, was also tested for its ability to enhance vinyl chloride-induced hepatotoxicity (Conolly and Jaeger 1979; Conolly et al. 1978; Jaeger et al. 1977; Reynolds et al. 1975b). Pretreatment of rats with Aroclor 1254 for several days prior to exposure to vinyl chloride resulted in an increase in serum activity of hepatic enzymes (Conolly and Jaeger 1979; Conolly et al. 1978; Jaeger et al. 1977; Reynolds et al. 1975b) and areas of hepatic necrosis (Conolly et al. 1978; Reynolds et al. 1975b). Additional support for a role for CYP in the enhanced toxicity of vinyl chloride was obtained using SKF525A, a CYP inhibitor. If SKF525A was administered following phenobarbital pretreatment and before vinyl chloride exposure, it blocked the ability of phenobarbital pretreatment to enhance vinyl chloride-induced hepatotoxicity (Jaeger et al. 1977).

The role of glutathione conjugation in vinyl chloride-induced toxicity was also examined (Conolly and Jaeger 1979; Jaeger et al. 1977). The investigators hypothesized that depletion of glutathione might enhance the toxicity of vinyl chloride by preventing the excretion of toxic intermediary metabolites. However, diethylmaleate, an agent known to deplete hepatic glutathione levels, had no effect on the toxicity produced by vinyl chloride following pretreatment with either phenobarbital (Jaeger et al. 1977) or Aroclor 1254 (Conolly and Jaeger 1979). Trichloropropene oxide (TCPO), another agent known to deplete hepatic glutathione, produced enhancement of the hepatic toxicity produced by Aroclor 1254 pretreatment and vinyl chloride exposure but only when the animals had been fasted prior to the vinyl chloride exposure (Conolly and Jaeger 1979). In this study, the authors hypothesized that the enhancement of vinyl chloride toxicity was a result of the ability of TCPO to inhibit epoxide hydrolase rather than its ability to deplete glutathione levels.

Although the depletion of cellular glutathione levels did not appear to enhance vinyl chloride toxicity, treatment with cysteine, the rate-limiting precursor in hepatic glutathione synthesis, increased hepatic glutathione levels and provided partial protection against the toxic effects produced by Aroclor 1254 and vinyl chloride (Conolly and Jaeger 1979).

Mastrangelo et al. (2004) showed that alcohol increased the risk of hepatocellular carcinoma and liver fibrosis in vinyl chloride workers. Possible mechanisms for this synergistic effect include alcohol induction of CYP2E1 and decreased liver glutathione levels resulting in increased formation of mutagenic metabolites (Voigt 2005). CYP2E1 induction may also increase hepatocellular proliferation and formation of ROS. In the experiment by Radike et al. (1981), ethanol-consuming rats exposed to vinyl chloride for a year had an enhanced incidence of hepatic angiosarcomas, hepatomas, and lymphosarcomas, earlier onset of the tumors, and an enhanced death rate. The incidence of vinyl chloride-induced angiosarcomas was potentiated by ethanol, whereas the increased incidences of hepatoma and lymphosarcomas by ethanol were additive in nature.

The effects of smoking on chromosomal aberrations in vinyl chloride-exposed workers was examined by Hrivnak et al. (1990), who found no effect of smoking in 43 workers exposed for an average of 11.2 years to levels of vinyl chloride ranging from 0.8 to 16 ppm. Most cytogenetic studies of the effects of smoking in humans have reported no effect on chromosomal aberrations, although the sister chromatid exchange frequency is usually elevated (Wong et al. 1998).

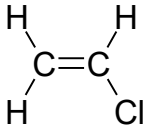
A study that examined the interaction between vinyl chloride and trichloroethylene using both inhalation exposures of rats and pharmacokinetic modeling found that trichloroethylene exposure inhibited vinyl chloride in a competitive manner (Barton et al. 1995). This interaction was observed only at high concentrations (both chemicals >10 ppm), and the study authors concluded that the interaction is not likely to be important for environmental exposures.

CHAPTER 4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Vinyl chloride is a manmade substance. Information regarding the chemical identity of vinyl chloride is located in Table 4-1. This information includes synonyms, chemical formula and structure, and identification numbers.

Table 4-1. Chemical Identity of Vinyl Chloride

Characteristic	Information	Reference
Chemical name	Vinyl chloride	NLM 2021
Synonym(s) and registered trade name(s)	Chloroethene; chloroethylene; 1-chloroethylene; ethylene monochloride; monovinyl chloride; monochloroethene; monochloroethylene; MVCs; Trovidur; VC; VCM; vinyl chloride monomer	Fire 1986; NLM 2021
Chemical formula	C_2H_3Cl	NLM 2021
Chemical structure		NLM 2021
CAS Registry Number	75-01-4	NLM 2021

CAS = Chemical Abstracts Service

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Vinyl chloride is a colorless, flammable gas with a sweet odor. Information regarding the physical and chemical properties of vinyl chloride is located in Table 4-2.

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

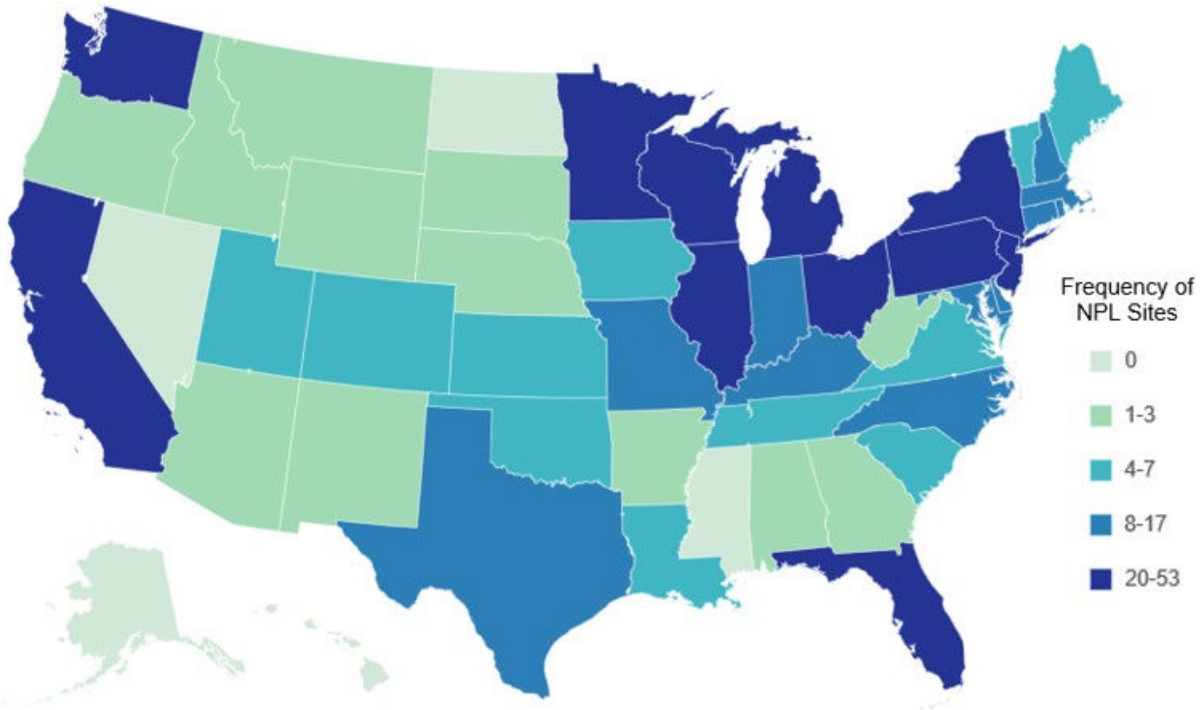
Property	Information	Reference
Molecular weight	62.5	Lewis 1996
Color	Colorless	Budavari 1989
Physical state	Gas	Budavari 1989
Melting point	-153.8°C	Budavari 1989
Boiling point	-13.4°C	Cowfer and Gorensek 2006
Density:		
at -14.2°C	0.969 g/cm^3	Cowfer and Gorensek 2006
at 15°C	0.9195 g/cm^3	Lewis 1996
at 20°C	0.9106 g/cm^3	NIOSH 1986
Vapor density	2.16	Fire 1986
Odor	Sweet	NLM 2021
Odor threshold:		
Water	3.4 ppm	Amoore and Hautala 1983
Air	3,000 ppm	Amoore and Hautala 1983
Solubility:		
Water at 25°C	2,763 mg/L	EPA 1985a
	1,100 mg/L	Cowfer and Gorensek 2006
Organic solvent(s)	Soluble in hydrocarbons, oil, alcohol, chlorinated solvents, and most common organic liquids	Cowfer and Gorensek 2006
Partition coefficients:		
Log K_{ow}	1.38	NIOSH 1986
Log K_{oc}	2.38–2.95	Lu et al. 2011
Vapor pressure:		
at 20°C	2,530 mmHg	Budavari 1989
at 25°C	2,600 mmHg	Lewis 1996
Henry's law constant:		
10.3°C	0.0147 (atm-m^3)/mol	Gossett 1987
17.5°C	0.0193 (atm-m^3)/mol	Gossett 1987
24.8°C	0.0278 (atm-m^3)/mol	Gossett 1987
34.6°C	0.0358 (atm-m^3)/mol	Gossett 1987
Autoignition temperature	472°C	Lewis 1996
Flashpoint	-78°C (closed cup)	Budavari 1989
Flammability limits	3.6–33 volume %	NIOSH 1986
Conversion factors:		
ppm to mg/m^3 in air	1 ppm=2.6 mg/m^3	NIOSH 1990
mg/m^3 to ppm in air	1 mg/m^3=0.38 ppm	NIOSH 1990
Explosive limits	4–22 volume %	Lewis 1996

CHAPTER 5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Vinyl chloride has been identified in at least 593 of the 1,867 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (ATSDR 2019). However, the number of sites in which vinyl chloride has been evaluated is not known. The number of sites in each state is shown in Figure 5-1. Of these sites, 589 are located within the United States, 1 site is located in the Virgin Islands, and 3 sites are located in Puerto Rico (not shown).

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



Source: ATSDR 2019

- The major route of exposure to vinyl chloride is through inhalation. This mostly occurs in the occupational setting but can occur near manufacturing facilities, hazardous waste sites, and natural gas extraction sites, where the air may be contaminated.
- Inhalation of cigarette and cigar smoke can also be an exposure route.
- In air, vinyl chloride will degrade photochemically with a half-life of 1–2 days.

- Vinyl chloride released to water is mostly expected to volatilize into the atmosphere. Small amounts could degrade by photochemical reaction and biodegradation.
- Vinyl chloride released to the soil is expected to volatilize or leach into groundwater.
- Aerobically, vinyl chloride is expected to degrade by 25% in a week and by >99% in 15.4 weeks. The rate of anaerobic degradation is dependent on the components of the media (e.g., increased iron).

5.2 PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

5.2.1 Production

Vinyl chloride was first produced commercially in the 1930s by reacting hydrogen chloride with acetylene. Currently, vinyl chloride is produced commercially by the chlorination of ethylene through one of two processes, direct chlorination or oxychlorination. Direct chlorination reacts ethylene with chlorine to produce 1,2-dichloroethane. Similarly, oxychlorination produces 1,2-dichloroethane, but this is accomplished by reacting ethylene with dry hydrogen chloride and oxygen.

After both processes, the 1,2-dichloroethane is subjected to high pressures (2.5–3.0 megapascals) and temperatures (550–550°C). This causes the 1,2-dichloroethane to undergo pyrolysis, or thermal cracking, which forms the vinyl chloride monomer and hydrogen chloride. The vinyl chloride monomer is then isolated (Cowfer and Magistro 1985). The technical-grade product is available in 99.9% purity (NLM 2021). Efforts are being made to minimize by-product formation (hydrocarbons, chlorinated hydrocarbons, and unreacted material) in 1,2-dichloroethane pyrolysis (Cowfer and Magistro 1985).

Table 5-1 summarizes the facilities in the United States that either manufacture or process vinyl chloride. The Toxic Release Inventory (TRI21 2022) provides the data for Table 5-1 including the maximum amounts of vinyl chloride that are present at these sites and the end uses of vinyl chloride. Table 5-2 lists the 12 reporting facilities that solely manufacture vinyl chloride for commercial purposes and their production capacities (EPA 2021). Because of confidential business information, specific quantities are not available (EPA 2021).

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

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AL	1	100,000	999,999	6
AR	1	1,000	9,999	1, 2, 3, 5, 9, 12
IL	1	1,000,000	9,999,999	6
KY	3	1,000,000	9,999,999	1, 4, 6
LA	8	10,000,000	49,999,999	1, 3, 4, 5, 6, 12, 13
MO	1	1,000	9,999	1, 5, 14
MS	1	10,000,000	49,999,999	6
NC	1	0	99	6, 7, 8, 11
NE	1	1,000	9,999	9, 12
NJ	2	1,000,000	49,999,999	6, 12
NY	1	0	99	12
OH	3	100	9,999	6, 12
TX	12	100	499,999,999	1, 3, 4, 5, 6, 9, 12, 13, 14
UT	1	1,000	9,999	9, 12
WA	1	Not available	Not available	Not available

[a]Post office state abbreviations used.
[b]Amounts on site reported by facilities in each state.
[c]Activities/Uses:

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

Source: TRI21 2022 (Data are from 2021)

Table 5-2. U.S. Production Capacity of Vinyl Chloride

U.S. Producer	Location	Capacity (million pounds per year)
Axiall	Plaquemine, Louisiana	CBI
Axiall	Westlake, Louisiana	CBI
Axiall	Westlake, Calcasieu, Louisiana	1,026
C-K Tech	Plaquemine, Louisiana	CBI
Formosa Plastics	Baton Rouge, Louisiana	1,188
Formosa Plastics	Point Comfort, Texas	1,497
GEON Oxy Vinyl	Laporte, Texas	CBI
Olin Blue Cube	Freeport, Texas	CBI
Oxy Vinyls LP	Deer Park, Texas	CBI
Oxychem Ingleside	San Patricio, Texas	CBI
Westlake Vinyls	Geismar, Louisiana	540
Westlake Vinyls	Calvert City, Kentucky	1,316

Table 5-2. U.S. Production Capacity of Vinyl Chloride

U.S. Producer	Location	Capacity (million pounds per year)
U.S. total capacity: 10,000 - <20,000 million pounds		

CBI = Confidential Business Information

Source: EPA 2021 (data are from 2015)

5.2.2 Import/Export

One facility reported 37,000 pounds imported in 2015, down from 48,700 pounds in 2014 (EPA 2021); no further import data were located. Export volumes for 2004 and 2005 were 2.367 and 1.88 billion pounds, respectively (ICIS 2006). Current export volumes were not located.

5.2.3 Use

Vinyl chloride is an important industrial chemical because of its wide variety of end-use products and the low cost of producing polymers from it. About 99% of the global vinyl chloride capacity is used for the production of PVC and its copolymers (Dreher et al. 2014).

Vinyl chloride has been used in the past as a refrigerant, as an extraction solvent for heat-sensitive materials, and in the production of chloroacetaldehyde and methyl chloroform (IARC 1979). In the United States, limited quantities of vinyl chloride were used as an aerosol propellant and as an ingredient of drug and cosmetic products; however, these practices were banned by the EPA in 1974 (IARC 1979; NLM 2021).

5.2.4 Disposal

Since vinyl chloride has been identified by EPA as a hazardous material, its disposal is regulated under the Federal Resource Conservation and Recovery Act (RCRA) (EPA 1993). The Department of Transportation monitors compliance with RCRA (and therefore disposal) (DOT 1993). The recommended method of disposal is total destruction by incineration.

The temperature of the incinerator must be sufficient to ensure the complete combustion of the vinyl chloride in order to prevent the formation of phosgene. The recommended temperature range for

incineration is 450–1,600°C, with residence times of seconds for gases and liquids, and hours for solids (NLM 2021). If in solution, the vinyl chloride product may need to be adsorbed onto a combustible material prior to incineration. Alternately, vinyl chloride can also be dissolved in a flammable solvent prior to incineration. An acid scrubber should be used in conjunction with the incinerator in order to remove any hydrogen chloride that is produced by the combustion process (NLM 2021).

Vinyl chloride can also be chemically destroyed. This destruction method is used, especially with small quantities. Generally, 1–2 days is sufficient for complete chemical destruction (NLM 2021).

Aqueous byproduct solutions from the production of vinyl chloride are usually steam-stripped. This step removes volatile organic compounds. The remaining solution is then neutralized. Lastly, the solution is treated in an activated sludge system to remove nonvolatile organic compounds (Cowfer and Gorensek 2006).

5.3 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2005). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ ≥10 full-time employees; if their facility is included in Standard Industrial Classification (SIC) Codes 10 (except 1011, 1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and if their facility produces, imports, or processes ≥25,000 pounds of any TRI chemical or otherwise uses >10,000 pounds of a TRI chemical in a calendar year (EPA 2005).

5.3.1 Air

Estimated releases of 428,185 pounds (~194 metric tons) of vinyl chloride to the atmosphere from 38 domestic manufacturing and processing facilities in 2021, accounted for about 99.9% of the estimated

total environmental releases from facilities required to report to the TRI (TRI21 2022). These releases are summarized in Table 5-3.

Table 5-3. Releases to the Environment from Facilities that Produce, Process, or Use Vinyl Chloride[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AL	1	1,820	0	0	0	0	1,820	0	1,820
AR	1	6	0	0	108	0	6	108	114
IL	1	19,115	0	0	21	0	19,115	21	19,135
KY	3	117,526	1	0	0	7	117,526	8	117,534
LA	8	117,553	31	0	1	51	117,584	52	117,636
MO	1	287	0	0	0	0	287	0	287
MS	1	4,779	0	0	0	0	4,779	0	4,779
NC	1	68	0	0	0	0	68	0	68
NE	1	23	0	0	0	2	23	2	25
NJ	2	24,407	10	0	10	0	24,417	10	24,427
NY	1	0	0	0	0	0	0	0	0
OH	3	10	0	0	0	0	10	0	10
TX	12	142,591	8	0	0	88	142,598	88	142,686
UT	1	0	0	0	0	0	0	0	0
WA	1	0	0	0	0	0	0	0	0
Total	38	428,185	49	0	140	148	428,233	289	428,522

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

RF = reporting facilities; UI = underground injection

Source: TRI21 2022 (Data are from 2021)

The major sources of vinyl chloride releases to the environment are believed to be emissions and effluents from plastic industries, primarily vinyl chloride and PVC manufacturers. Worldwide emissions of vinyl chloride into the atmosphere during 1982 totaled approximately 400 million pounds (Hartmans et al. 1985); no updated estimates were located. Another emission source is tobacco smoke, which has been found to contain 5.6–27.3 ng vinyl chloride per cigarette or little cigar (Hoffmann et al. 1976) and as high as 34.8 ng per cigarette from conventional cigarettes utilizing human puffing behavior (Zenzen et al. 2012). The combustion of coal and the incineration of municipal waste can also release small quantities of vinyl chloride to the atmosphere (Dempsey 1993; Miller et al. 1994). Vinyl chloride may be found in groundwater near military installations as a breakdown product of chlorinated solvents (Bove et al. 2014; Ruckart et al. 2013).

EPA's National Emission Inventory (NEI) database contains detailed information about sources that emit criteria air pollutants and their precursors, and hazardous air pollutants (HAPs) for the 50 United States, Washington DC, Puerto Rico, and the U.S. Virgin Islands. In 2011, there were 920,128 pounds of vinyl chloride released to air from 15 different emissions categories, the most prominent being waste disposal and industrial processes, accounting for roughly 30 and 60% of all of the emissions, respectively (EPA 2014a). Over an 11-year emission study within the Greater Houston area, spanning from 2003 to 2013, vinyl chloride was released in an emission event at a high of 6,520 kg in 2005 from Dow Texas Operations Freeport (Luong and Zhang 2017). This event contributed 99% of the emissions for that year. Vinyl chloride detected at hazardous waste sites may not necessarily arise from industrial sources. The bacterial degradation of chlorinated solvents such as trichloroethylene, tetrachloroethylene, and 1,1,1-trichloroethane can produce vinyl chloride as a degradation product, and this may be the origin of vinyl chloride at these sites (Smith and Dragun 1984).

5.3.2 Water

Estimated releases of 49 pounds (~0.02 metric tons) of vinyl chloride to surface water from 38 domestic manufacturing and processing facilities in 2021, accounted for about 0.01% of the estimated total environmental releases from facilities required to report to the TRI21 (TRI21 2022). This estimate includes releases to wastewater treatment and publicly owned treatment works (POTWs) (TRI21 2022). These releases are summarized in Table 5-3.

Vinyl chloride released in wastewater from the plastics industries is expected to volatilize fairly rapidly (on the order of hours to days) into the atmosphere. Anaerobic reductive dehalogenation of trichloroethylene, tetrachloroethylene, and 1,1,1-trichloroethane also releases vinyl chloride into groundwater at hazardous waste sites (Smith and Dragun 1984) or other locations where the proper conditions are found in the subterranean strata. Since vinyl chloride possesses high mobility in soils, it leaches into groundwater from spills, landfills, and industrial sources that may release it to soil (TRI21 2022). According to data collected from the analysis of leachates and monitoring wells at sites where groundwater was contaminated by municipal solid waste landfill leachate, vinyl chloride was present in both the leachates and the groundwater samples (Sabel and Clark 1984).

5.3.3 Soil

Estimated releases of 140 pounds (~0. 06 metric tons) of vinyl chloride to soil from 38 domestic manufacturing and processing facilities in 2021, accounted for about 0.03% of the estimated total environmental releases from facilities required to report to the TRI21 (TRI21 2022). These releases are summarized in Table 5-3.

The bacterial degradation of chlorinated solvents such as trichloroethylene, tetrachloroethylene, and 1,1,1-trichloroethane can produce vinyl chloride as a degradation product, and this may be a significant source of vinyl chloride at hazardous waste sites (Smith and Dragun 1984).

5.4 ENVIRONMENTAL FATE

5.4.1 Transport and Partitioning

Air. Based on a vapor pressure of 2,660 mmHg at 25°C, essentially all vinyl chloride in the atmosphere is expected to exist solely as a gas (Eisenreich et al. 1981; Verschueren 1983). Consequently, removal from the atmosphere by dry deposition is not expected to be an important fate process.

Water. The primary transport process for vinyl chloride from natural water systems is volatilization into the atmosphere. The Henry's law constant of vinyl chloride has been measured as 0.0278 atm-m^3/mol at 24.8°C (Gossett 1987), which suggests that vinyl chloride should partition rapidly to the atmosphere. The half-life for vinyl chloride volatilization from a typical pond, river, and lake has been estimated to be 43.3, 8.7, and 34.7 hours, respectively. These values are based on an experimentally

determined reaeration rate ratio of approximately 2 and assumed oxygen reaeration rates of 0.008, 0.04, and 0.01 per hour for a typical pond, river, and lake, respectively (EPA 1982a).

Predicted half-lives should be considered rough estimates since the presence of various salts in natural water systems may affect the volatility of vinyl chloride significantly (EPA 1979a). Many salts can form complexes with vinyl chloride and increase its water solubility; therefore, the presence of salts in natural waters may significantly influence the amount of vinyl chloride remaining in the water (EPA 1975). The half-life of vinyl chloride in bodies of water is also affected by depth and turbidity.

Sediment and Soil. The relatively high vapor pressure of vinyl chloride indicates that the compound volatilizes quite rapidly from dry soil surfaces (Verschueren 1983). The effective half-life (due to volatilization and degradation) of vinyl chloride incorporated 10 cm deep in dry soil is predicted to be 12 hours (Jury et al. 1984). Vinyl chloride is soluble in water and can therefore leach through the soil and enter groundwater before evaporation can occur (Cowfer and Gorensek 2006).

The soil organic carbon adsorption coefficient (K_{oc}) for vinyl chloride was determined to range from 240 to 890 in seven natural clayey till samples (Lu et al. 2011). These K_{oc} values suggest a low sorption tendency, meaning that this compound would be highly mobile in soil. Thus, vinyl chloride has the potential to leach into groundwater.

Other Media. Vinyl chloride is soluble in most common organic solvents (Cowfer and Gorensek 2006). In situations where organic solvents exist in relatively high concentrations (e.g., landfills, hazardous waste sites), co-solvation of vinyl chloride could reduce its volatility, thus causing it to have greater mobility than indicated by measured K_{oc} values.

