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 gas or 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 partitions to the atmosphere. Vinyl chloride has been detected at low levels 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 as a byproduct during 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., hazardous waste sites, 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 multiple 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 or nearly eliminated 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-duration 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