Vinyl chloride's small octanol/water partition coefficient (log K_{ow} of 1.23) indicates that the potential for bioconcentration in aquatic organisms is low (EPA 1982a). Using a log K_{ow} of 1.23 and a regression-derived equation (Meylan et al. 1999), the bioconcentration factor (BCF) for vinyl chloride is estimated as 3. Freitag et al. (1985) measured BCFs for vinyl chloride in algae, fish, and activated sludge. The vinyl chloride BCFs for algae, fish, and activated sludge were 40, <10, and 1,100, respectively. The very low value for fish, in comparison to the algae and activated sludge, may suggest a detoxification process in more highly developed organisms such as fish. Lu et al. (1977) examined the bioaccumulation of ^{14}C-vinyl chloride in a closed model aquatic ecosystem over a 3-day period. The high volatility of vinyl

chloride minimized any potential bioaccumulation. The relatively low tissue concentrations found in fish suggest that vinyl chloride is not biomagnified in aquatic food chains to any substantial degree.

5.4.2 Transformation and Degradation

Air. Reaction of gaseous vinyl chloride with photochemically generated hydroxyl radicals is predicted to be the primary degradation mechanism for this compound in the atmosphere (Cox et al. 1974; Howard 1976; Perry et al. 1977). The rate constant for this reaction was measured as 6.96×10^{-12} cm^3/molecule-second (Kwok and Atkinson 1994). This rate constant corresponds to an atmospheric half-life of about 18 hours assuming a hydroxyl radical concentration of 1.5×10^6 molecules/cm^3. Products of this reaction are hydrochloric acid, formaldehyde, formyl chloride, carbon monoxide, carbon dioxide, chloro-acetaldehyde, acetylene, chloroethylene epoxide, chloroacetylchloranil, and water (Müller and Korte 1977; Woldbaek and Klaboe 1978). Under conditions of photochemical smog, the half-life of vinyl chloride would be reduced to a few hours (Carassiti et al. 1977). Reaction with ozone, nitrate radicals, and direct photolysis are less important degradation mechanisms of vinyl chloride in the atmosphere (EPA 1976a, 1985b; Zhang et al. 1983). Vinyl chloride in the gas phase does not absorb light of wavelengths above 220 nm (EPA 1976a). Since atmospheric ozone blocks almost all sunlight with wavelengths <295 nm, direct photolysis is likely to occur very slowly, if at all, in the atmosphere (EPA 1976a).

Water. The primary removal process for vinyl chloride from surface waters is volatilization into the atmosphere. Vinyl chloride in water does not absorb ultraviolet radiation above 218 nm; therefore, direct photolysis in the aquatic environment is expected to occur very slowly, if at all (EPA 1976a). In sunlit surface waters containing photosensitizers, such as humic materials, photodegradation may be more rapid. If so, in some waters, sensitized photodegradation may be an important removal mechanism (EPA 1976a). Vinyl chloride decomposed rapidly when irradiated with ultraviolet light in the presence of acetone, a high energy triplet sensitizer, or hydrogen peroxide, a free radical source (EPA 1976a).

The hydrolytic half-life of vinyl chloride is estimated to be <10 years at 25°C (EPA 1976a). Since the volatilization rate of vinyl chloride is much more rapid than the predicted rate of hydrolysis, hydrolysis is not a significant aquatic fate (EPA 1976a, 1979a). Vinyl chloride is not oxidized chemically by reaction with photochemically generated molecular oxygen in natural water systems (EPA 1976a). Experiments carried out at 20 mg/L vinyl chloride in water saturated with molecular oxygen at elevated temperatures showed that, after 12 hours at 85°C, no degradation of vinyl chloride was observed. At temperatures and

oxygen concentrations in natural waters, therefore, vinyl chloride is not expected to degrade by molecular oxygen at a significant rate (EPA 1976a).

Biodegradation of vinyl chloride in water typically occurs via three important pathways: (1) anaerobic reductive dechlorination producing ethene; (2) anaerobic oxidation to carbon dioxide under iron or manganese reducing conditions; and (3) aerobic ultimate biodegradation to carbon dioxide (SERDP/ESTCP 2012). The degradation of vinyl chloride under anaerobic conditions was studied using iron-enriched aquifer microcosms obtained from a site contaminated with various chlorinated compounds (Smits et al. 2011). Two separate microcosm columns were prepared in which one column was fed solely vinyl chloride while the second column had both vinyl chloride and acetate in the influent. Degradation of vinyl chloride and formation of ethene was noticeable in the vinyl chloride and acetate influent column. This suggests a reductive dechlorination pathway for vinyl chloride degradation; however, ethene was not produced in the column where vinyl chloride was the only substance in the influent, suggesting that oxidation to carbon dioxide was the important degradation pathway in this column.

Vinyl chloride (1 ppm) was rapidly degraded under aerobic conditions in a laboratory study that used soil-water microcosms from aquifer material without the addition of other nutrients, such as nitrogen or phosphorus (Davis and Carpenter 1990). About 25% of the vinyl chloride was degraded after 1 week and >99% was degraded after 108 days. Sixty-five percent of labeled vinyl chloride was recovered as $^{14}CO_2$ after 108 days, demonstrating the extent of the mineralization.

Rhodococcus sp. strain SM-1, a member of the order *Actinomycetales*, obtained from a trichloroethylene-degrading consortium was found to degrade vinyl chloride to CO_2 by using propane as an energy source during growth experiments or cell suspension experiments (Phelps et al. 1991). Vinyl chloride concentrations decreased by more than 90%; growth cultures and cell suspensions incorporated about 10% of the transformed vinyl chloride into biomass (Phelps et al. 1991). *Mycobacterium vaccae* JOB5 degraded 100% of vinyl chloride in a 2-hour incubation (Wackett et al. 1989).

Degradation of vinyl chloride generally occurs slowly in anaerobic groundwater and sediment; however, under methanogenic or Fe(III)-reducing conditions, anaerobic degradation occurs more rapidly. Vinyl chloride was mineralized approximately 34% in 84 hours in anaerobic aquifer microcosms supplemented with Fe(III) and held under Fe(III)-reducing conditions (Bradley and Chapelle 1996).

Sediment and Soil. Most vinyl chloride present on soil surfaces will volatilize to the atmosphere. Vinyl chloride is also mobile in soil and susceptible to leaching (Lyman et al. 1982). Because vinyl chloride is soluble in organic solvents (Cowfer and Gorensek 2006), the presence of other organic solvents, such as those found at hazardous waste sites, may affect the mobility of the substance in the soil. Photodegradation on the surface of soils is possible since sensitized photodegradation in water occurs; however, this is not expected to be an important environmental fate process for vinyl chloride in most soils and sediment.

Several laboratory studies indicated that both aerobic and anaerobic biodegradation of vinyl chloride can occur in soils and aquifer materials via a number of mechanisms (Barrio-Lage et al. 1990; Castro et al. 1992a, 1992b; Davis and Carpenter 1990), although these degradation processes were generally slow. Nelson and Jewell (1993) investigated methanotrophic degradation of vinyl chloride using a laboratory-scale, methanotrophic, attached-film, expanded-bed bioreactor. The study authors found that this technique is an efficient way to degrade vinyl chloride, with the removal efficiency >90%. Under methanotrophic conditions, vinyl chloride was mineralized between 5 and 44% over 37 days using creek bed sediment microcosms obtained from a naval station near Jacksonville, Florida (Bradley and Chapelle 1997). Slightly higher mineralization rates were observed under Fe(III)-reducing conditions. With vinyl chloride-oxidizing transfer cultures and microcosms derived from authentic site materials, vinyl chloride oxidation was sustained at what can be considered anaerobic conditions with dissolved oxygen concentrations below 0.02 and 0.1 mg/L, respectively (Gossett 2010). Vinyl chloride was degraded approximately 50 and 100% in 25 and 19 days under these respective conditions (Gossett 2010).

5.5 LEVELS IN THE ENVIRONMENT

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

An overview summary of the range of concentrations detected in environmental media is presented in Table 5-4.

Table 5-4. Vinyl Chloride Detected in Samples Collected Throughout the United States from 2011 to 2021

Type	Number of samples	Number of positive	Concentration range
Ambient air	58	0	0.039–0.052 ppb (detection limit)
Indoor air	4	0	0.039–0.052 ppb (detection limit)
Groundwater[a]	6,838	254	0.2–7,380 ppb; 0.1–20 ppb (lower quantification limit)
Surface water[a]	1,358	0	<0.02–5.0 ppb (lower quantification limit)
Wastewater	2	0	0.1 ppb (lower quantification limit)
Leachate	48	0	0.5–1.0 ppb (lower quantification limit)
Sediment	306	1	1,300 ppb; 0.5–1,000 ppb (lower quantification limit)
Soil	45	4	2.4–9.6 ppb (values are below reporting limit)

[a]Samples reported are from 2017 to 2021.

Source: WQP 2021

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

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

Medium	Median[a]	Geometric mean[a]	Geometric standard deviation[a]	Number of quantitative measurements	NPL sites
Water (ppb)	34	55.9	17.1	505	266
Soil (ppb)	733	962	34.1	45	38
Air (ppbv)	1.6 (4.09 µg/m^3)	3.25 (8.31 µg/m^3)	26.4 (67.5 µg/m^3)	56	37

[a]Concentrations found in ATSDR site documents from 1981 to 2019 for 1,867 NPL sites (ATSDR 2019). Maximum concentrations were abstracted for types of environmental media for which exposure is likely. Pathways do not necessarily involve exposure or levels of concern.

5.5.1 Air

Air in rural/remote and urban/suburban areas of the United States typically contains very low or no detectable amounts of vinyl chloride (EPA 1982b; Grimsrud and Rasmussen 1975a, 1975b; Harkov et al. 1984; Pratt et al. 2000; Stephens et al. 1986; Wallace et al. 1984). In a background air toxics concentration study for North America conducted in 2001–2002, vinyl chloride concentrations were estimated to be <0.02 µg/m^3 (<0.0075 ppb) (McCarthy et al. 2006). In a residential region of Southwest

Memphis surrounded by fossil fuel burning, steel, refining, and food processing industries, vinyl chloride was found in 38% of 103 samples at a mean concentration of 0.02 μg/m^3 (Jia and Foran 2013).

Concentrations in air samples collected in 2000–2017 at Denton Airport South, Texas, were reported as 0.02–0.08 parts per billion carbon (ppbC; 0.03–0.10 μg/m^3) in 19 of 1,085 samples (Lim and John 2020). This area has seen an increase in unconventional energy production on the Barnett Shale (Lim and John 2020). Vinyl chloride was not detected (detection limit 0.1–0.14 μg/m^3) in 58 ambient air or 4 indoor air data points compiled for 2011–2021 for from Palermo Wellfield Superfund Site, as reported in the EPA STOrage and RETrieval (STORET) database (WQP 2021).

Vinyl chloride levels in atmospheric samples collected across the United States in 2013 are available from the Air Quality System (AQS), which is the EPA's repository of ambient air quality data that has >5,000 active monitors nationwide (EPA 2014b). The 24-hour maximum concentrations were 0.005–2.37 ppbv (0.01–6.06 μg/m^3) at sites where vinyl chloride was detected.

Vinyl chloride concentrations were reported at 0.12–12 μg/m^3 (0.047–4.697 ppb) for flowback pits used to store natural gas drilling hydraulic fracturing waste (Bloomdahl et al. 2014).

5.5.2 Water

Vinyl chloride has been detected at varying concentrations in surface water, groundwater, and drinking water throughout the United States (Table 5-4). Vinyl chloride was not reported above the lower quantification limit of 0.02–5.0 μg/L (ppb) in approximately 1,360 ambient surface water samples as reflected in data points compiled for 2017–2021 from EPA's STORET and National Water Information System (NWIS) databases (WQP 2021).

During an assessment of groundwater in the United States from 1985 to 2001, vinyl chloride was detected at a median concentration of 1.1 μg/L (positive detections only) in samples obtained from >50 of the nation's most important river basins and aquifers (USGS 2006). It was also detected in 0.083% of 2,401 samples of domestic wells at a level of 0.20 μg/L and in 0.042% of samples at a level of 1 μg/L. Vinyl chloride was not detected in any samples at assessment levels >5 μg/L. The median level of vinyl chloride in these domestic wells (positive detections only) was 0.74 μg/L (USGS 2006).

Vinyl chloride was detected in 6 out of 518 monitoring wells sampled in 19 urban land-use watersheds in the United States during a U.S. Geological Survey (USGS) analysis of groundwater contaminants conducted from 1996 to 2002 (Squillace et al. 2004). The median level was reported as 0.2 µg/L and the maximum concentration was 8.1 µg/L. Vinyl chloride was found in 1.12% of 448 groundwater supply wells monitored from 2002 to 2009 across the United States at an assessment level of 0.05 µg/L and in 0.89% of samples at an assessment level of 0.10 µg/L (USGS 2014). Vinyl chloride was detected in 254 of 6,838 (3.7%) groundwater data points compiled for 2017 to 2021 from EPA STORET and NWIS databases at concentrations of 0.2 to 7,380 µg/L (WQP 2021). This includes data from hazardous waste sites.

Vinyl chloride was detected at levels ranging from 11 to 23 ng/L in water samples collected from 15 PVC or chlorinated polyvinyl chloride (CPVC)-utilizing homes located in Ithaca, New York (Walter et al. 2011). Most of the samples obtained from the homes tested negative for vinyl chloride, but each of the positive detections occurred from homes using municipal (chlorinated) water and CPVC type pipe. During an assessment of drinking water sources from 2002 to 2010, vinyl chloride was not detected in 300 samples from 20 surface water sites across the United States (USGS 2014).

In a study of three landfills located in Orange County, Florida, vinyl chloride was detected in water samples obtained at four of nine wells with average concentrations ranging from 2.0 to 26.5 µg/L (Hallbourg et al. 1992). Vinyl chloride levels in 50 domestic wells located distal and proximal to shale-gas wells in upland areas of Marcellus Shale region of New York and Pennsylvania were <0.06 µg/L (ppb) (McMahon et al. 2019).

5.5.3 Sediment and Soil

Data (Table 5-4) from the EPA Great Lakes National Program reported vinyl chloride in one (1,300 ppb) of 212 sediment samples collected in 2011–2021 at a level above the quantification or reporting limit of 1.2–7,300 ppb (WQP 2021). Vinyl chloride was not detected (detection limit not reported) in sediment samples at any other sites reported in the EPA STORET database. Vinyl chloride was detected in 4 of 45 soil data points reported for 2011–2021 and included in the EPA STORET database, but not at levels above the lower reporting level of 9.4–38 ppb (WQP 2021).

5.5.4 Other Media

In the past, vinyl chloride was detected in various foods and bottled drinking water samples as a result of migration from PVC food wrappings and containers (Benfenati et al. 1991; Gilbert et al. 1980). The Food and Drug Administration (FDA) regulates the use of PVC polymers in food packaging materials and the amount of residual monomer in polymers and as a result, there has been a significant reduction in the reported levels of vinyl chloride in food samples based on data collected since the early 1970s (WHO 1999). Since the late 1970s, modifications to the vinyl chloride and PVC manufacturing and production processes have greatly reduced the amount of residual vinyl chloride monomer in food packaging and other PVC-related items.

To determine whether the residual vinyl chloride levels in PVC containing food packages in current use are <10 ppb, a survey and analysis of PVC-containing food packages were conducted (McNeal et al. 2003). The results showed that vinyl chloride levels found in the packages ranged from none detected (<1 ppb) to about 275 ppb. The package containing 275 ppb residual vinyl chloride was not a food contact material (McNeal et al. 2003).

Dietary exposure to vinyl chloride from PVC packages used for food was estimated by several agencies and based upon estimated average intakes in the United Kingdom and the United States, an exposure of <0.0004 μg/kg/day was estimated for the late 1970s and early 1980s (WHO 1999). Because vinyl chloride levels in food and drinking water are now well below detection limits, exposure levels from ingestion are expected to be even lower.

During an EPA study, detectable levels of vinyl chloride were found in indoor air samples taken from two of seven new 1975 model cars. Levels of vinyl chloride in indoor air in the two cars ranged from 0.4 to 1.2 ppm (EPA 1976b). Ventilation of the car interiors led to the dissipation of vinyl chloride. The cars involved in the study had a high ratio of plastic to interior volume and were expected to provide worst-case concentrations for vinyl chloride in interior car air (EPA 1976b). Because of the limited nature of these data and the fact that this study is somewhat dated, no conclusions can be drawn regarding levels of vinyl chloride monomer in interior air of cars currently being produced.

Vinyl chloride has been detected in tobacco smoke. Cigarette smoke and smoke from small cigars was found to contain 5.6–27.3 ng vinyl chloride per cigarette (Hoffmann et al. 1976). The study authors suggested that the inorganic chloride concentrations in the tobacco determine the amount of vinyl chloride

formed upon combustion of tobacco and released with the smoke (Hoffmann et al. 1976). Vinyl chloride was detected in cigarette smoke at levels ranging from 6.31 to 8.04 ng per cigarette for Electrically Heated Cigarette Smoking Systems (EHCSS) and <12.4–18.0 ng per cigarette for conventional lit-end cigarettes in a test using three versions of an EHCSS and four different brands of conventional cigarettes under International Organization for Standardization smoking conditions (Zenzen et al. 2012). When additional smoking regiments were utilized, smoke from conventional cigarettes was found to contain vinyl chloride up to 34.8 ng per cigarette.

5.6 GENERAL POPULATION EXPOSURE

A review of vapor intrusion data from 148 ATSDR public health assessments completed between 1994 and 2009 identified 42 sites with detected concentrations of vinyl chloride in groundwater, soil gas, or air (Burk and Zarus 2013). Indoor air was sampled at 13 of the sites, with vinyl chloride detected at levels ranging from 0.021 to 35 µg/m^3, which are all below ATSDR's inhalation MRLs (50–1,300 mg/m^3). Vinyl chloride was detected in groundwater at 31 of the sites ranging from 0.148 to 27,000 µg/L, and 14 of the sites had vinyl chloride groundwater concentrations at levels of concern from noncancer effects from vapor intrusion. Twelve of the 14 sites with groundwater concentrations at levels of concern from noncancer effects from vapor intrusion did not report measured indoor air concentrations for vinyl chloride.

Inhalation of ambient or workplace air containing vinyl chloride is the most likely route of exposure for the general population. Typical values for the average daily intake of vinyl chloride by inhalation in urban/suburban and rural/remote areas not near emission sources are very small, since only trace levels of vinyl chloride are usually found in ambient air. Assuming that the average adult intake of air is 20 m^3/day, the average daily intake of vinyl chloride by people living in the vicinity of emission sources has been estimated to range from trace amounts to 2,100 µg (EPA 1979b, 1982b; Gordon and Meeks 1977).

The majority of drinking water supplies in the United States do not contain detectable levels of vinyl chloride (EPA 1982b; Westrick et al. 1984). Based on this conclusion, it is estimated that the average daily intake of vinyl chloride by ingestion of drinking water for most people in the United States is below the limit of detection (0.028 µg/kg/day [EPA 1982b]). Estimates provided by EPA (1985a) indicate that 0.9% of the U.S. population is exposed to levels of vinyl chloride in drinking water ≥1 µg/L, and 0.3% of the population is exposed to levels >5 µg/L while the EPA maximum contaminant level (MCL) is 2 µg/L.

Individuals located near or downwind of production facilities, hazardous waste disposal sites, and landfills may be exposed to atmospheric levels of vinyl chloride higher than ambient background levels. Concentrations around <5–30.7 μg/m^3 (<0.002–0.012 ppm) were measured in the air above some landfills (Baker and MacKay 1985; Stephens et al. 1986). Homes near one hazardous waste site in southern California were found to contain levels as high as 1,040 μg/m^3 (0.4 ppm) of vinyl chloride (Stephens et al. 1986) and homes near another site contained levels between 2.6 and 23.4 μg/m^3 (0.001–0.009 ppm) (Miller and Beizer 1985). These concentrations are several times greater than ambient air levels that are generally <0.02 μg/m^3 (McCarthy et al. 2006). Individuals living near hazardous waste sites and landfills may also be exposed to vinyl chloride in their drinking water. Workers involved in the production or use of vinyl chloride are likely to be exposed to levels greater than the levels that the general public is exposed to.

Cigarette smoke and smoke from small cigars have been found to contain vinyl chloride at levels of 5.6–27 ng per cigarette (Hoffmann et al. 1976) and as high as 34.8 ng per cigarette from conventional cigarettes utilizing human puffing behavior (Zenzen et al. 2012). Therefore, people who smoke may be potentially exposed to higher levels of vinyl chloride than nonsmokers.

Children are likely to be exposed to vinyl chloride via the same pathways that affect non-occupationally exposed adults; namely inhalation of ambient air and ingestion of food items or drinking water that may contain low levels of vinyl chloride. Children's plastic products such as bath toys, squeeze toys, and dolls are often made from PVC. Chewing or sucking on these toys has the potential to release any unpolymerized vinyl chloride from the object; however, no quantitative data exist regarding this potential exposure route and it is unlikely that there are significant levels of vinyl chloride in PVC-based toys. No body burden studies that quantitatively or qualitatively identified vinyl chloride in children were located.

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

The National Occupational Exposure Survey (NOES) conducted by the National Institute for Occupational Safety and Health (NIOSH) from 1981 to 1983 estimated that 81,314 workers employed at 3,711 plant sites were potentially exposed to vinyl chloride in the United States (NOES 1990). The NOES database does not contain information on the frequency, concentration, or duration of exposure; the survey provides only estimates of workers potentially exposed to chemicals in the workplace. Employees involved in the handling and processing of PVC resins are exposed to lower levels of vinyl

chloride than employees at vinyl chloride and PVC manufacturing facilities since finished products contain only minute quantities of vinyl chloride present as residual monomer.

Exposure is believed to occur primarily through inhalation with some minor absorption through the skin (Hefner et al. 1975a). Upon exposure to 800 or 7,000 ppm of vinyl chloride vapor over a 2–2.5-hour period, 0.023–0.031% was absorbed dermally by monkeys (Hefner et al. 1975a). The authors concluded that significant percutaneous absorption is not likely to occur at relatively low concentrations (1–5 ppm) that might be encountered in the workplace.

Workers who are involved in welding applications that use PVC pipes or other PVC materials may be exposed to higher levels of vinyl chloride from subsequent fumes. Airborne vinyl chloride levels of less than the detection limit of 0.05 ppm (0.13 mg/m^3) to 0.1 ppm (0.26 mg/m^3) were observed during the thermal welding of PVC pipes (Williamson and Kavanagh 1987). The exposure concentration of vinyl chloride for employees working near flowback pits in the Marcellus Shale natural gas drilling sites was determined to be 0.028–2.8 $\mu g/m^3$ (0.011–1.096 ppb) (Bloomdahl et al. 2014).

In the United States, vinyl chloride is an Occupational Safety and Health Administration (OSHA) regulated substance. Current OSHA regulations impose a permissible exposure limit (PEL) of 1 ppm (2.6 mg/m^3) averaged over an 8-hour period or a short-term exposure of no more than 5 ppm over a 15-minute period (Cowfer and Gorensek 2006). Where concentrations cannot be lowered below the PEL of 1 ppm, employers must create an area with controlled access and a respirator program conforming to OSHA standards.

CHAPTER 6. ADEQUACY OF THE DATABASE

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

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

6.1 INFORMATION ON HEALTH EFFECTS

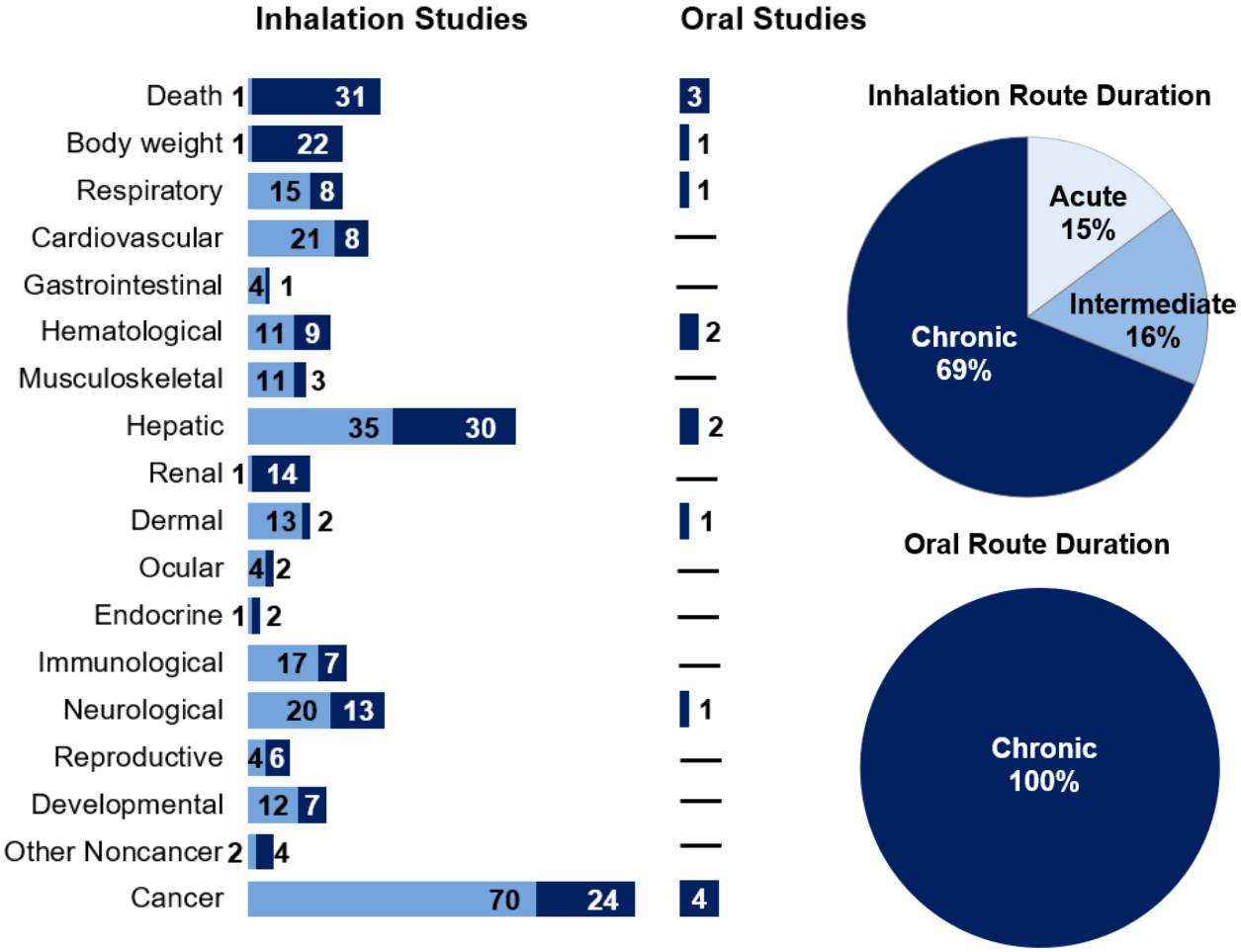
Studies evaluating the health effects of inhalation, oral, and dermal exposure of humans and animals to vinyl chloride that are discussed in Chapter 2 are summarized in Figure 6-1. The purpose of this figure is to illustrate the information concerning the health effects of vinyl chloride. The number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

6.2 IDENTIFICATION OF DATA NEEDS

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

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

Cancer, hepatic, and neurological effects were the most studied endpoints
The majority of the studies examined inhalation exposure in **humans** (versus **animals**)



*Includes studies discussed in Chapter 2; the number of studies include those finding no effect. No dermal studies in humans or animals were located. Most studies examined multiple endpoints.

Acute-Duration MRLs. The inhalation database is adequate to derive an acute-duration inhalation MRL. The oral database is inadequate to derive an acute-duration oral MRL (no acute oral studies are available). Acute oral studies providing data at low doses are needed.

Intermediate-Duration MRLs. The inhalation database is adequate to derive an intermediate-duration inhalation MRL. The oral database is inadequate to derive an intermediate-duration oral MRL (no intermediate-duration oral studies were available). Intermediate-duration oral studies providing data at low doses are needed.

Chronic-Duration MRLs. The inhalation database is inadequate to derive a chronic-duration inhalation MRL as data for the most likely sensitive effect (hepatic) was not reported for noncancer effects in chronic studies. Chronic inhalation studies providing data on noncancer liver effects at low doses are needed. The oral database is adequate to derive a chronic chronic-duration MRL.

Health Effects. Identification of data needs for health effects in animal studies is limited to targets included in the systematic review.

Hepatic Toxicity. Hepatic effects are fairly well studied in humans. Liver effects in animals have been characterized in acute- and intermediate-duration inhalation studies and chronic oral studies. Data on potential noncancer hepatic effects following chronic-duration inhalation exposure and acute- and intermediate-duration oral exposure may be helpful.

Immunotoxicity. Studies of workers occupationally exposed to vinyl chloride suggest that an autoimmune-like syndrome may develop. Immunotoxicity studies in animals that are known to have a propensity for developing autoimmune diseases may be useful in further evaluating this syndrome.

Neurotoxicity. Vinyl chloride is a central nervous system depressant following brief high-level inhalation exposures in humans. Limited animal studies found degenerative effects in central nervous system tissue following chronic inhalation exposure to high levels of vinyl chloride. A study examining the effects of a range of lower doses would be informative. In addition, studies present suggestive evidence that vinyl chloride may also produce peripheral nerve damage in humans exposed chronically via inhalation. Animal studies examining histopathological and electrophysiological endpoints in peripheral nerves would be helpful for assessing what doses

may be associated with this effect. Epidemiological studies examining exposed populations for subclinical peripheral nerve damage would also be helpful.

Developmental Toxicity. Older epidemiological studies that addressed developmental toxicity in offspring of vinyl chloride workers have limitations. A few recent case-control studies evaluated the association between potential developmental effects and exposure to multiple compounds in air and drinking water during pregnancy; these found no effects. Additional, multiple- and low-dose concentration exposures in animal studies may help to further elucidate potential developmental effects and whether a dose-response exists. There are no developmental studies for oral exposures. Because of this deficiency, oral studies examining a range of developmental end points would be useful in assessing the possibility of these effects in humans.

Epidemiology and Human Dosimetry Studies. Virtually all of the data on effects in humans following inhalation exposure to vinyl chloride come from epidemiological studies of workers exposed during the production of PVC. Many of these studies are limited by the absence of information on individual exposure levels. In North America and Western Europe, only limited numbers of females have been studied. For the most part, studies examining the carcinogenic potential of vinyl chloride are adequate to distinguish an increased incidence of the rare cancer, angiosarcoma. However, many studies used cohorts that were too small to detect increases in other types of cancer (respiratory, central nervous system, lymphatic, or hematopoietic). Epidemiological studies designed to investigate reproductive and developmental effects of vinyl chloride have not been useful, in part because of a poor choice of statistical analysis, inadequate controls, lack of effects due to current low levels of exposure, or failure to account for nutritional status and exposures to other chemicals. Additional cohort studies of these end points would be useful for examining these effects in humans.

Biomarkers of Exposure and Effect. Vinyl chloride measured in expired air is an adequate indicator of recent, moderate-to-high-level exposures. However, for low-level exposures or exposures that occur over 1–2 hours prior to the time of measurement, this biomarker is not useful. Thiodiglycolic acid, a major urinary metabolite of vinyl chloride, has been used to monitor workers occupationally exposed to vinyl chloride; however, this biomarker is rapidly excreted and not specific for vinyl chloride; because it may also be produced as a result of the metabolism of 1,1-dichloroethene, ethylene oxide, or 2,2-dichloroethylether. The DNA adducts 1,N^6-ethenoadenosine and 3,N^4-ethenocytidine, remain in the body longer than free vinyl chloride or thiodiglycolic acid; however, these adducts may also result from exposure to other compounds (e.g., vinyl bromide, ethyl carbamate, acrylonitrile, 2-cyanoethylene,

1,2-dichloroethane). Studies attempting to identify a metabolite more specific to vinyl chloride may be helpful in developing a biomarker suitable for medical surveillance, thereby useful for early detection and initiation of possible treatment.

Vinyl chloride-induced genetic alterations have been identified in the Ki-*ras* oncogene and the p53 tumor suppressor gene. Oncoproteins and p53 antibodies have been detected in the serum of cancer patients with angiosarcoma. Statistical analyses suggest a relationship between vinyl chloride exposure and the presence of these serum biomarkers. Further investigation into the ability of these assays to predict individuals at increased risk for developing angiosarcoma of the liver would be useful. Further work identifying the correlation between specific DNA adducts and genotoxicity would also be useful.

Absorption, Distribution, Metabolism, and Excretion. There are few data on humans for all toxicokinetic parameters across all exposure routes. There are a number of animal studies describing the absorption, distribution, metabolism, and excretion of vinyl chloride administered via the oral route and the inhalation route but few describing the toxicokinetics of vinyl chloride administered via the dermal route. No information is available regarding dermal absorption of vinyl chloride from liquid or solid media (i.e., water, soil). Dermal exposure from these media is expected to be minimal; however, a study confirming this assumption would be useful. Furthermore, the intermediary metabolites of vinyl chloride appear to be responsible for many of the toxic effects observed. Therefore, information regarding differences in the metabolic pattern according to gender, age, nutritional status, and species and correlations to differences in health effects would also be useful.

Comparative Toxicokinetics. The absorption, distribution, metabolism, and excretion of vinyl chloride have been studied in animals but information on toxicokinetics in humans is extremely limited. Human and animal data indicate that similar target organs (liver, central nervous system) for the toxic effects of vinyl chloride exist, suggesting some similarities of kinetics. Limited information is available regarding interspecies differences in kinetics. Most toxicokinetic studies have been conducted using rats, but one study in primates indicates that metabolism may saturate at lower concentrations in primates than rats. This could suggest a lower saturation point in humans also. Modeling studies might continue to provide information on the toxicokinetics of vinyl chloride in humans.

Children's Susceptibility. Data needs relating to prenatal exposure and developmental effects are discussed in the Developmental Toxicity subsection above. Carcinogenicity studies with animals suggest that younger animals may be more sensitive to the toxicity and carcinogenicity of vinyl chloride than

mature animals. Further mechanistic research may be useful in establishing the mechanism of early life stage sensitivity in laboratory animals and determining whether it is anticipated to be relevant to humans. No studies were located that specifically address the toxicokinetics of vinyl chloride in children; however, the toxicokinetic behavior of vinyl chloride in children is expected to be similar to that in adults. Further information on the toxicokinetics and toxicodynamics of vinyl chloride and metabolites during pregnancy, lactation, and early childhood would be valuable.

Physical and Chemical Properties. The physical and chemical properties of vinyl chloride are sufficiently well characterized to permit estimation of its environmental fate (Amoore and Hautala 1983; Cowfer and Gorensek 2006; EPA 1985a; Fire 1986; NLM 2021; IARC 1979; Lewis 1996; Lyman et al. 1982).

Production, Import/Export, Use, Release, and Disposal. Vinyl chloride is released primarily to the atmosphere via emissions from vinyl chloride and PVC manufacturing facilities (Hartmans et al. 1985; SRI 1990a, 1990b, 1993, 1994; TRI21 2022). The risk of exposure to vinyl chloride is highest for workers in the plastics industry and populations living near industrial areas or hazardous waste sites. Production, use, and manufacturing methods are well described in the literature (Cowfer and Magistro 1985; NLM 2021; IARC 1979; SRI 1990a, 1990b, 1993, 1994; TRI21 2022; USITC 1994). More current information on releases and disposal methods might assist in estimating potential exposures to vinyl chloride, particularly for populations living near hazardous waste sites.

Environmental Fate. Vinyl chloride primarily partitions to the air where it is degraded relatively quickly by photochemically produced hydroxyl radicals (Kwok and Atkinson 1994). It is removed from surface water and soils mainly by volatilization and photodegradation (EPA 1976a). Biodegradation and hydrolysis also occur (Barrio-Lage et al. 1990; Castro et al. 1992a, 1992b; Davis and Carpenter 1990; EPA 1976a; Gossett 2010), but these reactions are generally slow as compared to the volatilization rate. More information regarding the transformation and degradation in soil and water would be helpful for defining the potential pathways for human exposure.

Bioavailability from Environmental Media. Vinyl chloride can be absorbed following inhalation (Bolt et al. 1977; Krajewski et al. 1980; Withey 1976), oral (Feron et al. 1981; Watanabe et al. 1976a; Withey 1976), and to a much lesser extent, dermal exposure (Hefner et al. 1975a). These routes of exposure may be of concern to humans because of the potential for vinyl chloride to contaminate air (Bloomdahl et al. 2014; Gordon and Meeks 1977; Jia and Foran 2013; Lim and John 2020; McCarthy et

al. 2006; Stephens et al. 1986), water (McMahon et al. 2019; Squillace et al. 2004; USGS 2006, 2014; Walter et al. 2011), and food (Gilbert et al. 1980; McNeal et al. 2003). Information regarding the bioavailability from ingestion and dermal contact with contaminated soils would be helpful, particularly for populations living near hazardous waste sites, although vinyl chloride is not believed to be considerably absorbed through skin.

Food Chain Bioaccumulation. Vinyl chloride can bioconcentrate to a limited extent in aquatic organisms (EPA 1982a; Freitag et al. 1985). Biomagnification of vinyl chloride in terrestrial and aquatic food chains does not appear to be important because of its high volatility and the fact that it is readily metabolized by higher-trophic-level organisms (Freitag et al. 1985; Lu et al. 1977). No data were located regarding biomagnification in terrestrial food chains.

Exposure Levels in Environmental Media. Vinyl chloride has been detected in air, water, sediment, soil, cigarette smoke, and food (references in Section 5.5). Site-specific data on concentrations of vinyl chloride in air, soil, and water would be helpful in estimating the risk of exposure for populations living in the vicinity of hazardous waste sites. Current data on the extent of release (if any) of vinyl chloride from PVC pipes and from car interiors are also needed to estimate the risk of exposure of the general population.

Exposure Levels in Humans. Vinyl chloride has been detected in exhaled breath of humans (Baretta et al. 1969; Conkle et al. 1975), but no other body burden studies are available. More information on exposure levels for populations living in the vicinity of hazardous waste sites would be helpful. This information is necessary for assessing the need to conduct health studies on these populations. It is noted that it is difficult to directly analyze for vinyl chloride in humans, which may limit the practicality of conducting these tests.

Exposures of Children. No data exist regarding the levels of vinyl chloride in children. Children are exposed to vinyl chloride by the same pathways that affect adults; inhalation of ambient air and the ingestion of foods or drinking water. It would be useful to determine if there exists any free unpolymerized vinyl chloride that can be extracted from PVC children's toys.

6.3 ONGOING STUDIES

There are several ongoing studies evaluating the potential adverse effects of vinyl chloride exposure in humans and laboratory animals, as well as underlying mechanisms of toxicity (Table 6-1).

Table 6-1. Ongoing Studies on Vinyl Chloride

Investigator	Affiliation	Research description	Sponsor
Human, animal, and mechanistic research			
Matthew C. Cave	University of Louisville	Collaborative research program, the Environmental Liver Disease Revolutionizing Innovative, Visionary Environmental Health Research Program (ELD-RIVER)	NIEHS
Human studies			
Craig J. McClain	University of Louisville	Environmental exposure and cardiometabolic disease	NIEHS
Animal toxicity studies (some with associated mechanistic studies)			
Juliane I. Beier	University of Pittsburgh	Vinyl chloride-induced changes to the epitranscriptome: interaction with diet	NIEHS
Sanjay Srivastava	University of Louisville	Molecular and cellular mechanisms of cardiometabolic toxicity of VOCs	NIEHS
Mechanistic studies			
Yuan Liu	Florida International University	Trinucleotide repeat instability via DNA damage and repair	NIEHS

DNA = deoxyribonucleic acid; NIEHS = National Institute of Environmental Health Sciences; VOC = volatile organic compound

Source: National Institute of Health (NIH) RePORTER 2021

CHAPTER 7. REGULATIONS AND GUIDELINES

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

ATSDR develops MRLs, which are substance-specific guidelines intended to serve as screening levels by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites. See Section 1-3 and Appendix A for detailed information on the MRLs for vinyl chloride.

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

Agency	Description	Information	Reference
	Air		
EPA	RfC	$1x10^{-1}$ mg/m^3 (0.04 ppm)	EPA 2000
WHO	Indoor air quality guidelines	No data	WHO 2010
	Ambient air quality guidelines		WHO 2000
	10^{-6} Cancer risk	1 µg/m^3	
	Water & Food		
EPA	Drinking water standards and health advisories		EPA 2018a
	1-Day health advisory (10-kg child)	3 mg/L	
	10-Day health advisory (10-kg child)	3 mg/L	
	DWEL	0.1 mg/L	
	10^{-4} Cancer risk	0.002 mg/L	
	National primary drinking water regulations		EPA 2009
	MCL	0.002 mg/L	
	PHG	0 mg/L	
	RfD	$3x10^{-3}$ mg/kg/day	EPA 2000
WHO	Drinking water quality guidelines	0.0003 mg/L	WHO 2017
FDA	Substances Added to Food[a]	Vinyl chloride monomer not listed	FDA 2022
	Allowable level in bottled water	0.002 mg/L	FDA 2017
	Cancer		
HHS	Carcinogenicity classification	Known to be a human carcinogen	NTP 2016

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

Agency	Description	Information	Reference
EPA	Carcinogenicity classification	Known/likely human carcinogen	EPA 2000
	Oral slope factor (continuous lifetime exposure during adulthood)	$7.2x10^{-1}$ per mg/kg/day	
	Oral slope factor (continuous lifetime exposure from birth)	1.4 per mg/kg/day	
IARC	Carcinogenicity classification	Group 1[b]	IARC 2012
	Occupational		
OSHA	PEL (8-hour TWA) for general industry, shipyards, and construction	1 ppm	OSHA 2021a, 2021b, 2021c
	Ceiling PEL (15-minute TWA) for general industry, shipyards, and construction	5 ppm	
NIOSH	REL (up to 10-hour TWA)	No data[c]	NIOSH 2019
	Emergency Criteria		
EPA	AEGLs-air		EPA 2018b
	AEGL 1[d]		
	10-minute	450 ppm	
	30-minute	310 ppm	
	60-minute	250 ppm	
	4-hour	140 ppm	
	8-hour	70 ppm	
	AEGL 2[d]		
	10-minute	2,800 ppm	
	30-minute	1,600 ppm	
	60-minute	1,200 ppm	
	4-hour	820 ppm	
	8-hour	820 ppm	
	AEGL 3[d]		
	10-minute	12,000 ppm[e]	
	30-minute	6,800 ppm[e]	
	60-minute	4,800 ppm[e]	
	4-hour	3,400 ppm	
	8-hour	3,400 ppm	

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

Agency	Description	Information	Reference
DOE	PACs-air		DOE 2018a
	PAC-1[f]	250 ppm	
	PAC-2[f]	1,200 ppm	
	PAC-3[f]	4,800 ppm	

[a]The Substances Added to Food inventory replaces EAFUS and contains the following types of ingredients: food and color additives listed in FDA regulations, flavoring substances evaluated by FEMA or JECFA, GRAS substances listed in FDA regulations, substances approved for specific uses in food prior to September 6, 1958, substances that are listed in FDA regulations as prohibited from use in food, delisted color additives, and some substances "no longer FEMA GRAS".
[b]Group 1: carcinogenic to humans.
[c]Potential occupational carcinogen.
[d]Definitions of AEGL terminology are available from EPA (2018c).
[e]Greater than or equal to 10% of the Lower Explosion Limit range, 38,000–293,000 ppm. Safety considerations against the hazard of explosion must be taken into account.
[f]Definitions of PAC terminology are available from DOE (2018b).

AEGL = acute exposure guideline levels; DOE = Department of Energy; DWEL = drinking water equivalent level; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; FEMA = Flavor and Extract Manufacturers Association of the United States; GRAS = generally recognized as safe; HHS = Department of Health and Human Services; IARC = International Agency for Research on Cancer; JECFA = Joint FAO/WHO Expert Committee on Food Additives; MCL = maximum contaminant level; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = protective action criteria; PEL = permissible exposure limit; PHG = public health goal; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TWA = time-weighted average; WHO = World Health Organization

CHAPTER 8. REFERENCES

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APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

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

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

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

APPENDIX A

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Office of Innovation and Analytics, Toxicology Section, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published MRLs. For additional information regarding MRLs, please contact the Office of Innovation and Analytics, Toxicology Section, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop S102-1, Atlanta, Georgia 30329-4027.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Vinyl chloride
CAS Numbers: 75-01-4
Date: January 2023
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Acute
Provisional MRL: 0.5 ppm; 1.3 mg/m^3 (provisional)
Critical Effect: Delayed ossification
References: John et al. 1977, 1981
Point of Departure: NOAEL of 50 ppm; NOAEL$_{HEC}$ = 15 ppm
Uncertainty Factor: 30
LSE Graph Key: 14
Species: Mouse

MRL Summary: A provisional acute-duration inhalation MRL of 0.5 ppm (1.3 mg/m^3) was derived for vinyl chloride based on a developmental endpoint of delayed ossification NOAEL of 50 ppm and a LOAEL of 500 ppm for mice administered vinyl chloride for 7 hours/day on GDs 6–15 (John et al. 1977, 1981). The inhalation concentration of 50 ppm was duration adjusted (NOAEL$_{ADJ}$) to a continuous exposure of 15 ppm. The partition coefficient in mice is greater than that in humans; therefore, a default value of 1 is used for the ratio resulting in a NOAEL$_{HEC}$ of 15 ppm. The NOAEL$_{HEC}$ of 15 ppm was divided by a total uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustment and 10 for human variability).

Selection of the Critical Effect: Available data indicate that developmental effects are the most sensitive target for toxic effects following acute-duration inhalation exposure to vinyl chloride (Table A-1). Delayed ossification was observed in both mice and rabbits at 500 ppm, which is the lowest LOAEL identified for developmental effects (John et al. 1977, 1981). The mouse study included a lower concentration (50 ppm), which was a NOAEL. Exposure of pregnant rats to 2,500 ppm 7 hours/day over GDs 6–15 resulted in ureter dilatation in the offspring (John et al. 1977, 1981).

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). This endpoint was not chosen as the basis of the acute-duration inhalation MRL because absolute kidney weights were similar to controls and no other parameters were available to evaluate the potential for renal toxicity (i.e., no clinical chemistry, urinalysis or histopathology data). A number of studies in animals identified acute-duration LOAELs for frank narcosis and severe lung, liver, and kidney damage following exposures of 10,000–400,000 ppm of vinyl chloride (Table 2-1).

Table A-1. Summary of Candidate Critical Effects for Acute Inhalation MRL for Vinyl Chloride

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
Developmental effects[a]					
Rat (Sprague-Dawley)	GDs 6–15 10 days 7 hours/day	500	2,500	Ureter dilatation (developmental)	John et al. 1977, 1981
Mouse (CF-1)	GDs 6–15 10 days	50	500	Delayed ossification	John et al. 1977, 1981

Table A-1. Summary of Candidate Critical Effects for Acute Inhalation MRL for Vinyl Chloride

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
	7 hours/day				
Rabbit (New Zealand)	GDs 6–18 13 days 7 hours/day	ND	500	Delayed ossification	John et al. 1977, 1981
Hepatic effects					
Rat (Sprague-Dawley)	GDs 6–15 10 days 7 hours/day	500	2,500	9 and 10% increase in absolute and relative liver weight, respectively	John et al. 1977, 1981
Renal effects					
Rat (Sprague-Dawley)	GDs 6–19 4–6 hours/day	10	100	20% increase in relative kidney weight	Thornton et al. 2002

[a]Selected critical effect.

GD = gestational day; LOAEL = lowest-observed-adverse-effect level; MRL = Minimal Risk Level; ND = not determined; NOAEL = no -observed-adverse-effect level

Selection of the Principal Study: The study by John et al. (1977, 1981) was selected as the principal study for the derivation of an acute-duration inhalation MRL based on the NOAEL of 50 ppm for delayed ossification. This study identified the lowest LOAEL for developmental endpoints (500 ppm).

Summary of the Principal Study:

John JA, Smith FA, Leong BKJ, et al. 1977. The effects of maternally inhaled vinyl chloride on embryonal and fetal development in mice, rats, and rabbits. Toxicol Appl Pharmacol 39:497-513.

John JA, Smith FA, Schwetz BA. 1981. Vinyl chloride: Inhalation teratology study in mice, rats, and rabbits. Environ Health Perspect 41:171-177.

CF-1 mice (19–26 per group) were exposed to vinyl chloride at concentrations of 0, 50, or 500 ppm for 7 hours/day on GDs 6–15 (John et al. 1977, 1981). Concurrent control groups (47 animals total) were used, one for each dose level. Control groups were sham-exposed to filtered room air. Whole body exposure was conducted in chambers of 3.7 m^3 volume under dynamic conditions. Animals were observed daily for clinical signs, and maternal body weights were measured several times during gestation. Animals were euthanized on GD 18 by carbon dioxide inhalation. Maternal liver weight was measured and uterine horns were examined. Fetuses were weighed, measured (crown-rump length), sexed, and subjected to gross and histopathological examinations.

No adverse maternal or fetal effects were noted at 50 ppm, with the exception of a slight increase in crown-rump length that was not observed at 500 ppm. Maternal body weight gain decreased along with food consumption at 500 ppm. At 500 ppm, delayed ossification of the skull and sternebrae was observed. The increase in resorptions at 500 ppm was considered to have been within historical control limits. Significant changes in the percentage of implantations resorbed, litter size, and fetal body weight

would not have been observed at 500 ppm if comparison had been made to the other control group (the sham-exposed group for the 50 ppm concentration). There was frank maternal toxicity at 500 ppm (17% death). The data for delayed ossification are not amenable to benchmark dose (BMD) modeling, because only one of two dose groups showed a response that was different from controls. A LOAEL of 500 ppm and a NOAEL of 50 ppm were identified based on delayed ossification in fetuses.

Selection of the Point of Departure for the MRL: The NOAEL of 50 ppm was selected as the POD.

Adjustment for Intermittent Exposure: The intermittent exposure duration of 7 hours/day was duration-adjusted ($NOAEL_{ADJ}$) to continuous exposure according to the following equation:

$NOAEL_{ADJ}$ = NOAEL (50 ppm) x 7 hours/24 hours per day = 14.58 ppm.

Human Equivalent Concentration: Following EPA (1994) methodology, the human equivalent concentration ($NOAEL_{HEC}$) for an extrarespiratory effect produced by a category 3 gas, such as vinyl chloride, is calculated by multiplying the duration-adjusted animal NOAEL by the ratio of the blood:gas partition coefficients in animals and humans ($[H_{b/g}]_A$ / $[H_{b/g}]_H$). Since the partition coefficient in mice is greater than that in humans a default value of 1 is used for the ratio resulting in a $NOAEL_{HEC}$ of 14.58 ppm.

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

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

Provisional MRL = $NOAEL_{HEC}$ ÷ (UF)
14.58 ppm ÷ (3 x 10) = 0.486 ppm ≈ 0.5 ppm

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Delayed ossification (500 ppm, the lowest concentration tested) was the only developmental effect observed in a rabbit developmental study (John et al. 1977, 1981).

Agency Contacts (Chemical Managers): Rae Benedict

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Vinyl chloride
CAS Numbers: 75-01-4
Date: January 2023
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Intermediate
MRL: 0.02 ppm; 0.05 mg/m^3 (provisional)
Critical Effect: Increased incidence of centrilobular hypertrophy
Reference: Thornton et al. 2002
Point of Departure: $BMCL_{10}$: 2.05 ppm ($BMCL_{HEC}$: 0.5 ppm)
Uncertainty Factor: 30
LSE Graph Key: 30
Species: Rat

MRL Summary: A provisional intermediate-duration inhalation MRL of 0.02 ppm (0.05 mg/m^3) was derived for vinyl chloride based on the benchmark concentration lower confidence limit 10% ($BMCL_{10}$) of 2.05 ppm for the increased incidence of centrilobular hypertrophy of the liver in F1 female rats exposed for 16–19 weeks, including exposure during gestation and lactation (Thornton et al. 2002). The $BMCL_{10}$ was adjusted to continuous duration exposure and converted to a human equivalent concentration ($BMCL_{10HEC}$) of 0.5125 ppm. A total uncertainty factor of 30 (3 for species extrapolation using a dosimetric conversion and 10 for human variability) was applied to the $BMCL_{10HEC}$ to derive the provisional MRL of 0.02 ppm.

Selection of the Critical Effect: No dose-response data are available for humans. Available data indicate that the liver is the most sensitive endpoint for toxic effects following intermediate-duration inhalation exposure to vinyl chloride (Table A-2). Liver effects observed at the lowest LOAEL concentration of approximately 10 ppm include increased liver weight (Bi et al. 1985; Thornton et al. 2002) and centrilobular hypertrophy (Thornton et al. 2002). Fatty liver changes were also observed in two studies of rats exposed to 50 ppm for 10 months (Sokal et al. 1980; Wisniewska-Knypl et al. 1980) and one study in mice exposed to 286.7 ppm for 16 weeks (Wang et al. 2019a). Centrilobular degeneration and necrosis was observed in rabbits exposed to 200 ppm for 6 months (Torkelson et al. 1961). Adverse histopathological changes in the liver of rats and mice exposed to 2,000–3,000 ppm were observed in several other intermediate-duration inhalation studies (Lester et al. 1963; Schaffner 1978; Torkelson et al. 1961; Wisniewska-Knypl et al. 1980).

Table A-2. Summary of Candidate Critical Effects for Intermediate Inhalation MRL for Vinyl Chloride

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
Hepatic effects[a]					
Rat (Wistar)	3, 6 months 6 days/week 6 hours/day	ND	11.1	Increased relative liver weight at 6 months	Bi et al. 1985
Rat (Wistar)	10 months 5 days/week 5 hours/day	ND	50	Fatty changes	Sokal et al. 1980

Table A-2. Summary of Candidate Critical Effects for Intermediate Inhalation MRL for Vinyl Chloride

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
Rat (Sprague-Dawley)	2 generations 16 weeks (M) 19 weeks (F) 4-6 hours/day	ND	10[a]	Centrilobular hypertrophy in F1 female rats	Thornton et al. 2002
Rat (NS)	6 months 5 days/week 0.5– 7 hours/day	ND	100	Increased relative liver weight	Torkelson et al. 1961
Rabbit (NS)	6 months 5 days/week 7 hours/day	100	200	Centrilobular degeneration and necrosis	Torkelson et al. 1961
Rat (Wistar)	10 months 5 days/week 5 hours/day	ND	50	Fatty changes	Wisniewska-Knypl et al. 1980
Mouse (C57BL/6N)	16 weeks 5 days/week 2 hours/day	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	Wang et al. 2019a
Reproductive effects					
Rat (Wistar)	3, 6 months 6 days/week 6 hours/day		100	Decreased testes weight with testicular necrosis at 6 months	Bi et al. 1985
Renal effects					
Rat (Wistar)	3, 6 months 6 days/week 6 hours/day		2,918	Increased relative kidney weight at 3 months	Bi et al. 1985
Rat (Wistar)	10 months 5 days/week 5 hours/day	50	500	Increased relative kidney weight	Sokal et al. 1980
Immunological effects					
Rat (Wistar)	10 months 5 days/week 5 hours/day	ND	50	Increased relative spleen weight	Sokal et al. 1980

Table A-2. Summary of Candidate Critical Effects for Intermediate Inhalation MRL for Vinyl Chloride

Species	Duration	NOAEL (ppm)	LOAEL (ppm)	Effect	Reference
Mouse (CD-1)	2–8 weeks 5 days/week 6 hours/day	ND	10	Increased spontaneous lymphocyte proliferation	Sharma and Gehring 1979

[a]Selected critical effect.

F = female(s); LOAEL = lowest-observed-adverse-effect level; M = male(s); MRL = Minimal Risk Level; ND = not determined; NOAEL = no-observed-adverse-effect level

Testicular lesions characterized as degenerative seminiferous tubule changes or spermatogenic epithelial necrosis were observed in male rats exposed for 6–10 months to 100–500 ppm vinyl chloride (Bi et al. 1985; Sokal et al. 1980). Decreased white blood cell counts resulted from exposure of rats to 20,000 ppm for 3 months (Lester et al. 1963), while increased lymphocyte proliferation resulted in mice exposed to 10 ppm for up to 8 weeks (Sharma and Gehring 1979). Exposures of 10–20,000 ppm resulted in increases and decreases in various relative organ weights (Bi et al. 1985; Sokal et al. 1980), including the liver (Bi et al. 1985; Sharma and Gehring 1979; Thornton et al. 2002; Torkelson et al. 1961).

Selection of the Principal Study: Thornton et al. (2002) was chosen as the principal study for derivation of the intermediate-duration inhalation MRL. The study identified the lowest LOAEL for critical liver effects including centrilobular hypertrophy and increased liver weight in rats. The study provided data for centrilobular hypertrophy in F1 offspring, a minimally adverse effect in a sensitive subpopulation (offspring) of the target organ (liver) that is sensitive to both inhalation and oral exposures. A hematological effect was also observed at 10 ppm in mice (Sharma and Gehring 1979). However, Sharma and Gehring (1979) was not selected as the principal study due to the short exposure duration (2–8 weeks) and lack of other study support.

Summary of the Principal Study:

Thornton SR, Schroeder RE, Robison RL, et al. 2002. Embryo-fetal developmental and reproductive toxicology of vinyl chloride in rats. Toxicol Sci 68:207-219.

Groups of male and female Sprague-Dawley rats (30/sex/group) were exposed to vinyl chloride vapor concentrations of 0, 10, 100, or 1,100 ppm, 6 hours/day for 10 weeks prior to mating and during a 3-week mating period. F0 males were exposed during the gestational period and sacrificed following the completion of parturition. F0 females were exposed during gestation and lactation (with the exception of a break in exposure from GD 21 through postnatal day 4 to allow for delivery of litters). All F0 rats were observed twice daily for clinical signs. Body weights and food consumption were monitored. F1 litters were examined for live and dead pups and on lactation day 4, litters were culled to eight pups (equal numbers of male and female pups where possible). All F0 female rats (including those that did not produce offspring) were sacrificed after the F1 rats had been weaned. Reproductive tissues, adrenal glands, brain, kidneys, liver, lungs, spleen, thymus, mammary glands, nasal tissues, pituitary, and trachea from each of the F0 rats were individually weighed and subjected to histopathologic examinations. At weaning, 15 male and female F1 rats/group were selected for gross and microscopic examinations. Other F1 rats were randomly selected to form groups of 30/sex/group, and these F1 rats were subjected to the same treatment as the F0 rats during the production of an F2 generation. At weaning, 15 male and female

F2 rats/group were subjected to gross and microscopic examinations. Sperm parameters were assessed in 15 F0 and 15 F1 male rats of each exposure group.

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. Slight 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 in 2/30 and 6/30 of the 10-ppm F0 and F1 female rats, respectively. No incidences of centrilobular hypertrophy were found in any of the control rats. Compared to an incidence of 0/30 for this lesion in controls, the incidence of 6/30 in the 10-ppm F1 female rats exceeded the level of statistical significance ($p<0.05$ according to Fisher's Exact Test performed by ATSDR).

Selection of the Point of Departure for the Provisional MRL: The $BMCL_{10}$ value of 2.05 ppm for increased incidence of centrilobular hypertrophy in the liver of F1 female rats was selected as the basis of the provisional MRL.

BMD modeling was performed for the candidate liver endpoints in Table A-3 when data were amenable to modeling. Data modeled are shown in Tables A-4 and A-5. The data were fit to all available dichotomous or continuous models in EPA's Benchmark Dose Software (BMDS) (version 3.2) using a benchmark response (BMR) of 1 standard deviation (liver weight data) or 10% extra risk (centrilobular hypertrophy). Adequate model fit was judged by four criteria: goodness-of-fit statistics (p-value >0.1), visual inspection of the dose-response curve, BMCL that is not 10 times lower than the lowest non-zero dose, and scaled residual within ±2 units at the data point (except the control) closest to the predefined BMR. Among all of the models providing adequate fit to the data, the lowest BMCL (95% lower confidence limit on the BMD) was selected as the POD when the difference between the BMCLs estimated from these models was ≥3 fold; otherwise, the BMCL from the model with the lowest Akaike Information Criterion (AIC) was chosen.

Table A-3. Summary of Candidate Critical Liver Effects for Intermediate Inhalation Provisional MRL for Vinyl Chloride[a]

Effect	Sex/generation	NOAEC (ppm)	LOAEC (ppm)
Absolute liver weight	F0 males	ND	10
	F1 males	10	100
Relative liver weight	F0 males	10	100
	F1 males	10	100
Centrilobular hypertrophy	F0 females	10	100
	F1 females	ND	10

[a]Thornton et al. (2002); exposure occurred 10 weeks prior to mating and during a 3-week mating period; F0 males were further exposed during the gestational period and F0 females were further exposed during gestation and lactation.

LOAEC = lowest-observed-adverse-effect level; MRL = Minimal Risk Level; NOAEC = no-observed-adverse-effect level; ND = not determined

Table A-4. Absolute and Relative Liver Weight in F0 And F1 Male Rats Following Inhalation Exposure to Vinyl Chloride[a]

	Exposure concentration (ppm)			
Endpoint	0	10	100	1,100
Number of animals	15	15	15	15
Absolute liver weight (g)				
F0 males	14.32±2.13[b]	16.20±2.19[c]	16.22±1.59[d]	16.72±0.86[d]
F1 males	14.13±2.36	15.07±2.74	16.62±2.27[c]	17.01±1.49[d]
Relative liver weight				
F0 males	2.83±0.26	3.05±0.29[c]	3.09±0.20[c]	3.26±0.19[d]
F1 males	2.98±0.33	3.01±0.19	3.32±0.36[d]	3.38±0.19[d]

[a]Exposure for 6 hours/day for 10 weeks prior to mating and during mating and gestation (males and females) and lactation (females).
[b]Mean±standard deviation.
[c]Statistically significantly ($p<0.05$) different from controls.
[d]Statistically significantly ($p<0.01$) different from controls.

Source: Thornton et al. 2002

Table A-5. Incidences of Centrilobular Hypertrophy in the Liver for F0 And F1 Female Rats Following Inhalation Exposure to Vinyl Chloride[a]

	Exposure concentration (ppm)			
	0	10	100	1,100
F0 females	0/30	2/30	26/30[b]	30/30[b]
F1 females	0/30	6/30[b]	30/30[b]	30/30[b]

[a]Exposure for 6 hours/day for 10 weeks prior to mating and during mating and gestation (males and females) and lactation (females).
[b]Statistically significantly ($p<0.05$) different from controls according to Fisher's Exact Test performed by ATSDR.

Source: Thornton et al. 2002

None of the BMD models (with constant variance or nonconstant variance) provided adequate fit to the data for increased absolute liver weight in F0 males or to relative liver weight in F1 males. Therefore, a NOAEL/LOAEL approach was used for these endpoints.

For absolute liver weight in F1 males, the BMD software (BMDS) could not adequately fit the full dataset, but it was able to provide an adequate fit after dropping the highest dose (1,100 ppm). Dropping the highest dose (or doses) is a valid technique in this case. First, the dataset had enough non-zero dose groups with significant responses to remove the highest dosage without loss of BMD trend. Second, the POD for this dataset would visually be in the lower dose groups, but the high dose group is very far away from these lower groups. This situation can lead to models straining to fit the high group (because of leverage) at the cost of losing adequate fit of lower groups. With the highest dose dropped, five frequentist, constant variance models provided adequate fit to the data. BMCLs for models providing adequate fit were sufficiently close (differed by <3-fold), so the simplest model with the lowest AIC was selected (Linear). The restricted linear model estimated a BMC_{1SD} and $BMCL_{1SD}$ of 110 and 68 ppm,

respectively. BMDS states a warning when fitting the reduced dataset, as the estimated BMD was higher than the new highest dose (100 ppm), which normally raises extrapolation error concerns. However, the estimated BMD (109.8) was still less than the removed high dose, so the estimate would not be much of an extrapolation. Since BMD falls well below the dropped dose of 1,100 ppm, the extrapolation warning (BMD>higher dose) may not be a concern. The results of the BMD modeling are summarized in Table A-6.

Table A-6. Model Predictions (Constant Variance) for Absolute Liver Weight in F1 Male Rats Following Inhalation Exposure to Vinyl Chloride[a]

Model	BMC_{1SD}[b] (ppm)	$BMCL_{1SD}$[b] (ppm)	p-Value[c]	AIC	Scaled residuals[d] Dose near BMC	Scaled residuals[d] Dose near control
Highest dose dropped from dataset						
Exponential (model 2)[e]	109.69	70.36	0.40	212.52	-0.06	-0.57
Exponential (model 3)[e]	109.72	70.36	0.40	212.52	-0.05	-0.57
Exponential (model 4)[e]			NA	213.80	-3.3×10^{-6}	-4.1×10^{-6}
Exponential (model 5)[e]			NA	213.80	-5.8×10^{-8}	-2.7×10^{-7}
Hill[e]			<0.0001	215.80	-0.00023	-9.7×10^{-5}
Polynomial (2-degree)[e]	109.77	67.61	0.41	212.49	-0.06	-0.55
Power[f]	109.77	67.61	0.41	212.49	-0.06	-0.55
Linear[e,g]	**109.77**	**67.61**	**0.41**	**212.49**	**-0.06**	**-0.55**

[a]Exposure for 6 hours/day for 10 weeks prior to mating and during mating and gestation (males and females) and lactation (females).
[b]BMC and BMCL values for models that do not provide adequate fit are not included in the table.
[c]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[d]Scaled residuals at concentrations immediately below and above the BMC.
[e]Power restricted to ≥1.
[f]Coefficients restricted to be positive.
[g]Selected model. For the full dataset, none of the models provided adequate fit to the variance data (constant or nonconstant). With the highest dose dropped, constant variance models provided adequate fit to the variance data. With constant variance model applied, all models provided adequate fit to the means except for the Hill and Exponential 4 and 5 models. BMCLs for models providing adequate fit were sufficiently close (differed by <3-fold), so the simplest model with the lowest AIC is selected (Linear).

AIC = Akaike Information Criterion; BMC = benchmark concentration (maximum likelihood estimate of the exposure concentration associated with the selected benchmark response); BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response); NA = not applicable (Goodness of fit test cannot be calculated); SD = standard deviation

Source: Thornton et al. 2002

For relative liver weight in F0 males, no constant variance models provided an adequate fit to the dataset with the nonconstant variance model applied, only the Hill and Exponential 4 and 5 models provided adequate fit to the data. The BMD computation failed for the Hill model; the lower limit included zero and the BMDL was not estimated. BMCLs for models providing adequate fit were sufficiently close (differed by <3-fold), so the model with the lowest AIC was selected (Exponential 4). The Exponential 4 model estimated a BMC_{1SD} and $BMCL_{1SD}$ of 216 and 72 ppm, respectively. The results of the BMD modeling are summarized in Table A-7.

Table A-7. Model Predictions (Nonconstant Variance) for Relative Liver Weight in F0 Male Rats Following Inhalation Exposure to Vinyl Chloride[a]

Model	BMC_{1SD}[b] (ppm)	$BMCL_{1SD}$[b] (ppm)	p-Value[c]	Scaled residuals[d]		
				AIC	Dose near BMC	Dose near control
Exponential (model 2)[e]			0.02	8.08	-0.07	-2.16
Exponential (model 3)[e]			0.02	8.08	-0.08	-2.16
Exponential (model 4)[e,f]	**216.31**	**71.99**	**0.11**	**5.08**	**-0.40**	**-1.20**
Exponential (model 5)[e]	225.86	70.96	0.11	5.09	-0.38	-1.22
Hill[d]	246.14	0	0.14	4.72	-0.57	-1.04
Polynomial (3-degree)[e]			0.02	8.03	-0.09	-2.15
Polynomial (2-degree)[e]			0.02	8.03	-0.09	-2.15
Power[e]			0.02	8.03	-0.09	-2.15
Linear[g]			0.02	8.03	-0.09	-2.15

[a]Exposure for 6 hours/day for 10 weeks prior to mating and during mating and gestation (males and females) and lactation (females).
[b]BMC and BMCL values for models that do not provide adequate fit are not included in the table.
[c]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[d]Scaled residuals at concentrations immediately below and above the BMC.
[e]Power restricted to ≥1.
[f]Selected model. None of the constant variance models provided adequate fit to the data. With the nonconstant variance model applied, only the Hill and Exponential 4 and 5 models provided adequate fit to the data. The BMC computation failed for the Hill model; the lower limit included zero and the BMCL was not estimated; therefore the Hill model was unusable. BMCLs for models providing adequate fit were sufficiently close (differed by <3-fold), so the model with the lowest AIC was selected (Exponential 4).
[g]Coefficients restricted to be positive.

AIC = Akaike Information Criterion; BMC = benchmark concentration (maximum likelihood estimate of the exposure concentration associated with the selected benchmark response); BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response; SD = standard deviation

Source: Thornton et al. 2002

For the incidence of centrilobular hypertrophy in the liver in F0 females, all models provided an adequate fit to the data except for the Probit model. BMCLs for models providing an adequate fit were not sufficiently close (differed by $\geq$3-fold), so the model with the lowest BMCL was selected (1-degree multistage). The 1-degree multistage model estimated a BMC_{10} and $BMCL_{10}$ of 6.16 and 4.4 ppm, respectively. The results of the BMD modeling are summarized in Table A-8.

Table A-8. Results from BMD Analysis of Incidences of Centrilobular Hypertrophy in the Liver in F0 Female Rats Following Inhalation Exposure to Vinyl Chloride[a]

Model	BMC_{10}[b] (ppm)	$BMCL_{10}$[b] (ppm)	p-Value[c]	AIC	Scaled residuals[d]	
					Dose near BMC	Dose near control
Gamma[e]	13.01	5.89	1.00	44.26	0.0006	-0.0032
Logistic	31.04	20.79	0.54	44.13	0.7257	-0.8500
Log-Logistic[f]	12.64	6.89	0.98	42.34	0.0301	-0.0007
Log-Probit[g]	12.14	7.58	0.97	44.26	0.0028	-0.0007
Multistage (1-degree)[g,h]	**6.16**	**4.40**	**0.31**	**45.03**	**-1.3638**	**-0.0007**
Multistage (2-degree)[h]	14.06	5.78	1.00	44.26	1.71×10^{-5}	-0.0007
Multistage (3-degree)[h]	14.92	5.76	1.00	42.26	2.16×10^{-6}	-0.0007
Probit			0.01	55.73	-1.1734	-1.9041
Weibull[e]	12.79	5.85	0.90	44.27	-0.1025	-0.0017
Dichotomous Hill	12.64	6.89	0.98	42.34	0.0301	-0.0007

[a]Exposure for 6 hours/day for 10 weeks prior to mating and during mating and gestation (males and females) and lactation (females).
[b]BMC and BMCL values for models that do not provide adequate fit are not included in the table.
[c]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[d]Scaled residuals at doses immediately below and above the BMC.
[e]Power restricted to ≥1.
[f]Slope restricted to ≥1.
[g]Selected model. All models provided adequate fit to the data except for the Probit model. BMCLs for models providing adequate fit differed by ≥3-fold; therefore, the model with the lowest BMCL was selected (1-degree Multistage).
[h]Betas restricted to ≥0.

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

Source: Thornton et al. 2002

For the incidence of centrilobular hypertrophy in the liver in F1 females, all models provided an adequate fit to the data except for the Probit model. The BMD computation failed for the Weibull model and a BMCL was not estimated; this model was deemed unusable. BMCLs for models providing an adequate fit were not sufficiently close (differed by ≥3-fold), so the model with the lowest BMCL was selected (1-degree multistage). The 1-degree multistage model estimated a BMC_{10} and $BMCL_{10}$ of 3.03 and 2.05 ppm, respectively. The results of the BMD modeling are summarized in Table A-9.

Table A-9. Results from BMD Analysis of Incidences of Centrilobular Hypertrophy in the Liver in F1 Female Rats Following Inhalation Exposure to Vinyl Chloride[a]

Model	BMC_{10}[b] (ppm)	$BMCL_{10}$[b] (ppm)	p-Value[c]	AIC	Scaled residuals[d]	
					Dose near BMC	Dose near control
Gamma[e]	6.53	3.10	0.98	34.11	-0.0241	-0.0007
Logistic	11.34	7.58	0.41	36.75	0.9450	-1.4034
Log-Logistic[f]	8.21	5.21	1.00	32.04	-0.0021	-0.0007
Log-Probit[g]	8.59	5.09	1.00	34.02	7.296×10^{-11}	-0.0007
Multistage (1-degree)[g,h]	**3.03**	**2.05**	**0.33**	**37.28**	**-0.0007**	**-0.0007**
Multistage (2-degree)[h]	6.75	2.72	1.00	34.02	-2.32×10^{-8}	-0.0007
Multistage (3-degree)[h]	6.76	2.61	1.00	36.02	3.527×10^{-8}	-0.0007
Probit			0.001	60.13	-0.4459	-2.6297
Weibull[e]	5.11	0.00	0.84	34.65	-0.2606	-0.0007
Dichotomous Hill	8.21	5.21	1.00	34.04	-0.0021	-0.0007

[a]Exposure for 6 hours/day for 10 weeks prior to mating and during mating and gestation (males and females) and lactation (females).
[b]BMC and BMCL values for models that do not provide adequate fit are not included in the table.
[c]Values <0.1 fail to meet conventional χ^2 goodness-of-fit criteria.
[d]Scaled residuals at doses immediately below and above the BMC.
[e]Power restricted to ≥1.
[f]Slope restricted to ≥1.
[g]Selected model. All models provided adequate fit to the data except for the Probit model and the Weibull model did not estimate a BMCL. BMCLs for models providing adequate fit differed by ≥3-fold; therefore, the model with the lowest BMCL was selected (1-degree Multistage).
[h]Betas restricted to ≥0.

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

Source: Thornton et al. 2002

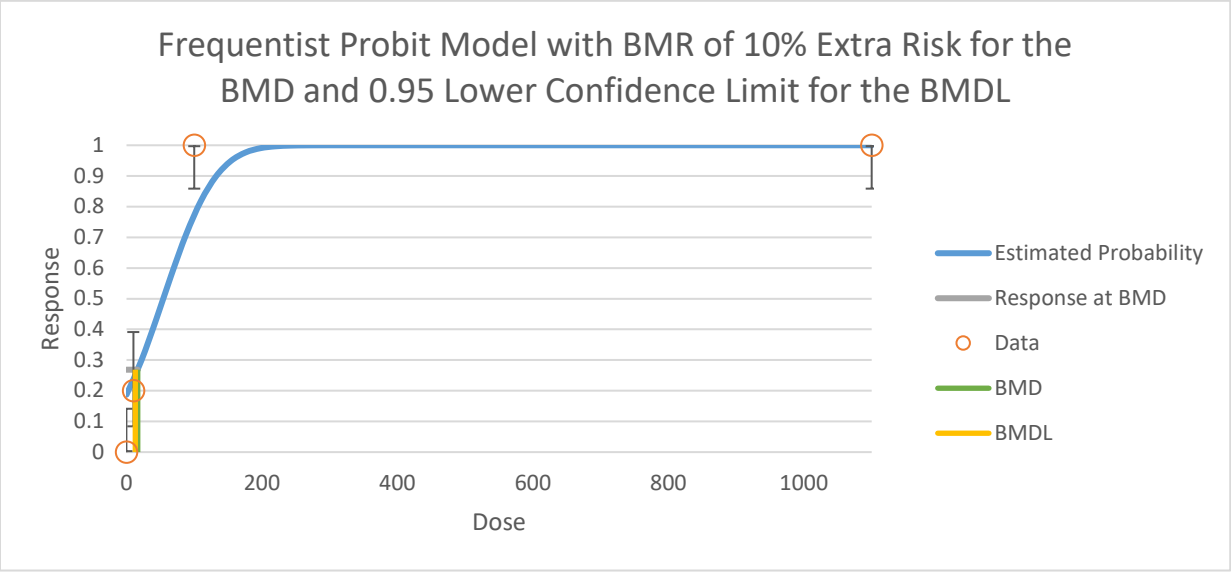
Table A-10 summarizes the potential candidate PODs for the provisional intermediate-duration inhalation MRL for vinyl chloride. Based on the lowest available critical values (BMC, NOAEL), centrilobular hypertrophy (in F1 females) was identified as the critical effect following intermediate-duration inhalation exposure to vinyl chloride. The 1-degree multistage model fit to the centrilobular hypertrophy data in F1 female rats is presented in Figure A-1. The corresponding $BMCL_{10}$ of 2.05 is used as the POD in further calculations.

Table A-10. Candidate Points of Departure for the Intermediate-Duration Inhalation Provisional MRL

Endpoint	NOAEC (ppm)	LOAEC (ppm)	BMC_{10} (ppm)	$BMCL_{10}$ (ppm)
Increased absolute liver weight F0 males	ND	10		
Increased absolute liver weight F1 males			110	68
Increased relative liver weight F0 males			216	72
Increased relative liver weight F1 males	10	100		
Centrilobular hypertrophy F0 females			6.16	4.4
Centrilobular hypertrophy F1 females			3.03	2.05

BMC = benchmark concentration; BMCL = 95% lower confidence limit on the BMC; LOAEL = lowest-observed-adverse-effect level; MRL = Minimal Risk Level; NOAEL = no-observed-adverse-effect level

Figure A-1. Fit of 1-Degree Multistage Model to Data for Incidences of Centrilobular Hypertrophy in the Liver in F1 Female Rats Following Inhalation Exposure to Vinyl Chloride (Thornton et al. 2002)



Calculations

Intermittent Exposure: The intermittent exposure duration of 6 hours/day was duration-adjusted ($BMCL_{10ADJ}$) to continuous exposure according to the following equation:

$$BMCL_{10ADJ} = BMCL_{10} \text{ (2.05 ppm) x 6 hours/24 hours per day} = 0.5125 \text{ ppm}$$

Human Equivalent Concentration: Following EPA (1994) methodology, the human equivalent concentration ($BMCL_{10HEC}$) for an extrarespiratory effect produced by a category 3 gas, such as vinyl chloride, is calculated by multiplying the animal $BMCL_{10ADJ}$ by the ratio of the blood:gas partition coefficients in animals and humans $[(H_{b/g})_A / H_{b/g})_H]$. Since the partition coefficient in rats is greater than that in humans, a default value of 1 is used for the ratio and the animal $BMCL_{10ADJ}$ is equivalent to the $BMCL_{10HEC}$. Several PBPK models are available for vinyl chloride; however, none of these models included an evaluation of exposure during mating, gestation, or lactation. Therefore, PBPK models could not be used to calculate a $BMCL_{10HEC}$ from the Thornton et al. (2002) study. The provisional intermediate-duration inhalation MRL of 0.02 ppm was derived by dividing the $BMCL_{10HEC}$ of 0.5125 ppm for centrilobular hypertrophy in female Sprague-Dawley rats by a factor of 30 (3 for species extrapolation using a dosimetric conversion and 10 for human variability).

Uncertainty Factor: The $BMCL_{10}$ was divided by a total uncertainty factor (UF) of 30:

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

Provisional MRL = $BMCL_{10HEC} \div$ (UF)
0.5125 ppm ÷ (3 x 10) = 0.017 ≈ 0.02 ppm

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Liver enlargement and/or histopathological changes have been noted in a number of intermediate-duration inhalation studies in animals (Bi et al. 1985; Lester et al. 1963; Schaffner 1978; Sokal et al. 1980; Torkelson et al. 1961; Wisniewska-Knypl et al. 1980). The studies by Thornton et al. (2002) and Bi et al. (1985) show these effects at a somewhat lower dosage. In support of using an effect level of 10 ppm, there was also a finding of immunostimulation in mice at 10 ppm (Sharma and Gehring 1979).

Agency Contacts (Chemical Managers): Rae Benedict

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Vinyl chloride
CAS Numbers: 75-01-4
Date: January 2023
Profile Status: Draft for Public Comment
Route: Inhalation
Duration: Chronic

MRL Summary: There are insufficient data for derivation of a chronic-duration inhalation MRL for vinyl chloride.

Rationale for Not Deriving an MRL: In the absence of exposure level data, the human database did not provide a suitable LOAEL or NOAEL for derivation of a chronic-duration inhalation MRL. The animal database mostly reported cancer and death. One study (Bi et al. 1985) reported body weight, organ weight, reproductive (histological), and cancer effects. A NOAEL (11.1 ppm) and a LOAEL (105.6 ppm) were identified for testicular effects (increases in the number of degenerative seminiferous tubule changes) in a chronic-duration inhalation study (Bi et al. 1985). However, the results of the Thornton et al. (2002) study for intermediate-duration exposure suggest that liver effects (increased liver weight, centrilobular hypertrophy) would occur at lower concentrations (10 ppm) than the reported testicular effects. Bi et al. (1985) did not report noncancer liver histopathology; therefore, this study cannot be used to derive a chronic inhalation MRL. Though several other chronic-duration studies did report carcinogenicity in rats chronically exposed to 5–250 ppm vinyl chloride (Drew et al. 1983; Lee et al. 1977a, 1978; Maltoni et al. 1981), they did not report the incidence of noncancerous or precancerous histopathological lesions in any tissue. Therefore, no chronic-duration inhalation MRL was derived for vinyl chloride.

Agency Contacts (Chemical Managers): Rae Benedict

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Vinyl chloride
CAS Numbers: 75-01-4
Date: January 2023
Profile Status: Draft for Public Comment
Route: Oral
Duration: Acute

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

Rationale for Not Deriving an MRL: No acute-duration oral MRLs was derived for vinyl chloride because of an absence of data on the effects of oral exposure to vinyl chloride for this duration category.

Agency Contacts (Chemical Managers): Rae Benedict

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Vinyl chloride
CAS Numbers: 75-01-4
Date: January 2023
Profile Status: Draft for Public Comment
Route: Oral
Duration: Intermediate

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

Rationale for Not Deriving an MRL: No intermediate-duration oral MRLs was derived for vinyl chloride because of an absence of data on the effects of oral exposure to vinyl chloride for this duration category.

Agency Contacts (Chemical Managers): Rae Benedict

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Vinyl chloride
CAS Numbers: 75-01-4
Date: January 2023
Profile Status: Draft for Public Comment
Route: Oral
Duration: Chronic
MRL: 0.003 mg/kg/day (3 µg/kg/day) (provisional)
Critical Effect: Liver cell polymorphisms
References: Til et al. 1983, 1991
Point of Departure: NOAEL of 0.17 mg/kg/day ($NOAEL_{HED}$ of 0.09 mg/kg/day)
Uncertainty Factor: 30
LSE Graph Key: 5
Species: Rat

MRL Summary: A provisional chronic-duration oral MRL of 0.003 mg/kg/day (3 µg/kg/day) is proposed for vinyl chloride based on a NOAEL of 0.17 mg/kg/day and a LOAEL of 17 mg/kg/day for liver cell polymorphisms in rats administered vinyl chloride for 149 weeks (Til et al. 1983,1991). The PBPK-modeled equivalent human NOAEL associated with the rat NOAEL ($NOAEL_{HED}$) of 0.17 mg/kg/day was 0.09 mg/kg/day. The $NOAEL_{HED}$ was divided by a total uncertainty factor of 30 (3 for species extrapolation using a dosimetric conversion and 10 for human variability) to arrive at an MRL of 0.003 mg/kg/day.

Selection of the Critical Effect: No dose-response data are available for humans. Available data indicate that the liver is the most sensitive endpoint for toxic effects following chronic-duration oral exposure to vinyl chloride (Table A-11). A number of effects were observed in rats given 1.7 mg/kg/day, including hepatocellular alterations (Feron et al. 1981), liver cell polymorphisms, and increased mortality (Til et al. 1983, 1991). Liver cell polymorphism is related to cytotoxicity and is considered a nonneoplastic lesion (Schoental and Magee 1957, 1959). The LOAEL of 1.7 mg/kg/day for liver cell polymorphism (in both sexes) and hepatic cysts in female rats was the lowest identified LOAEL and was associated with the lowest identified NOAEL (0.17 mg/kg/day) for any chronic effect. Doses of 14.1 mg/kg/day in female rats resulted in extensive hepatic necrosis, 100% early mortality, humpback position, lethargy, and emaciation (Feron et al. 1981). Decreased blood clotting time was also observed in rats given 14.1 mg/kg/day (Feron et al. 1981). Chronic gavage doses of 30 mg/kg/day vinyl chloride in rats resulted in increased collagen deposition and skin thickness (Knight and Gibbons 1987).

Table A-11. Summary of Candidate Critical Effects for Chronic Oral MRL for Vinyl Chloride

Species	Duration/route	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Hepatic effects					
Rat (Wistar)	84 weeks–2.7 years 5 days/week 4 hours/day (F), (GO)	ND	1.7	Cellular alteration	Feron et al. 1981
Rat (Wistar)	149 weeks 4 hours/day (F)	0.17[a]	1.7	Liver cell polymorphism	Til et al. 1983, 1991

Table A-11. Summary of Candidate Critical Effects for Chronic Oral MRL for Vinyl Chloride

Species	Duration/route	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Effect	Reference
Hematological					
Rat (Wistar)	84 weeks–2.7 years 5 days/week 4 hours/day (F), (GO)	5	14.1	Decreased clotting time	Feron et al. 1981
Neurological					
Rat (Wistar)	84 weeks–2.7 years 5 days/week 4 hours/day (F), (GO)	5	14.1	Humpback position, lethargy, emaciation	Feron et al. 1981
Dermal effects					
Rat (Wistar)	2 years 1 time/day (GO)		30	Increased skin thickness, collagen	Knight and Gibbons 1987

F = female(s); G = gavage (no vehicle); GO = gavage (oil vehicle); LOAEL = lowest-observed-adverse-effect level; M = male(s); MRL = Minimal Risk Level; NOAEL = no-observed-adverse-effect level; ND = not determined

Selection of the Principal Study: The study by Til et al. (1983,1991) was selected as the principal study for the derivation of a chronic-duration oral provisional MRL based on the NOAEL of 0.17 mg/kg/day for liver cell polymorphisms. This study identified the lowest LOAEL (1.7 mg/kg/day) for the critical effect.

Summary of the Principal Study:

Til HP, Immel HR, Feron VJ. 1983. Lifespan oral carcinogenicity study of vinyl chloride in rats. Final report. Civo Institutes, TNO. Report No. V 93.285/291099.

Til HP, Feron VJ, Immel HR. 1991. Lifetime (149-week) oral carcinogenicity study of vinyl chloride in rats. Food Chem Toxicol 29:713-718.

Groups of Wistar rats (100/sex/group in controls and the two lowest exposure groups; 50/sex at the highest exposure level) were administered vinyl chloride in the daily diet at intended initial dietary concentrations of 0, 0.46, 4.6, or 46 ppm for 149 weeks. Due to rapid evaporative loss of vinyl chloride from the food, liquid vinyl chloride was mixed with PVC granules to produce a mixture in which vinyl chloride was effectively encapsulated in PVC granules (Feron et al. 1975). The study authors trained the rats to a feeding schedule of 4 hours/day prior to the initiation of exposure to vinyl chloride in the diet. The authors noted that food consumption per hour was fairly constant during the 4-hour feeding period. Loss of vinyl chloride from food during the first hour, the second hour, and the final 2 hours was calculated. Periodic food intake measurements were made for the first hour, the second hour, and the final 2 hours. Based on these measurements, the study authors calculated the average oral intake of the combined sexes during the daily 4-hour feeding periods to be 0, 0.018, 0.17, and 1.7 mg/kg/day for the 0-, 0.49-, 4.49-, and 44.1-ppm groups, respectively. Measurements of vinyl chloride in the feces were made periodically at 1 hour prior to the feeding period, the end of the 4-hour feeding period, and 4 and 9 hours later. The study authors considered the vinyl chloride content in the feces to have remained encapsulated

in the PVC granules and thus not to have been available for absorption from the gastrointestinal tract. The amount of vinyl chloride in the feces was subtracted from the calculated daily oral intake of vinyl chloride to arrive at what the study authors termed "actual oral exposure levels" of 0, 0.014, 0.13, and 1.3 mg/kg/day for the 0-, 0.49-, 4.49-, and 44.1-ppm groups, respectively. The incidence of cell polymorphism was recorded by sex and estimated absorbed dose group (Table A-12). Results of toxicokinetic assessments for vinyl chloride indicate that, following absorption, vinyl chloride and its metabolites are not excreted in appreciable amounts in the feces. Types and incidences of neoplastic and nonneoplastic liver lesions were determined at the end of the study.

Effects noted in study and corresponding doses: The critical nonneoplastic effect was determined to be liver cell polymorphism, which was classified by severity (slight, moderate, severe). The incidences of this lesion are listed in Table A-12.

Table A-12. Incidences of Male and Female Wistar Rats Exhibiting Slight, Moderate, or Severe Liver Cell Polymorphism Following Daily Oral Exposure to Vinyl Chloride in the Diet for 149 Weeks

	Estimated oral intake, absorbed (mg/kg/day)							
	Males				Females			
	0	0.014	0.13	1.3	0	0.014	0.13	1.3
Number of rats examined	99	99	99	49	98	100	96	49
Slight	27	23	26	19	46	41	49	23
Moderate	4	4	7	10[a]	14	13	8	15[b]
Severe	1	1	1	3	2	3	4	9[c]

[a]Significantly different from controls according to Fisher's exact test ($p<0.001$).
[b]Significantly different from controls according to Fisher's exact test ($p<0.05$).
[c]Significantly different from controls according to Fisher's exact test ($p<0.0001$).

Source: Til et al. 1983, 1991

Selection of the Point of Departure for the Provisional MRL: A LOAEL of 1.7 mg/kg/day was identified for statistically significantly increased incidences of liver cell polymorphism in male and female rats. The NOAEL for nonneoplastic liver effects is 0.17 mg/kg/day. An increase in the incidence of female rats with many hepatic cysts was also observed at the highest dose (1.7 mg/kg/day). Other histopathologic lesions, described as hepatic foci of cellular alteration, were observed at all dose levels in female rats and in high-dose male rats, but were not used to derive an MRL because they are considered to be preneoplastic lesions. MRLs are protective only for non-neoplastic effects and do not reflect cancer risk.

EPA (2000) applied the Clewell et al. (1995) PBPK model for vinyl chloride to the low-, mid-, and high-dose groups (estimated absorbed doses of 0.014, 0.13, and 1.3 mg/kg/day, respectively) to generate dose metrics of 0.3, 3, and 30 mg vinyl chloride metabolites/L liver, respectively. The EPA approach was reviewed and was considered appropriate for deriving the chronic oral MRL.

The dose metric, "number of rats examined," and the "moderate" and "severe" polymorphism categories (Table A-12) were used in modeling. The "number of rats examined" were summed, regardless of sex, for each dose group, resulting in a low-dose, mid-dose, and high-dose groups. For example, the low-dose

group males numbered 99 and the low-dose females numbered 100 to result in 199 rats that were examined in that group (Tables A-12 and A-13). Likewise, the "moderate" and "severe" cell polymorphism incidence data were combined (i.e., summed) for each group, regardless of sex, resulting in one data category of moderate+severe (Table A-13). The moderate+severe polymorphism data had one control group and three exposure groups (low-dose, mid-dose, and high-dose). These combinations resulted in the following cell polymorphism data that were used for modeling: 21/197 controls, 21/199 low-dose, 20/196 mid-dose, and 37/98 high-dose rats) (Til et al. (1983, 1991).

Table A-13. Incidences of Male and Female Wistar Rats Exhibiting Moderate or Severe Liver Cell Polymorphism Following Daily Oral Exposure to Vinyl Chloride in the Diet for 149 Weeks

	Estimated oral intake, absorbed (mg/kg/day)			
	0	0.014	0.13	1.3
	Dose metric (mg metabolite/L liver)			
	0	0.3	3	30
Number of rats examined	197 (99, 98)[a]	199 (99, 100)	195 (99, 96)	98 (49, 49)
Moderate+severe cell polymorphism	21 (4, 1, 14, 2)[b]	21 (4, 1, 13, 3)	20 (7, 1, 8, 4)	37 (10, 3, 15, 9)

[a]Data in parentheses are the incidence numbers for males and females taken from Table A-12.
[b]Data in parentheses are moderate and severe cell polymorphism incidence numbers for males and females.

Source: Til et al. 1983, 1991

The resulting incidence data for each dose metric (0.3, 3, and 30 mg metabolite/L liver) were subjected to BMD modeling in order to statistically identify a threshold response for vinyl chloride-induced effects. The resulting dose metric values are shown in Table A-14.

Table A-14. LED_{10} Values Generated from Various Models to Liver Cell Polymorphism Incidence Data from Oral Exposure of Male and Female Rats to Vinyl Chloride in the Diet for 149 Weeks in the Study of Til et al. (1991)

Model	LED_{10} (mg/L liver)[a]	p-Value
Weibull (power ≥1)	24.0	0.88
Gammahit	21.4	0.88
Quantal quadratic	13.8	0.96
Logistic	12.9	0.47
Multistage	11.8	0.79
Probit	11.6	0.44
Quantal linear	6.5	0.46
NOAEL	3.00 (0.13 mg/kg/day)	
LOAEL	29.9 (1.3 mg/kg/day)	

[a]LED_{10} is the lower 95% confidence limit of a 10% change in numbers exhibiting polymorphism evaluated as either moderate or severe. The NOAEL and LOAEL are shown for comparison.

Source: EPA 2000

Although all models provided adequate fit to the data, the LED_{10} values ranged from 6.5 to 24.01 mg/L liver (nearly a 4-fold range) and all modeled LED_{10} values were higher than the NOAEL of the study. Because there was no biological reason to choose the results of one model over another and the dose-response characteristics present additional uncertainty due to the large gaps between dose levels, the BMD modeling results were not used to derive the POD. Assuming that all dietary vinyl chloride was absorbed, the human equivalent dose of 0.09 mg/kg/day, calculated from the rat NOAEL of 0.17 mg/kg/day (Til et al. 1983, 1991), served as the basis for the chronic-duration oral MRL for vinyl chloride. The provisional chronic-duration oral MRL of 0.003 mg/kg/day was derived by dividing the PBPK-modeled equivalent human NOAEL of 0.09 mg/kg/day for liver cell polymorphisms by a factor of 30 (3 for species extrapolation using a dosimetric conversion and 10 for human variability).

Human Equivalent Concentration: In deriving the provisional MRL, the rat NOAEL of 0.17 mg/kg/day was converted to a human equivalent dose using the PBPK models described in Clewell et al. (2001) and EPA (2000) to extrapolate from rats to humans. Source code and parameter values for running the rat and human models in ACSL were transcribed from Appendix C of EPA (2000). Parameter values used in the interspecies extrapolation are presented in Table A-15. Accuracy of the implementation of the model in ACSL (v. 11.8.4) was checked against observations reported in Gehring et al. (1978), also reported in Clewell et al. (2001) (results shown in Figure A-2). The visual fit of the observed and predicted values appears adequately good at low doses. The total amount of vinyl chloride metabolized in 24 hours per L of liver volume was the rat internal dose metric that was used in determining the human dose that would result in an equivalent human dose metric. One kilogram of liver was assumed to have an approximate volume of 1 L. Exposures in the Til et al. (1983, 1991) rat dietary study were simulated as 4-hour oral exposures, for which the average daily dose (ADD) was equivalent to the NOAEL dose for liver effects (ADD=0.17 mg/kg/day). This dose was uniformly distributed over a 4-hour period (i.e., 0.0425 mg/kg/hour for 4 hours, followed by 16 hours at 0 mg/kg/hour). Dose metrics reflect the cumulative amount of vinyl chloride metabolized over the 24-hour period.

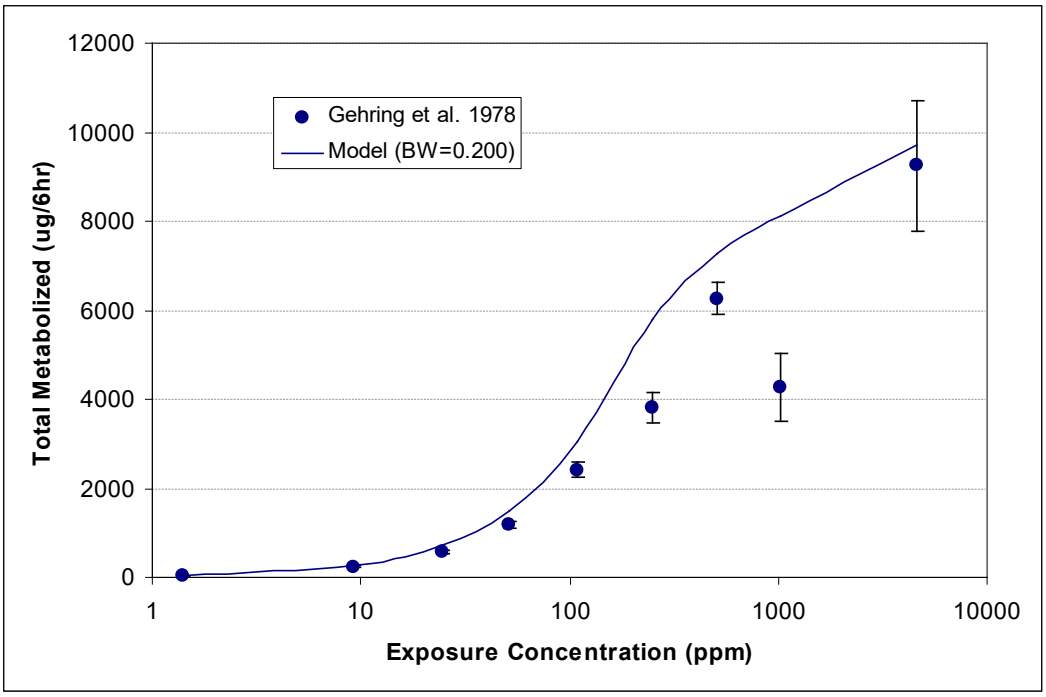
Table A-15. Parameter Values for Rat and Human Models

Parameter	Definition	Model	
		Rat	Human
BW	Body weight (kg)	0.377 (M) 0.204 (F)	70
VLC	Liver volume (fraction of body)	0.05	0.026
VFC	Fat volume (fraction of body)	0.12	0.19
VSC	Slowly-perfused tissue volume (fraction of body)	0.75	0.63
VRC	Rapidly-perfused tissue volume (fraction of body)	0.05	0.064
QCC	Cardiac output (L/hour-kg body weight)	18.0	16.5
QPC	Alveolar ventilation rate (L/hour-kg body weight)	21.0	24.0
QLC	Liver blood flow (fraction of cardiac output)	0.25	0.26
QFC	Fat blood flow (fraction of cardiac output)	0.09	0.05
QSC	Slowly-perfused blood flow (fraction of cardiac output)	0.15	0.19
QRC	Rapidly-perfused blood flow (fraction of cardiac output)	0.51	0.5
PB	Blood:air partition coefficient	2.4	1.16
PL	Liver:blood partition coefficient	0.7	1.45
PF	Fat:blood partition coefficient	10.0	20.7
PS	Slowly-perfused partition coefficient	4.0	0.83
PR	Rapidly-perfused partition coefficient	0.7	1.45
VMAX1C	Maximum rate of oxidative metabolism (mg/hour-kg body weight)	4.0	4.0
VMAX2C	Maximum rate of oxidative metabolism (mg/hour-kg body weight)	2.0	0.1
KM1	Michaelis-Menten coefficient for oxidative metabolism (mg/L)	0.1	0.1
KM2	Michaelis-Menten coefficient for oxidative metabolism (mg/L)	10.0	10.0
KCO2C	Rate constant for formation of CO_2 from oxidative metabolite ($hour^{-1}$)	1.6	1.6
KGSMC	Rate constant for conjugation with GSH ($hour^{-1}$)	0.13	0.13
KFEEC	Rate constant for conjugation, not with GSH ($hour^{-1}$)	35.0	35.0
CGSZ	Initial GSH concentration in liver (µmol/L)	5,800	5,800
KBC	Rate constant for GSH catabolism ($hour^{-1}$)	0.12	0.12
KS	Coefficient controlling resynthesis of GSH (µmol/L)	2,000	2,000
KZC	Zero-order rate constant for resynthesis of GSH (µmol/hour)	28.5	28.5
Ka	Gastrointestinal absorption rate constant ($hour^{-1}$)	3.0	

F= female; GSH = glutathione; M = male

Source: EPA 2000

Figure A-2. Predicted and Observed Relationship Between Air Exposure Concentration and Rate Metabolism of Vinyl Chloride in Rats*



*Measurements of metabolites (non-volatile ^{14}C in carcass) were made immediately following a 6-hour exposure to [^{14}C]vinyl chloride in air. Circles represent observations (±standard deviation); the line shows the corresponding simulations.

The human model was run iteratively, varying the ADD, until the model converged with the internal dose estimate shown in row 1 in Table A-7 (rat, male). The value for the Km1 for oxidative metabolism in humans was assumed to be equal to the Km1 value for rats (0.1 mg/L) (EPA 2000). The human ADD was assumed to be uniformly distributed over a 24-hour period. The resulting HED was 0.09 mg/kg/day (Table A-16). Additional simulations were performed assuming that the ADD was distributed over a 12-hour period (to simulate exposure from drinking water or food during the day only). The resulting dose metrics were very similar to the 24-hour estimates (data not shown).

Table A-16. Summary of Internal Dose Predictions and Corresponding Human and Rat Equivalent Doses

Species	BW (kg)	Km1 mg/L	ED (week)	EF1 (day/week)	EF2 (hour/day)	ADD (mg/kg/day)	DM (mg/L)
Wistar rat							
Male	0.377	0.1	149	7	4	0.17	3.16
Female	0.204	0.1	149	7	4	0.17	3.16
Human	70	0.1	3,640	7	24	0.09	3.16

ADD = average daily administered dose; BW = body weight; DM = dose metric equals the total amount of metabolite formed in 24 hours per L of liver; ED = exposure duration; EF = exposure frequency; Km1 = Michaelis-Menten constant for oxidative metabolism

The $NOAEL_{HED}$ of 0.09 mg/kg/day, associated with the rat NOAEL of 0.17 mg/kg/day (Til et al. 1983, 1991), served as the basis for the provisional chronic-duration oral MRL for vinyl chloride.

Uncertainty Factor: The PBPK-modeled equivalent human NOAEL of 0.09 mg/kg/day was divided by a total uncertainty factor (UF) of 30:

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

Provisional MRL = $NOAEL_{HED}$ ÷ (UF)
0.09 mg/kg/day ÷ (3 x 10) = 0.003 mg/kg/day

Other Additional Studies or Pertinent Information that Lend Support to this MRL: This provisional MRL is reinforced by a study by Feron et al. (1981) in which rats were fed diets containing PVC powder. Increased areas of cellular alteration (consisting of clear foci, basophilic foci, and eosinophilic foci) were observed in the liver of rats at an oral intake of vinyl chloride monomer of 1.8 mg/kg/day.

Agency Contacts (Chemical Managers): Rae Benedict

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR VINYL CHLORIDE

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

B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen was conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, chemical interactions, physical and chemical properties, production, use, environmental fate, environmental releases, and environmental and biological monitoring data for vinyl chloride. ATSDR primarily focused on peer-reviewed articles without publication date or language restrictions. Non-peer-reviewed studies that were considered relevant to the assessment of the health effects of vinyl chloride have undergone peer review by at least three ATSDR-selected experts who have been screened for conflict of interest. The inclusion criteria used to identify relevant studies examining the health effects of vinyl chloride are presented in Table B-1.

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

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

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

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

B.1.1 Literature Search

The current literature search was intended to update the 2006 toxicological profile for vinyl chloride; thus, the literature search was restricted to studies published between January 2004 and October 2020. The following main databases were searched in October 2020:

- PubMed
- National Technical Reports Library (NTRL)
- Scientific and Technical Information Network's TOXCENTER

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

The search was augmented by searching the Toxic Substances Control Act Test Submissions (TSCATS), NTP website, and National Institute of Health Research Portfolio Online Reporting Tools Expenditures

and Results (NIH RePORTER) databases using the queries presented in Table B-3. Additional databases were searched in the creation of various tables and figures, such as the TRI Explorer, the Substance Priority List (SPL) resource page, and other items as needed. Regulations applicable to vinyl chloride were identified by searching international and U.S. agency websites and documents.

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

Table B-2. Database Query Strings

Database search date	Query string
PubMed	
10/2020	("Vinyl Chloride"[mh] OR 75-01-4[rn] OR (("1-Chloroethene"[tw] OR "1-Chloroethylene"[tw] OR "Chlorethene"[tw] OR "Chlorethylene"[tw] OR "Chloroethene"[tw] OR "Chloroethylene"[tw] OR "Ethene, chloro-"[tw] OR "Ethylene monochloride"[tw] OR "Ethylene, chloro-"[tw] OR "F 1140"[tw] OR "Monochloroethene"[tw] OR "Monochloroethylene"[tw] OR "Monovinyl chloride"[tw] OR "Trovidur"[tw] OR "Vinyl C monomer"[tw] OR "Vinyl chloride"[tw] OR "Vinyl chlorine"[tw] OR "Vinylchloride"[tw]) NOT medline[sb]) OR (("1-Chloroethene"[tw] OR "1-Chloroethylene"[tw] OR "Chlorethene"[tw] OR "Chlorethylene"[tw] OR "Chloroethene"[tw] OR "Chloroethylene"[tw] OR "Ethene, chloro-"[tw] OR "Ethylene monochloride"[tw] OR "Ethylene, chloro-"[tw] OR "F 1140"[tw] OR "Monochloroethene"[tw] OR "Monochloroethylene"[tw] OR "Monovinyl chloride"[tw] OR "Trovidur"[tw] OR "Vinyl C monomer"[tw] OR "Vinyl chloride"[tw] OR "Vinyl chlorine"[tw] OR "Vinylchloride"[tw]) AND (to[sh] OR po[sh] OR ae[sh] OR pk[sh] OR ai[sh] OR ci[sh] OR bl[sh] OR cf[sh] OR ur[sh] OR "pharmacology"[sh:noexp] OR "environmental exposure"[mh] OR "endocrine system"[mh] OR "hormones, hormone substitutes, and hormone antagonists"[mh] OR "endocrine disruptors"[mh] OR "Computational biology"[mh] OR "Medical Informatics"[mh] OR Genomics[mh] OR Genome[mh] OR Proteomics[mh] OR Proteome[mh] OR Metabolomics[mh] OR Metabolome[mh] OR Genes[mh] OR "Gene expression"[mh] OR Phenotype[mh] OR genetics[mh] OR genotype[mh] OR Transcriptome[mh] OR ("Systems Biology"[mh] AND ("Environmental Exposure"[mh] OR "Epidemiological Monitoring"[mh] OR analysis[sh])) OR "Transcription, Genetic "[mh] OR "Reverse transcription"[mh] OR "Transcriptional activation"[mh] OR "Transcription factors"[mh] OR ("biosynthesis"[sh] AND (RNA[mh] OR DNA[mh])) OR "RNA, Messenger"[mh] OR "RNA, Transfer"[mh] OR "peptide biosynthesis"[mh] OR "protein biosynthesis"[mh] OR "Reverse Transcriptase Polymerase Chain Reaction"[mh] OR "Base Sequence"[mh] OR "Trans-activators"[mh] OR "Gene Expression Profiling"[mh] OR cancer[sb] OR (me[sh] AND ("humans"[mh] OR "animals"[mh])) OR toxicokinetics[mh:noexp]))) AND (2004:3000[dp] OR 2004:3000[mhda] OR 2004:3000[crdt] OR 2004:3000[edat])
NTRL	
10/2020	"Chlorethene" OR "Chlorethylene" OR "Chloroethene" OR "Chloroethylene" OR "Ethene, chloro-" OR "Ethylene monochloride" OR "Ethylene, chloro-" OR "Monochloroethene" OR "Monochloroethylene" OR "Monovinyl chloride" OR "Trovidur" OR "Vinyl C monomer" OR "Vinyl chloride" OR "Vinyl chlorine" OR "Vinylchloride" OR "F 1140"
Toxcenter	
10/2020	FILE 'TOXCENTER' ENTERED AT 18:17:45 ON 14 OCT 2020 CHARGED TO COST=EH038.05.01.LB.03 L1 11005 SEA FILE=TOXCENTER 75-01-4

Table B-2. Database Query Strings

Database search date	Query string
	L2 10830 SEA FILE=TOXCENTER L1 NOT TSCATS/FS L3 9602 SEA FILE=TOXCENTER L2 NOT PATENT/DT L4 2976 SEA FILE=TOXCENTER L3 AND PY>2003 ACT TOXQUERY/Q --------- L5 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?) L6 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT, IT) L7 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50) L8 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT L9 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?) L10 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?) L11 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?) L12 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE)) L13 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?) L14 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?) L15 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?) L16 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?) L17 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? OR SPERMATOB? OR SPERMATOC? OR SPERMATOG?) L18 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?) L19 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?) L20 QUE (ENDOCRIN? AND DISRUPT?) L21 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?) L22 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?) L23 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?) L24 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?) L25 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?) L26 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?) L27 QUE (NEPHROTOX? OR HEPATOTOX?) L28 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)

Table B-2. Database Query Strings

Database search date	Query string
	L29 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?) L30 QUE L5 OR L6 OR L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29 L31 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?) L32 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE) L33 QUE L30 OR L31 OR L32 L34 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?) L35 QUE L33 OR L34 --------- L36 1380 SEA FILE=TOXCENTER L4 AND L35 L37 295 SEA FILE=TOXCENTER L36 AND MEDLINE/FS L38 1136 DUP REM L36 (244 DUPLICATES REMOVED) ANSWERS '1-1136' FROM FILE TOXCENTER D SCAN L38

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS via ChemView	
10/2020	Compounds searched: 75-01-4
NTP	
10/2020	75-01-4 "Vinyl chloride" "Vinyl C monomer" "Vinyl chlorine" "Vinylchloride" "1-Chloroethene" "1-Chloroethylene" "Chloroethene" "Chloroethylene" "Chlorethene" "Chlorethylene" "Ethene, chloro-" "Ethylene, chloro-" "Ethylene monochloride" "Monochloroethene" "Monochloroethylene" "Monovinyl chloride" "F 1140" "Trovidur"
Regulations.gov	
10/2020	75-01-4
NIH RePORTER	
03/2021	Text Search: "1-Chloroethene" OR "1-Chloroethylene" OR "Chlorethene" OR "Chlorethylene" OR "Chloroethene" OR "Chloroethylene" OR "Ethene, chloro-" OR "Ethylene monochloride" OR "Ethylene, chloro-" OR "F 1140" OR "Monochloroethene" OR "Monochloroethylene" OR "Monovinyl chloride" OR "Trovidur" OR "Vinyl C

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
	monomer" OR "Vinyl chloride" OR "Vinyl chlorine" OR "Vinylchloride" (Advanced), Search in: Projects AdminIC: All, Fiscal Year: Active Projects
Other	Identified throughout the assessment process

The 2020 results were:

- Number of records identified from PubMed, NTRL, and TOXCENTER (after duplicate removal): 2,053
- Number of records identified from other strategies: 100
- Total number of records to undergo literature screening: 2,153

B.1.2 Literature Screening

A two-step process was used to screen the literature search to identify relevant studies on vinyl chloride:

- Title and abstract screen
- Full text screen

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

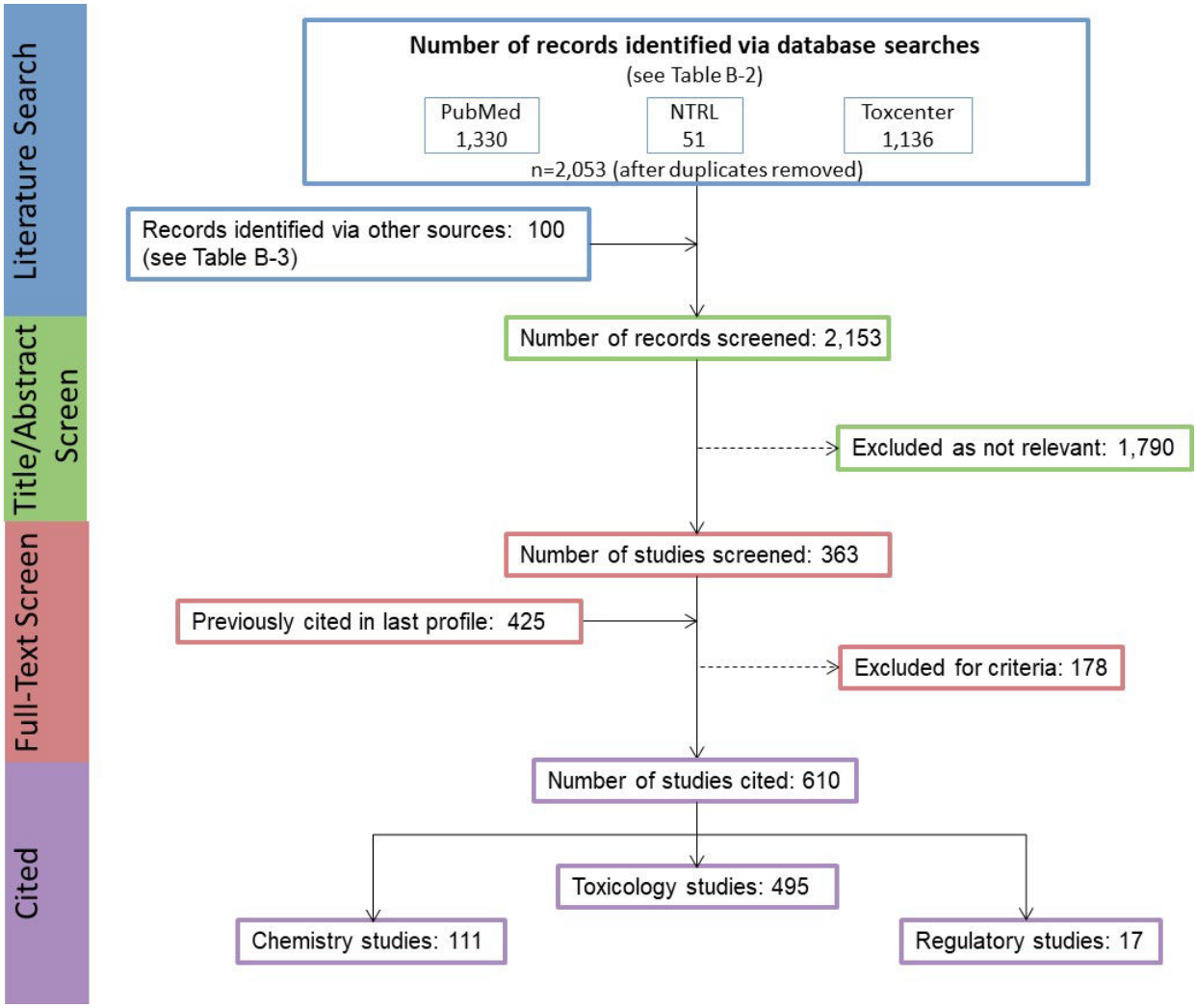
- Number of titles and abstracts screened: 2,153
- Number of studies considered relevant and moved to the next step: 363

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

- Number of studies undergoing full text review: 363
- Number of studies cited in the pre-public draft of the toxicological profile: 425
- Total number of studies cited in the profile: 610

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

Figure B-1. October 2020 Literature Search Results and Screen for Vinyl Chloride



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

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

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

C.1 PROBLEM FORMULATION

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

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

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

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

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

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

C.2 LITERATURE SEARCH AND SCREEN FOR HEALTH EFFECTS STUDIES

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

C.2.1 Literature Search

As noted in Appendix B, the current literature search was intended to update the 2006 toxicological profile for vinyl chloride; thus, the literature search was restricted to studies published between January 2004 and October 2020. See Appendix B for the databases searched and the search strategy.

A total of 2,153 records relevant to all sections of the toxicological profile were identified (after duplicate removal).

C.2.2 Literature Screening

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

Title and Abstract Screen. In the Title and Abstract Screen step, 2,153 records were reviewed; 80 documents were considered to meet the health effects inclusion criteria in Table C-1 and were moved to the next step in the process.

Full Text Screen. In the second step in the literature screening process for the systematic review, a full text review of 198 health effect documents (documents identified in the update literature search and documents cited in older versions of the profile) was performed. From those 198 documents, 225 studies were included in the qualitative review.

C.3 EXTRACT DATA FROM HEALTH EFFECTS STUDIES

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

Table C-2. Data Extracted From Individual Studies

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

A summary of the extracted data for each study is presented in the Supplemental Document for Vinyl Chloride and overviews of the results of the inhalation and oral exposure studies (no dermal exposure studies were identified) are presented in Sections 2.2–2.18 of the profile and in the Levels Significant Exposures tables in Section 2.1 of the profile (Tables 2-2 and 2-3, respectively).

C.4 IDENTIFY POTENTIAL HEALTH EFFECT OUTCOMES OF CONCERN

Overviews of the potential health effect outcomes for vinyl chloride identified in human and animal studies are presented in Tables C-3 and C-4, respectively. The available human studies evaluating noncancer effects examined a comprehensive set of endpoints for the inhalation route (no oral or dermal human studies were located). Occupational studies of inhalation exposure provide a thorough evaluation of respiratory, cardiovascular, hematological, musculoskeletal, hepatic, dermal, immunological, neurological, and developmental outcomes with health effects being observed for each outcome (except developmental). Animal inhalation studies examined a comprehensive set of endpoints, oral animal studies examined a limited number of health outcomes, and no dermal animal studies were available. Hepatic, immunological, neurological, developmental, and other noncancer (insulin resistance) effects

were considered sensitive noncancer outcomes (i.e., effects were observed at low concentrations or doses). Studies examining these potential outcomes were carried through to Steps 4–8 of the systematic review. Human studies that did not estimate exposure or include a comparison group (i.e., occupational health studies and case reports/series) were not included in the systematic review. Available cohort, case-control and cross-sectional studies were adequate for evaluating the sensitive health outcomes. There were 82 studies (published in 74 documents) examining these potential outcomes were carried through to Steps 4–8 of the systematic review.

APPENDIX C

Table C-3. Overview of the Health Outcomes for Vinyl Chloride Evaluated In Human Studies

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological	Neurological	Reproductive	Developmental	Other Noncancer	Cancer
Inhalation studies																	
Cohort		4	5		2		8					1	2	1	3		42
		2	4		2		7					1	2	1			33
Case control		1	1				5					4			5	1	12
		1	1				5					4				1	8
Population	1	9	10	3	6	5	16	1	6	3	1	9	13	3	4	1	5
	1	7	10	3	4	5	16	1	6	3	1	9	13	3		1	5
Case series		1	5	1	3	6	6		7	1		3	5				11
		1	5	1	2	6	6		7	1		2	5				11
Oral studies																	
Cohort																	
Case control																	
Population																	
Case series																	
Dermal studies																	
Cohort																	
Case control																	
Population																	
Case series																	

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

APPENDIX C

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

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological[a]	Neurological[a]	Reproductive[a]	Developmental	Other Noncancer	Cancer
Inhalation studies																	
Acute-duration	4	4	3		2		11	3		1	1	1	9		5		1
	2	4	2		2		7	3					7		4		1
Intermediate-duration	12	1	2		5	1	16	8	1			3	1	5	2	3	12
	2	1	1		3		13	3	1			3		3	2		12
Chronic-duration	1	2	1		1	1	1	2	1		1		3	1			12
	1	2	1		1	1	1	2	1		1		2	1			12
Oral studies																	
Acute-duration																	
Intermediate-duration																	
Chronic-duration	1				2		2		1								4
					1		2		1								4
Dermal studies																	
Acute-duration																	
Intermediate-duration																	
Chronic-duration																	

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

C.5 ASSESS THE RISK OF BIAS FOR INDIVIDUAL STUDIES

C.5.1 Risk of Bias Assessment

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

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

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

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

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

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

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

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

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

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

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

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

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

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

The results of the risk of bias assessment for the different types of vinyl chloride health effects studies (observational epidemiology and animal experimental studies) are presented in Tables C-8, C-9, and C-10, respectively.

Table C-8. Summary of Risk of Bias Assessment for Vinyl Chloride—Observational Epidemiology Studies

Reference	Risk of bias criteria and ratings						Risk of bias tier
	Selection bias	Confounding bias	Attrition / exclusion bias	Detection bias		Selective reporting bias	
	Comparison groups appropriate?	**Study design or analysis account for important confounding and modifying variables?***	Outcome data complete without attrition or exclusion from analysis?	**Confidence in exposure characterization?***	**Confidence in outcome assessment?***	All measured outcomes reported?	
Outcome: Hepatic Effects							
Inhalation—cohort							
Fedeli et al. 2019a	+	+	+	+	++	++	Second
Mundt et al. 2017	++	++	+	+	+	++	First
Hsieh et al. 2007	+	++	+	+	++	++	First
Maroni and Fanetti 2006	+	++	+	+	+	++	First
Zhu et al. 2005a	++	+	+	++	+	+	First
Hsiao et al. 2004	+	++	+	+	++	++	First
Maroni et al. 2003	+	++	+	+	+	++	First
Ward et al. 2001	+	+	+	+	+	+	First
Inhalation—cross-sectional							
Lee et al. 2020	–	+	++	++	++	++	First
Yuan et al. 2020	–	++	++	+	++	++	First
Wang et al. 2019b	+	++	+	+	++	++	First
Attarchi et al. 2007	++	+	–	++	+	++	First
Cheng et al. 1999b	–	++	+	+	++	++	First
Du et al. 1995	+	++	+	+	+	++	First
Tamburro et al. 1984	+	–	+	+	+	+	Second
Vihko et al. 1984	– –	– –	–	+	+	++	Second
NIOSH 1977	+	+	–	+	+	++	Second

Table C-8. Summary of Risk of Bias Assessment for Vinyl Chloride—Observational Epidemiology Studies

Reference	Risk of bias criteria and ratings: Selection bias — Comparison groups appropriate?	Confounding bias — **Study design or analysis account for important confounding and modifying variables?***	Attrition / exclusion bias — Outcome data complete without attrition or exclusion from analysis?	Detection bias — **Confidence in exposure characterization?***	Detection bias — **Confidence in outcome assessment?***	Selective reporting bias — All measured outcomes reported?	Risk of bias tier
Inhalation—case-control							
Cave et al. 2010	++	– –	+	+	+	++	Second
Mastrangelo et al. 2004	++	++	+	+	++	++	First
Du and Wang 1998	+	– –	+	–	+	+	Second
Liss et al. 1985	+	– –	–	–	+	+	Second
Outcome: Immunological Effects							
Inhalation—cross-sectional							
Saad et al. 2017	++	–	+	–	+	+	Second
Fucic et al. 1998	++	–	+	+	++	++	Second
Fucic et al. 1995	++	–	+	+	+	– –	Second
Bencko et al. 1988	–	–	+	–	+	+	Second
Bogdanikowa and Zawilska 1984	+	–	+	–	+	–	Second
Inhalation—case-control							
Cave et al. 2010	++	– –	+	+	++	++	Second
Black et al. 1983, 1986	++	–	+	–	+	+	Second
Grainger et al. 1980	+	–	+	–	+	+	Second
Outcome: Neurological Effects							
Inhalation—cohort							
Bove et al. 2014	++	+	+	++	++	++	First
Zhu et al. 2005a	++	+	+	++	–	+	First

Table C-8. Summary of Risk of Bias Assessment for Vinyl Chloride—Observational Epidemiology Studies

Reference	Risk of bias criteria and ratings						Risk of bias tier
	Selection bias	Confounding bias	Attrition / exclusion bias	Detection bias		Selective reporting bias	
	Comparison groups appropriate?	**Study design or analysis account for important confounding and modifying variables?***	Outcome data complete without attrition or exclusion from analysis?	**Confidence in exposure characterization?***	**Confidence in outcome assessment?***	All measured outcomes reported?	
Inhalation—cross-sectional							
Perticoni et al. 1986	+	–	–	–	++	++	Second
NIOSH 1977	+	+	–	–	+	++	Second
Spirtas et al. 1975	+	+	–	+	+	+	First
Outcome: Developmental Effects							
Inhalation—cohort							
Bao et al. 1988	+	–	+	+	+	–	Second
Inhalation—cross-sectional							
Infante et al. 1976a, 1976b; NIOSH 1977	+	+	–	–	+	++	Second
Inhalation—case-control							
Swartz et al. 2015	++	++	+	+	++	++	First
Talbott et al. 2015	++	++	+	+	++	++	First
Ruckart et al. 2013	+	+	+	+	+	++	First
Rosenman et al. 1989	+	–	+	–	+	+	Second
Theriault et al. 1983	+	–	+	–	–	+	Third
Edmonds et al. 1978	+	–	+	–	+	+	Second
Inhalation—ecological							
Infante 1976	+	–	+	–	+	+	Second
Edmonds et al. 1975	+	–	+	–	+	+	Second

Table C-8. Summary of Risk of Bias Assessment for Vinyl Chloride—Observational Epidemiology Studies

Reference	Risk of bias criteria and ratings: Selection bias — Comparison groups appropriate?	Confounding bias — **Study design or analysis account for important confounding and modifying variables?***	Attrition / exclusion bias — Outcome data complete without attrition or exclusion from analysis?	Detection bias — **Confidence in exposure characterization?***	Detection bias — **Confidence in outcome assessment?***	Selective reporting bias — All measured outcomes reported?	Risk of bias tier
Outcome: Other Noncancer (Insulin Resistance)							
Inhalation—cross-sectional							
Lee et al. 2020	–	+	++	++	++	++	First
Inhalation—case-control							
Cave et al. 2010	++	– –	+	+	+	++	Second

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

Table C-9. Summary of Risk of Bias Assessment for Vinyl Chloride— Human-Controlled Exposure Studies

	Risk of bias criteria and ratings							
	Selection bias		Performance Bias	Attrition / exclusion bias	Detection bias		Selective reporting bias	
Reference	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	**Were the research personnel and human subjects blinded to the study group during the study?***	Outcome data complete without attrition or exclusion from analysis?	**Confidence in exposure characterization?***	**Confidence in outcome assessment?***	All measured outcomes reported?	Risk of bias tier
Outcome: Neurological Effects								
Inhalation								
Lester et al. 1963	++		+	+	+	+	–	First
Patty et al. 1930	– –		–	+	+	+	–	Second

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

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

Reference	Risk of bias criteria and ratings									
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	**Is there confidence in the outcome assessment?***	Were all measured outcomes reported?	Did the study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Outcome: Hepatic Effects										
Inhalation acute exposure										
Jaeger et al. 1974 (rat; 1, 5 days)	–	–	+	+	–	–	+	++	NA	Second
John et al. 1977, 1981 (rat; 10 days)	–	–	+	+	++	–	+	++	NA	First
Mastromatteo et al. 1960 (rat; 30 minutes)	–	–	+	+	++	+	+	++	NA	First
Reynolds et al. 1975a (rat; 1, 5 days)	–	–	+	+	–	–	–	++	NA	Third
Reynolds et al. 1975b (rat; 1 day)	–	–	+	+	–	–	+	++	NA	Second
John et al. 1977, 1981 (mouse; 10 days)	–	–	+	+	++	–	+	++	NA	First
Mastromatteo et al. 1960 (mouse; 30 minutes)	–	–	+	+	++	+	+	++	NA	First
Mastromatteo et al. 1960 (guinea pig; 30 minutes)	–	–	+	+	++	+	+	++	NA	First
John et al. 1977, 1981 (rabbit; 13 days)	–	–	+	+	++	–	+	++	NA	First
Ungvary et al. 1978 (rat; 7–9 days)	–	–	+	+	++	–	+	++	NA	First
Hehir et al. 1981 (rat; 1-hour)	–	–	+	+	+	–	+	++	NA	First
Inhalation intermediate exposure										
Bi et al. 1985 (rat; 3, 6 months)	+	+	+	+	+	++	+	++	NA	First
Lester et al. 1963 (rat; 19 days)	–	–	++	+	+	++	+	++	NA	First
Lester et al. 1963 (rat; 92 days)	+	+	++	+	+	++	+	++	NA	First
Sokal et al. 1980 (rat; 10 months)	–	–	++	+	–	++	+	++	NA	First

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

Reference	Risk of bias criteria and ratings									
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	**Is there confidence in the outcome assessment?***	Were all measured outcomes reported?	Did the study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Thornton et al. 2002 (rat; 2-generation)	++	+	++	+	++	–	+	++	NA	First
Torkelson et al. 1961 (rat; 6 months)	–	–	++	+	+	+	+	++	NA	First
Wisniewska-Knypl et al. 1980 (rat; 10 months)	–	–	++	+	–	++	+	++	NA	First
Chen et al. 2019 (mouse; 12 weeks)	–	–	++	+	–	–	+	++	NA	Second
Lang et al. 2018 (mouse; 12 weeks)	–	–	++	+	–	–	+	++	NA	Second
Lang et al. 2020 (mouse; 12 weeks)	–	–	++	+	–	–	+	++	NA	Second
Schaffner 1978 (mouse; 6 months)	–	–	+	+	–	–	–	++	NA	Third
Sharma and Gehring 1979 (mouse; 2–8 weeks)	–	–	+	+	–	–	+	++	NA	Second
Wahlang et al. 2020 (mouse; 12 weeks)	–	–	++	+	–	–	+	++	NA	Second
Wang et al. 2019a (mouse; 16 weeks)	–	–	++	+	–	– –	+	++	NA	Second
Torkelson et al. 1961 (rabbit; 6 months)	–	–	++	+	+	+	+	++	NA	First
Du et al. 1979 (rat; 2–4 weeks)	+	+	++	+	–	– –	+	++	NA	First
Inhalation chronic exposure										
Bi et al. 1985 (rat; 12 months)	+	+	+	+	+	++	+	++	NA	First
Oral chronic exposure										
Til et al. 1983 (rat; 149 weeks)	++	+	++	+	++	++	+	++	NA	First
Feron et al. 1981 (rat; 2 years)	++	+	++	+	++	++	+	++	NA	First

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

Reference	Risk of bias criteria and ratings: Selection bias — Was administered dose or exposure level adequately randomized?	Selection bias — Was the allocation to study groups adequately concealed?	Performance bias — Were experimental conditions identical across study groups?	Performance bias — Were the research personnel blinded to the study group during the study?	Attrition/ exclusion bias — Were outcome data complete without attrition or exclusion from analysis?	Detection bias — Is there confidence in the exposure characterization?	Detection bias — **Is there confidence in the outcome assessment?***	Selective reporting bias — Were all measured outcomes reported?	Other bias — Did the study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Outcome: Immunological Effects										
Inhalation acute exposure										
Mastromatteo et al. 1960 (guinea pig; 30 minutes)	–	–	+	+	++	+	+	++	NA	First
Inhalation intermediate exposure										
Bi et al. 1985 (rat; 3, 6 months)	+	+	+	+	+	++	+	++	NA	First
Sokal et al. 1980 (rat; 10 months)	–	–	++	+	–	++	+	++	NA	Second
Sharma and Gehring 1979 (mouse; 2–8 weeks)	–	–	+	+	–	–	+	++	NA	Second
Outcome: Neurological Effects										
Inhalation acute exposure										
Jaeger et al. 1974 (rat; 1, 5 days)	–	–	+	+	–	–	+	++	NA	Second
Lester et al. 1963 (rat; 2 hours)	–	–	++	+	+	++	–	++	NA	Third
Mastromatteo et al. 1960 (rat; 30 minutes)	–	–	+	+	++	+	+	++	NA	First
Hehir et al. 1981 (rat; 2 weeks)	–	–	+	+	+	–	+	++	NA	First
Hehir et al. 1981 (rat; 1 hour)	–	–	+	+	+	–	+	++	NA	First
Hehir et al. 1981 (mouse; 1 hour)	–	–	+	+	+	–	+	++	NA	First
Mastromatteo et al. 1960 (mouse; 30 minutes)	–	–	+	+	++	+	+	++	NA	First

APPENDIX C

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

Reference	Risk of bias criteria and ratings									
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	**Is there confidence in the outcome assessment?***	Were all measured outcomes reported?	Did the study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Mastromatteo et al. 1960 (guinea pig; 30 minutes)	–	–	+	+	++	+	+	++	NA	First
Patty et al. 1930 (guinea pig; up to 8 hours)	–	–	+	+	+	–	+	++	NA	First
Inhalation intermediate exposure										
Hehir et al. 1981 (rat; 20 weeks)	–	–	+	+	+	–	+	++	NA	First
Inhalation intermediate exposure										
Viola 1970 (rat; 12 months)	–	–	–	+	+	–	+	++	NA	Second
Viola et al. 1971 (rat; 12 months)	–	–	+	+	+	+	+	++	NA	First
Feron and Kroes 1979 (rat; 12 months)	–	–	+	+	–	–	+	++	NA	Second
Outcome: Developmental Effects										
Inhalation acute exposure										
Thornton et al. 2002 (rat; GDs 6–19)	++	+	++	+	++	–	+	+	NA	First
John et al. 1977, 1981 (rat; 10 days)	–	–	+	+	++	–	+	++	NA	First
John et al. 1977, 1981 (mouse; 10 days)	–	–	+	+	++	–	+	++	NA	First
John et al. 1977, 1981 (rabbit; 13 days)	–	–	+	+	++	–	+	++	NA	First
Ungvary et al. 1978 (rat; 7-9 days)	–	–	+	+	++	–	+	++	NA	First
Inhalation intermediate exposure										
Sal'nikova and Kotsovskaya 1980 (rat; 21 days)	–	–	+	+	–	–	+	++	NA	Second
Mirkova et al. 1978	–	–	–	+	–	–	–	–	NA	Third

APPENDIX C

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

Reference	Risk of bias criteria and ratings									
	Selection bias		Performance bias		Attrition/ exclusion bias	Detection bias		Selective reporting bias	Other bias	
	Was administered dose or exposure level adequately randomized?	Was the allocation to study groups adequately concealed?	Were experimental conditions identical across study groups?	Were the research personnel blinded to the study group during the study?	Were outcome data complete without attrition or exclusion from analysis?	Is there confidence in the exposure characterization?	**Is there confidence in the outcome assessment?***	Were all measured outcomes reported?	Did the study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Outcome: Other Noncancer (Insulin Resistance)										
Inhalation intermediate exposure										
Chen et al. 2019 (mouse; 12 weeks)	–	–	++	+	–	–	+	++	NA	Second
Lang et al. 2018 (mouse; 12 weeks)	–	–	++	+	–	+	+	++	NA	First
Wahlang et al. 2020 (mouse; 12 weeks)	–	–	++	+	–	–	+	++	NA	Second

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

*Key question used to assign risk of bias tier

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

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

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

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

C.6.1 Initial Confidence Rating

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

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

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

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

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

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

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

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

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

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

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

The presence or absence of the key features and the initial confidence levels for studies examining hepatic, immunological, neurological, developmental and other noncancer (insulin resistance) observed in the observational epidemiology, human controlled-exposure and animal experimental studies are presented in Tables C-14, C-15, and C-16, respectively.

Table C-14. Presence of Key Features of Study Design for Vinyl Chloride—Observational Epidemiology Studies

	Key features				
Reference	Controlled exposure	Exposure prior to outcome	Outcomes assessed on an individual level	Comparison group	Initial study confidence
Outcome: Hepatic effects					
Inhalation—cohort					
Fedeli et al. 2019a	No	Yes	Yes	Yes	Moderate
Mundt et al. 2017	No	Yes	Yes	Yes	Moderate
Hsieh et al. 2007	No	Yes	Yes	Yes	Moderate

Table C-14. Presence of Key Features of Study Design for Vinyl Chloride—Observational Epidemiology Studies

Reference	Key features				Initial study confidence
	Controlled exposure	Exposure prior to outcome	Outcomes assessed on an individual level	Comparison group	
Maroni and Fanetti 2006	No	Yes	Yes	Yes	Moderate
Zhu et al. 2005a	No	Yes	Yes	Yes	Moderate
Hsiao et al. 2004	No	Yes	Yes	Yes	Moderate
Maroni et al. 2003	No	Yes	Yes	Yes	Moderate
Ward et al. 2001	No	Yes	Yes	Yes	Moderate
Inhalation—cross-sectional					
Lee et al. 2020	No	No	Yes	Yes	Low
Yuan et al. 2020	No	No	Yes	Yes	Low
Wang et al. 2019b	No	No	Yes	Yes	Low
Attarchi et al. 2007	No	No	Yes	Yes	Low
Cheng et al. 1999b	No	No	Yes	Yes	Low
Du et al. 1995	No	No	Yes	Yes	Low
Tamburro et al. 1984	No	No	Yes	Yes	Low
Vihko et al. 1984	No	No	Yes	No	Very low
NIOSH 1977	No	No	Yes	Yes	Low
Inhalation—case-control					
Cave et al. 2010	No	Yes	Yes	Yes	Moderate
Mastrangelo et al. 2004	No	Yes	Yes	Yes	Moderate
Du and Wang 1998	No	Yes	Yes	Yes	Moderate
Liss et al. 1985	No	Yes	Yes	Yes	Moderate
Outcome: Immunological effects					
Inhalation—cross-sectional					
Saad et al. 2017	No	No	Yes	Yes	Moderate
Fucic et al. 1998	No	No	Yes	Yes	Moderate
Fucic et al. 1995	No	No	Yes	Yes	Moderate
Bencko et al. 1988	No	No	Yes	Yes	Moderate
Bogdanikowa and Zawilska 1984	No	No	Yes	Yes	Moderate
Inhalation—case-control					
Cave et al. 2010	No	No	Yes	Yes	Low
Black et al. 1983, 1986	No	Yes	Yes	Yes	Moderate
Grainger et al. 1980	No	Yes	Yes	Yes	Moderate

Table C-14. Presence of Key Features of Study Design for Vinyl Chloride—Observational Epidemiology Studies

Reference	Key features				Initial study confidence
	Controlled exposure	Exposure prior to outcome	Outcomes assessed on an individual level	Comparison group	
Outcome: Neurological effects					
Inhalation—cohort					
Bove et al. 2014	No	Yes	Yes	Yes	Moderate
Zhu et al. 2005a	No	Yes	Yes	Yes	Moderate
Inhalation—cross-sectional					
Perticoni et al. 1986	No	No	Yes	Yes	Low
NIOSH 1977	No	No	Yes	Yes	Low
Spirtas et al. 1975	No	No	Yes	Yes	Low
Outcome: Developmental effects					
Inhalation—cohort					
Bao et al. 1988	No	Yes	Yes	Yes	Moderate
Inhalation—cross-sectional					
Infante et al. 1976a, 1976b; NIOSH 1977	No	No	Yes	Yes	Low
Inhalation—case-control					
Swartz et al. 2015	No	Yes	Yes	Yes	Moderate
Talbott et al. 2015	No	Yes	Yes	Yes	Moderate
Ruckart et al. 2013	No	Yes	Yes	Yes	Moderate
Rosenman et al. 1989	No	Yes	Yes	Yes	Moderate
Theriault et al. 1983	No	Yes	Yes	Yes	Moderate
Edmonds et al. 1978	No	Yes	Yes	Yes	Moderate
Inhalation—ecological					
Infante 1976	No	Yes	Yes	Yes	Moderate
Edmonds et al. 1975	No	Yes	Yes	Yes	Moderate
Other noncancer (insulin resistance)					
Inhalation—cross-sectional					
Lee et al. 2020	No	No	Yes	Yes	Low
Inhalation—case-control					
Cave et al. 2010	No	Yes	Yes	Yes	Moderate

Table C-15. Presence of Key Features of Study Design for Vinyl Chloride—Human-Controlled Exposure Studies

Reference	Key features: Comparison group	Sufficient number of subjects	Outcomes assessed with appropriate methods	Statistical analysis	Initial study confidence
Outcome: Neurological effects					
Inhalation					
Lester et al. 1963	Yes	Yes	Yes	No	Moderate
Patty et al. 1930	No	No	Yes	No	Very low

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

Reference	Key feature: Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	Initial study confidence
Outcome: Hepatic effects					
Inhalation acute exposure					
Jaeger et al. 1974 (rat; 1, 5 days)	Yes	No	Yes	No	Low
John et al. 1977, 1981 (rat; 10 days)	Yes	Yes	Yes	Yes	High
Mastromatteo et al. 1960 (rat; 30 minutes)	Yes	Yes	Yes	No	Moderate
Reynolds et al. 1975a (rat; 1, 5 days)	No	No	Yes	No	Low
Reynolds et al. 1975b (rat; 1 day)	Yes	No	Yes	No	Low
John et al. 1977, 1981 (mouse; 10 days)	Yes	Yes	Yes	Yes	High
Mastromatteo et al. 1960 (mouse; 30 minutes)	Yes	Yes	Yes	No	Moderate
Mastromatteo et al. 1960 (guinea pig; 30 minutes)	Yes	Yes	Yes	No	Moderate
John et al. 1977, 1981 (rabbit; 13 days)	Yes	Yes	Yes	Yes	High
Ungvary et al. 1978 (rat; 7–9 days)	Yes	Yes	Yes	Yes	High
Hehir et al. 1981 (rat; 1 hour)	Yes	Yes	Yes	No	Moderate

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

Reference	Key feature: Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	Initial study confidence
Inhalation intermediate exposure					
Bi et al. 1985 (rat; 3, 6 months)	Yes	Yes	Yes	Yes	High
Lester et al. 1963 (rat; 19 days)	Yes	Yes	Yes	Yes	High
Lester et al. 1963 (rat; 92 days)	Yes	Yes	Yes	Yes	High
Sokal et al. 1980 (rat; 10 months)	Yes	Yes	Yes	Yes	High
Thornton et al. 2002 (rat; 2-generation)	Yes	Yes	Yes	Yes	High
Torkelson et al. 1961 (rat; 6 months)	Yes	Yes	Yes	Yes	High
Wisniewska-Knypl et al. 1980 (rat; 10 months)	Yes	Yes	Yes	Yes	High
Chen et al. 2019 (mouse; 12 weeks)	Yes	Yes	Yes	Yes	High
Lang et al. 2018 (mouse; 12 weeks)	Yes	Yes	Yes	Yes	High
Lang et al. 2020 (mouse; 12 weeks)	Yes	Yes	Yes	Yes	High
Schaffner 1978 (mouse; 6 months)	No	Yes	Yes	No	Low
Sharma and Gehring 1979 (mouse; 2–8 weeks)	Yes	No	Yes	Yes	Moderate
Wahlang et al. 2020 (mouse; 12 weeks)	Yes	No	Yes	Yes	Moderate
Wang et al. 2019a (mouse; 16 weeks)	Yes	Yes	Yes	Yes	High
Torkelson et al. 1961 (rabbit; 6 months)	Yes	No	Yes	Yes	Moderate
Du et al. 1979 (rat; 2–4 weeks)	Yes	No	Yes	Yes	Moderate
Inhalation chronic exposure					
Bi et al. 1985 (rat; 12 months)	Yes	Yes	Yes	Yes	High
Oral chronic exposure					
Til et al. 1983 (rat; 149 weeks)	Yes	Yes	Yes	Yes	High
Feron et al. 1981 (rat; 2 years)	Yes	Yes	Yes	Yes	High
Outcome: Immunological effects					
Inhalation acute exposure					
Mastromatteo et al. 1960 (guinea pig; 30 minutes)	Yes	Yes	Yes	No	Moderate
Inhalation intermediate exposure					
Bi et al. 1985 (rat; 3, 6 months)	Yes	Yes	Yes	Yes	High
Sokal et al. 1980 (rat; 10 months)	Yes	Yes	Yes	Yes	High

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

Reference	Key feature: Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	Initial study confidence
Sharma and Gehring 1979 (mouse; 2–8 weeks)	Yes	No	Yes	Yes	Moderate
Outcome: Neurological effects					
Inhalation acute exposure					
Jaeger et al. 1974 (rat; 1, 5 days)	Yes	No	Yes	No	Low
Lester et al. 1963 (rat; 2 hours)	No	No	Yes	No	Low
Mastromatteo et al. 1960 (rat; 30 minutes)	Yes	Yes	Yes	No	Moderate
Hehir et al. 1981 (rat; 2 weeks)	Yes	Yes	Yes	No	Moderate
Hehir et al. 1981 (rat; 1 hour)	Yes	Yes	Yes	No	Moderate
Hehir et al. 1981 (mouse; 1 hour)	Yes	Yes	Yes	No	Moderate
Mastromatteo et al. 1960 (mouse; 30 minutes)	Yes	Yes	Yes	No	Moderate
Mastromatteo et al. 1960 (guinea pig; 30 minutes)	Yes	Yes	Yes	No	Moderate
Patty et al. 1930 (guinea pig; up to 8 hours)	Yes	Yes	Yes	No	Moderate
Inhalation intermediate exposure					
Hehir et al. 1981 (rat; 20 weeks)	Yes	Yes	Yes	No	Moderate
Inhalation chronic exposure					
Viola 1970 (rat; 12 months)	Yes	Yes	Yes	No	Moderate
Viola et al. 1971 (rat; 12 months)	Yes	Yes	Yes	No	Moderate
Feron and Kroes 1979 (rat; 12 months)	Yes	Yes	Yes	No	Moderate
Outcome: Developmental effects					
Inhalation acute exposure					
Thornton et al. 2002 (rat; GDs 6–19)	Yes	Yes	Yes	Yes	High
John et al. 1977, 1981 (rat; 10 days)	Yes	Yes	Yes	Yes	High
John et al. 1977, 1981 (mouse; 10 days)	Yes	Yes	Yes	Yes	High
John et al. 1977, 1981 (rabbit; 13 days)	Yes	Yes	Yes	Yes	High
Ungvary et al. 1978 (rat; 7–9 days)	Yes	Yes	Yes	Yes	High

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

Reference	Key feature: Concurrent control group	Key feature: Sufficient number of animals per group	Key feature: Appropriate parameters to assess potential effect	Key feature: Adequate data for statistical analysis	Initial study confidence
Inhalation intermediate exposure					
Sal'nikova and Kotsovskaya 1980 (rat; 21 days)	Yes	Yes	Yes	Yes	High
Mirkova et al. 1978 (rat; 21 days)	Yes	Yes	Yes	Yes	High
Other noncancer (insulin resistance)					
Inhalation intermediate exposure					
Chen et al. 2019 (mouse; 12 weeks)	Yes	Yes	Yes	Yes	High
Lang et al. 2018 (mouse; 12 weeks)	Yes	Yes	Yes	Yes	High
Wahlang et al. 2020 (mouse; 12 weeks)	Yes	No	Yes	Yes	Moderate

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

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

	Initial study confidence	Initial confidence rating
Outcome: Hepatic effects		
Inhalation acute exposure		
Animal studies		
Jaeger et al. 1974 (rat; 1, 5 days)	Low	High
John et al. 1977, 1981 (rat; 10 days)	High	
Mastromatteo et al. 1960 (rat; 30 minutes)	Moderate	
Reynolds et al. 1975a (rat; 1, 5 days)	Low	
Reynolds et al. 1975b (rat; 1 day)	Low	
John et al. 1977, 1981 (mouse; 10 days)	High	
Mastromatteo et al. 1960 (mouse; 30 minutes)	Moderate	
Mastromatteo et al. 1960 (guinea pig; 30 minutes)	Moderate	
John et al. 1977, 1981 (rabbit; 13 days)	High	
Ungvary et al. 1978 (rat; 7–9 days)	High	
Hehir et al. 1981 (rat; 1 hour)	Moderate	

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

	Initial study confidence	Initial confidence rating
Inhalation intermediate exposure		
Animal studies		
Bi et al. 1985 (rat; 3, 6 months)	High	High
Lester et al. 1963 (rat; 19 days)	High	
Lester et al. 1963 (rat; 92 days)	High	
Sokal et al. 1980 (rat; 10 months)	High	
Thornton et al. 2002 (rat; 2-generation)	High	
Torkelson et al. 1961 (rat; 6 months)	High	
Wisniewska-Knypl et al. 1980 (rat; 10 months)	High	
Chen et al. 2019 (mouse; 12 weeks)	High	
Lang et al. 2018 (mouse; 12 weeks)	High	
Lang et al. 2020 (mouse; 12 weeks)	High	
Schaffner 1978 (mouse; 6 months)	Low	
Sharma and Gehring 1979 (mouse; 2–8 weeks)	Moderate	
Wahlang et al. 2020 (mouse; 12 weeks)	Moderate	
Wang et al. 2019a (mouse; 16 weeks)	High	
Torkelson et al. 1961 (rabbit; 6 months)	Moderate	
Du et al. 1979 (rat; 2-4 weeks)	Moderate	
Inhalation chronic exposure		
Human studies		
NIOSH 1977	Low	Moderate
Zhu et al. 2005a	Moderate	
Liss et al. 1985	Moderate	
Tamburro et al. 1984	Low	
Vihko et al. 1984	Very low	
Du et al. 1995	Low	
Cheng et al. 1999b	Low	
Ward et al. 2001	Moderate	
Du and Wang 1998	Moderate	
Mastrangelo et al. 2004	Moderate	
Maroni et al. 2003	Moderate	
Cave et al. 2010	Moderate	
Hsieh et al. 2007	Moderate	
Attarchi et al. 2007	Low	
Maroni and Fanetti 2006	Moderate	
Hsiao et al. 2004	Moderate	
Mundt et al. 2017	Moderate	
Fedeli et al. 2019a	Moderate	
Wang et al. 2019b	Low	
Lee et al. 2020	Low	
Yuan et al. 2020		

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

	Initial study confidence	Initial confidence rating
Animal studies		
Bi et al. 1985 (rat; 12 months)	High	High
Oral chronic exposure		
Animal studies		
Til et al. 1983 (rat; 149 weeks)	High	High
Feron et al. 1981 (rat; 2 years)	High	
Outcome: Immunological effects		
Inhalation acute exposure		
Animal studies		
Mastromatteo et al. 1960 (guinea pig; 30 minutes)	Moderate	Moderate
Inhalation intermediate exposure		
Animal studies		
Bi et al. 1985 (rat; 3, 6 months)	High	High
Sokal et al. 1980 (rat; 10 months)	High	
Sharma and Gehring 1979 (mouse; 2–8 weeks)	Moderate	
Inhalation chronic exposure		
Human studies		
Cave et al. 2010	Low	Moderate
Fucic et al. 1995	Moderate	
Fucic et al. 1998	Moderate	
Bogdanikowa and Zawilska 1984	Moderate	
Grainger et al. 1980	Moderate	
Black et al. 1983, 1986	Moderate	
Saad et al. 2017	Moderate	
Bencko et al. 1988	Moderate	
Outcome: Neurological effects		
Inhalation acute exposure		
Human studies		
Patty et al. 1930	Very low	Moderate
Lester et al. 1963	Moderate	
Animal studies		
Jaeger et al. 1974 (rat; 1, 5 days)	Low	Moderate
Lester et al. 1963 (rat; 2 hours)	Low	
Mastromatteo et al. 1960 (rat; 30 minutes)	Moderate	
Hehir et al. 1981 (rat; 2 weeks)	Moderate	
Hehir et al. 1981 (rat; 1 hour)	Moderate	
Hehir et al. 1981 (mouse; 1 hour)	Moderate	
Mastromatteo et al. 1960 (mouse; 30 minutes)	Moderate	
Mastromatteo et al. 1960 (guinea pig; 30 minutes)	Moderate	
Patty et al. 1930 (guinea pig; up to 8 hours)	Moderate	

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

	Initial study confidence	Initial confidence rating
Inhalation intermediate exposure		
Animal studies		
Hehir et al. 1981 (rat; 20 weeks)	Moderate	Moderate
Inhalation chronic exposure		
Human studies		
NIOSH 1977	Low	Moderate
Zhu et al. 2005a	Moderate	
Spirtas et al. 1975	Low	
Perticoni et al. 1986	Low	
Bove et al. 2014	Moderate	
Animal studies		
Viola 1970 (rat; 12 months)	Moderate	Moderate
Viola et al. 1971 (rat; 12 months)	Moderate	
Feron and Kroes 1979 (rat; 12 months)	Moderate	
Outcome: Developmental effects		
Inhalation acute exposure		
Animal studies		
Thornton et al. 2002 (rat; GDs 6–19)	High	High
John et al. 1977, 1981 (rat; 10 days)	High	
John et al. 1977, 1981 (mouse; 10 days)	High	
John et al. 1977, 1981 (rabbit; 13 days)	High	
Ungvary et al. 1978 (rat; 7–9 days)	High	
Inhalation intermediate exposure		
Human studies		
Swartz et al. 2015	Moderate	Moderate
Talbott et al. 2015	Moderate	
Ruckart et al. 2013	Moderate	
Animal studies		
Sal'nikova and Kotsovskaya 1980 (rat; 21 days)	High	High
Mirkova et al. 1978 (rat; 21 days)	High	
Inhalation chronic exposure		
Human studies		
NIOSH 1977	Low	Moderate
Edmonds et al. 1975, 1978	Moderate	
Infante 1976	Moderate	
Rosenman et al. 1989	Moderate	
Theriault et al. 1983	Moderate	
Infante et al. 1976a, 1976b	Low	
Bao et al. 1988	Moderate	

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

	Initial study confidence	Initial confidence rating
Outcome: Other noncancer (insulin resistance)		
Inhalation intermediate exposure		
Animal studies		
Chen et al. 2019 (mouse; 12 weeks)	High	High
Lang et al. 2018 (mouse; 12 weeks)	High	
Wahlang et al. 2020 (mouse; 12 weeks)	Moderate	
Inhalation chronic exposure		
Human studies		
Lee et al. 2020	Low	Moderate
Cave et al. 2010	Moderate	

C.6.2 Adjustment of the Confidence Rating

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

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

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

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

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

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

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

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

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

	Initial confidence	Adjustments to the initial confidence rating	Final confidence
Outcome: Hepatic			
Human studies	Moderate	+1 consistency	High
Animal studies	High	-1 inconsistency	Moderate
Outcome: Immunological			
Human studies	Moderate	-1 risk of bias, +1 consistency	Moderate
Animal studies	High	-1 inconsistency, -1 indirectness	Low
Outcome: Neurological			
Human Studies	Moderate	None	Moderate
Animal Studies	Moderate	None	Moderate
Outcome: Developmental			
Human studies	Moderate	-1 risk of bias	Low
Animal studies	High	None	High
Outcome: Other noncancer (insulin resistance)			
Human studies	Moderate	-1 indirectness	Low
Animal studies	High	-1 risk of bias	Moderate

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

	Confidence in body of evidence	
Outcome	Human studies	Animal studies
Hepatic	High	Moderate
Immunological	Moderate	Low
Neurological	Moderate	Moderate
Developmental	Low	High
Other Noncancer (Insulin resistance)	Low	Moderate

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

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

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

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

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

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

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

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

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

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

Outcome	Confidence in body of evidence	Direction of health effect	Level of evidence for health effect
Human studies			
Hepatic	High	Health effect	High
Immunological	Moderate	Health effect	Moderate
Neurological	Moderate	Health effect	Moderate
Developmental	Low	No health effect	Inadequate
Other Noncancer (Insulin resistance)	Low	Health effect	Low
Animal studies			
Hepatic	Moderate	Health effect	Moderate
Immunological	Low	No health effect	Inadequate
Neurological	Moderate	Health effect	Moderate
Developmental	High	Health effect	High
Other Noncancer (Insulin resistance)	Moderate	No health effect	Inadequate

C.8 INTEGRATE EVIDENCE TO DEVELOP HAZARD IDENTIFICATION CONCLUSIONS

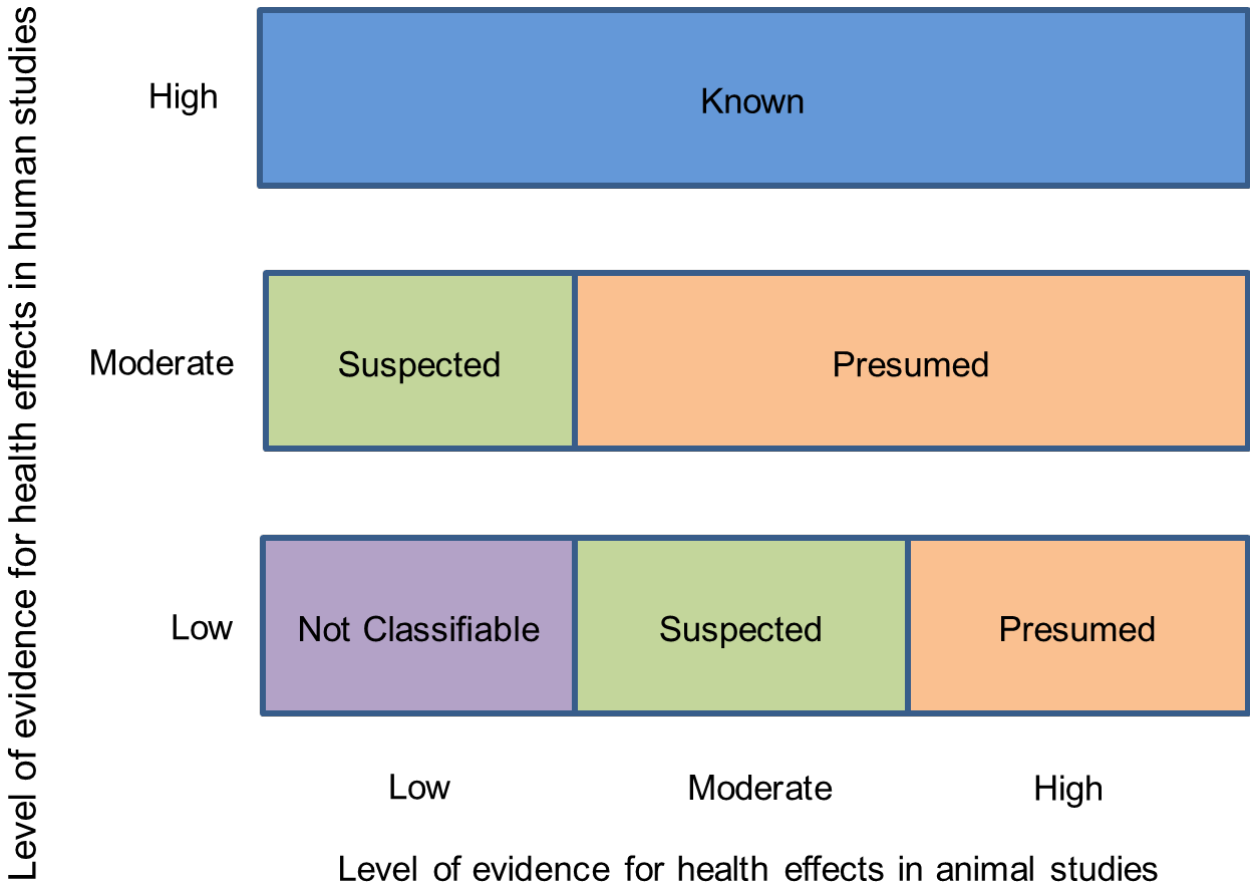
The final step involved the integration of the evidence streams for the human studies and animal studies to allow for a determination of hazard identification conclusions. For health effects, there were four hazard identification conclusion categories:

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

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

- **Known:** A health effect in this category would have:
    - High level of evidence for health effects in human studies **AND** a high, moderate, or low level of evidence in animal studies.
- **Presumed:** A health effect in this category would have:
    - Moderate level of evidence in human studies **AND** high or moderate level of evidence in animal studies **OR**
    - Low level of evidence in human studies **AND** high level of evidence in animal studies
- **Suspected:** A health effect in this category would have:
    - Moderate level of evidence in human studies **AND** low level of evidence in animal studies **OR**
    - Low level of evidence in human studies **AND** moderate level of evidence in animal studies
- **Not classifiable:** A health effect in this category would have:
    - Low level of evidence in human studies **AND** low level of evidence in animal studies

Figure C-1. Hazard Identification Scheme



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

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

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

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

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

Presumed Health Effects

- Hepatic
  - High level of evidence of hepatic effects in humans based on fibrosis, cirrhosis, and steatosis observed in vinyl chloride workers (Cave et al. 2010; Du and Wang 1998; Fedeli et al. 2019a; Hsiao et al. 2004; Hsieh et al. 2007; Maroni et al. 2003; Mastrangelo et al. 2004; Mundt et al. 2017; Ward et al. 2001; Yuan et al. 2020).
  - Moderate evidence level in animals including increased liver weight and histopathological liver lesions in rats and mice following inhalation (Bi et al. 1985; Lester et al. 1963; Sokal et al. 1980; Thornton et al. 2002; Torkelson et al. 1961; Wisniewska-Knypl et al. 1980) and oral exposure (Feron et al. 1981; Til et al. 1983, 1991).
- Neurological
  - Moderate level of evidence in humans based on neurological symptoms reported in human studies (Lester et al. 1963; NIOSH 1977; Patty et al. 1930; Spirtas et al. 1975; Zhu et al. 2005a) and a single report of peripheral neuropathy (Perticoni et al. 1986).
  - Moderate level of evidence in animals based on clinical signs in multiple acute inhalation studies (Hehir et al. 1981; Jaeger et al. 1974; Lester et al. 1963; Mastromatteo et al. 1960; Patty et al. 1930)

Suspected Health Effects

- Immunological
  - Moderate level of evidence in humans based on occupational worker studies demonstrating an increase in circulating immune complexes, immunoglobulins, complement factors, and levels of inflammatory cytokines (Bencko et al. 1988, Bogdanikowa and Zawilska 1984; Cave et al. 2010; Grainger et al. 1980; Saad et al. 2017; Ward 1976).
  - Inadequate evidence in animals due to limited information available on increased spleen weight in rats (Bi et al. 1985; Sokal et al. 1980) and a splenic lymphocyte proliferation assay in mice (Sharma and Gehring 1979)
- Developmental
  - Inadequate evidence in humans due to the absence of demonstrated developmental effects in a small number of ecological and case-control studies of birth defects (Edmonds et al. 1978; Infante 1976; Infante et al. 1976a, 1976b; NIOSH 1977; Rosenman et al. 1989; Ruckart et al. 2013; Swartz et al. 2015; Talbott et al. 2015; Theriault et al. 1983).
  - High level of evidence in animals based on developmental effects occurring at low concentrations in inhalation studies (John et al. 1977, 1981).

Not Classifiable

- Other noncancer (insulin resistance)
  - Low level of evidence level in humans based on two epidemiology studies with serum markers of increased insulin resistance (Cave et al. 2010; Lee et al. 2020).
  - Several intermediate-duration inhalation studies using glucose, insulin, and pyruvate tolerance tests (Chen et al. 2019; Lang et al. 2018) and measures of fasting blood glucose and glycogen storage (Wahlang et al. 2020). These studies used a single low concentration of vinyl chloride (0.85 ppm) and did not evaluate effects at higher concentrations.

Table C-21. Hazard Identification Conclusions for Vinyl Chloride

Outcome	Hazard identification
Hepatic	Presumed health effect
Immunological	Suspected health effect
Neurological	Presumed health effect
Developmental	Suspected health effect
Other noncancer (insulin resistance)	Not classifiable

APPENDIX D. USER'S GUIDE

Chapter 1. Relevance to Public Health

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

1. What effects are known to occur in humans?

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

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

Minimal Risk Levels (MRLs)

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

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

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

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

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

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

Chapter 2. Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

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

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

TABLE LEGEND

See Sample LSE Table (page D-5)

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

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

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

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

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

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

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

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

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

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

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

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

FIGURE LEGEND

See Sample LSE Figure (page D-6)

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

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

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

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

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

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

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

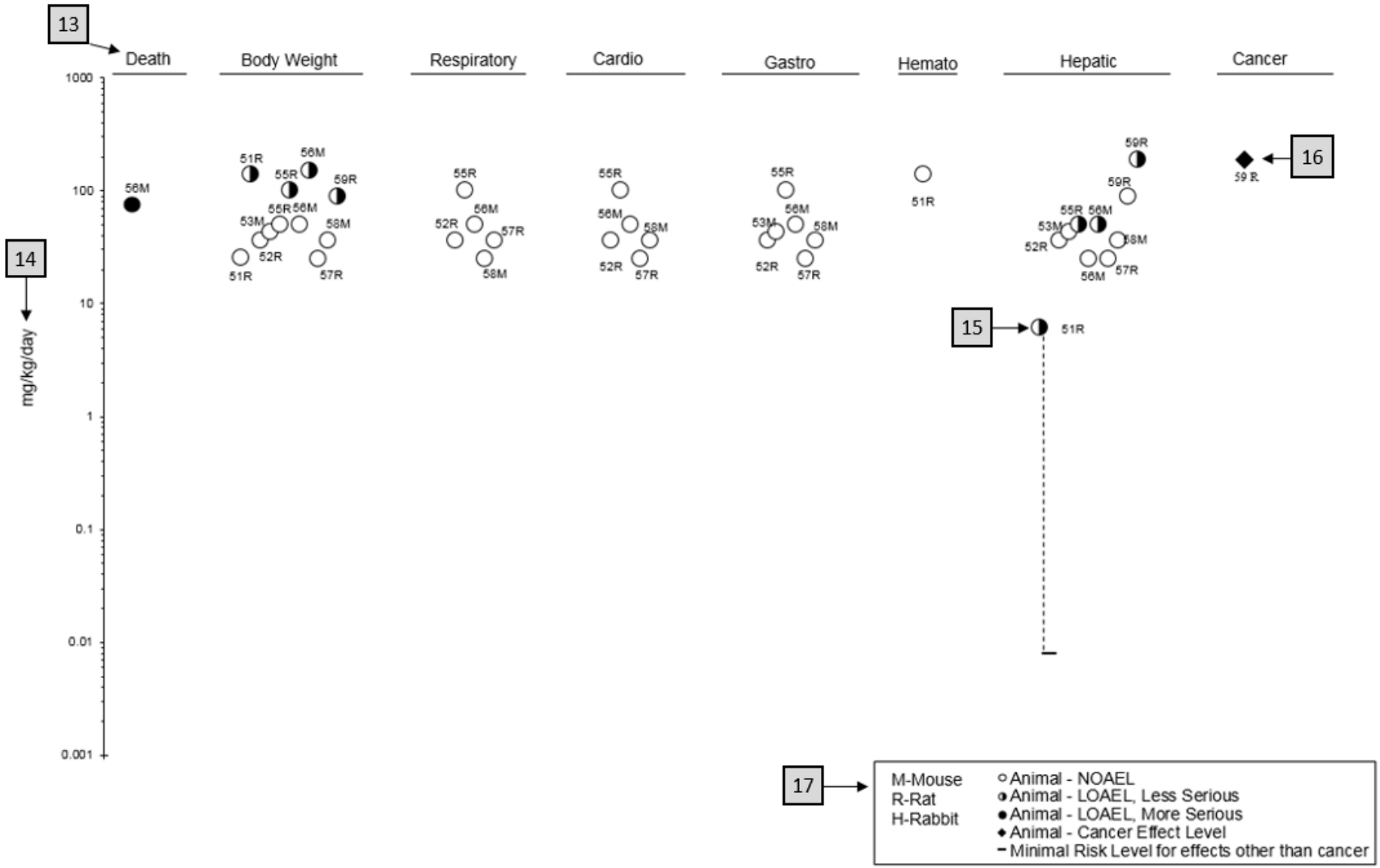
Table 2-X. Levels of Significant Exposure to [Chemical X] – Oral

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

[a]The number corresponds to entries in Figure 2-x.
[b]Used to derive an acute-duration oral minimal risk level (MRL) of 0.1 mg/kg/day based on the $BMDL_{05}$ of 10 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).
[c]Used to derive a chronic-duration oral MRL of 0.008 mg/kg/day based on the $BMDL_{10}$ of 0.78 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

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

12 → Chronic (≥365 days)



APPENDIX E. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

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

Primary Chapters/Sections of Interest

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

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

Pediatrics:

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

ATSDR Information Center

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

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

Physician Briefs discuss health effects and approaches to patient management in a brief/factsheet style. *Physician Overviews* are narrated PowerPoint presentations with Continuing Education credit available (see https://www.atsdr.cdc.gov/emes/health_professionals/index.html).

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

Fact Sheets (ToxFAQs™) provide answers to frequently asked questions about toxic substances (see https://www.atsdr.cdc.gov/toxfaqs/Index.asp).

Other Agencies and Organizations

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

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 395 E Street, S.W., Suite 9200, Patriots Plaza Building, Washington, DC 20201 • Phone: 202-245-0625 or 1-800-CDC-INFO (800-232-4636) • Web Page: https://www.cdc.gov/niosh/.

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

Clinical Resources (Publicly Available Information)

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

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

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

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

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

APPENDIX F. GLOSSARY

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

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

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

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

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

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

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

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

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

Carcinogen—A chemical capable of inducing cancer.

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

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

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

Ceiling Value—A concentration that must not be exceeded.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Incidence—The ratio of new cases of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

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

***In Vivo*—**Occurring within the living organism.

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

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{Lo})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Metabolism—Process in which chemical substances are biotransformed in the body that could result in less toxic and/or readily excreted compounds or produce a biologically active intermediate.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—The state of being diseased; the morbidity rate is the incidence or prevalence of a disease in a specific population.

Mortality—Death; the mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations, which are changes in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a hazardous substance.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Although effects may be produced at this dose, they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio that is greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) regulatory limit on the amount or concentration of a substance not to be exceeded in workplace air averaged over any 8-hour work shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests (insects or other organisms harmful to cultivated plants or animals).

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic endpoints. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—A type of physiologically based dose-response model that is comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information, including tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as blood:air partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which a group is followed over time and the pertinent observations are made on events occurring after the start of the study.

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation RfC is expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily oral exposure of the human population to a potential hazard that is likely to be without risk of deleterious noncancer health effects during a lifetime. The oral RfD is expressed in units of mg/kg/day.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). RQs are (1) ≥1 pound or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a hazardous substance. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a hazardous substance.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, existing health condition, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio/Relative Risk—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio that is greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Short-Term Exposure Limit (STEL)—A STEL is a 15-minute TWA exposure that should not be exceeded at any time during a workday.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which it is believed that nearly all workers may be repeatedly exposed, day after day, for a working lifetime without adverse effect. The TLV may be expressed as a Time-Weighted Average (TLV-TWA), as a Short-Term Exposure Limit (TLV-STEL), or as a ceiling limit (TLV-C).

Time-Weighted Average (TWA)—An average exposure within a given time period.

Toxicokinetic—The absorption, distribution, metabolism, and elimination of toxic compounds in the living organism.

Toxics Release Inventory (TRI)—The TRI is an EPA program that tracks toxic chemical releases and pollution prevention activities reported by industrial and federal facilities.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL), Reference Dose (RfD), or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis (3 being the approximate logarithmic average of 10 and 1).

Xenobiotic—Any substance that is foreign to the biological system.

APPENDIX G. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

AAPCC	American Association of Poison Control Centers
ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ACMT	American College of Medical Toxicology
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AEGL	Acute Exposure Guideline Level
AIC	Akaike's information criterion
AIHA	American Industrial Hygiene Association
ALT	alanine aminotransferase
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BCF	bioconcentration factor
BMD/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
C	centigrade
CAA	Clean Air Act
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
cm	centimeter
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DWEL	drinking water exposure level
EAFUS	Everything Added to Food in the United States
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
ERPG	emergency response planning guidelines
F	Fahrenheit
F1	first-filial generation
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FR	Federal Register

FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GGT	γ-glutamyl transferase
GRAS	generally recognized as safe
HEC	human equivalent concentration
HED	human equivalent dose
HHS	Department of Health and Human Services
HPLC	high-performance liquid chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	kilokilogram; 1 kilokilogram is equivalent to 1,000 kilograms and 1 metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Level of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
MRL	Minimal Risk Level
MS	mass spectrometry
MSHA	Mine Safety and Health Administration
Mt	metric ton
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NCEH	National Center for Environmental Health
ND	not detected
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences

NIOSH	National Institute for Occupational Safety and Health
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NTP	National Toxicology Program
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PAC	Protective Action Criteria
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PEHSU	Pediatric Environmental Health Specialty Unit
PEL	permissible exposure limit
PEL-C	permissible exposure limit-ceiling value
pg	picogram
PND	postnatal day
POD	point of departure
ppb	parts per billion
ppbv	parts per billion by volume
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
REL-C	recommended exposure level-ceiling value
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SD	standard deviation
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase (same as aspartate aminotransferase or AST)
SGPT	serum glutamic pyruvic transaminase (same as alanine aminotransferase or ALT)
SIC	standard industrial classification
SLOAEL	serious lowest-observed-adverse-effect level
SMR	standardized mortality ratio
sRBC	sheep red blood cell
STEL	short term exposure limit
TLV	threshold limit value
TLV-C	threshold limit value-ceiling value
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey

USNRC	U.S. Nuclear Regulatory Commission
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result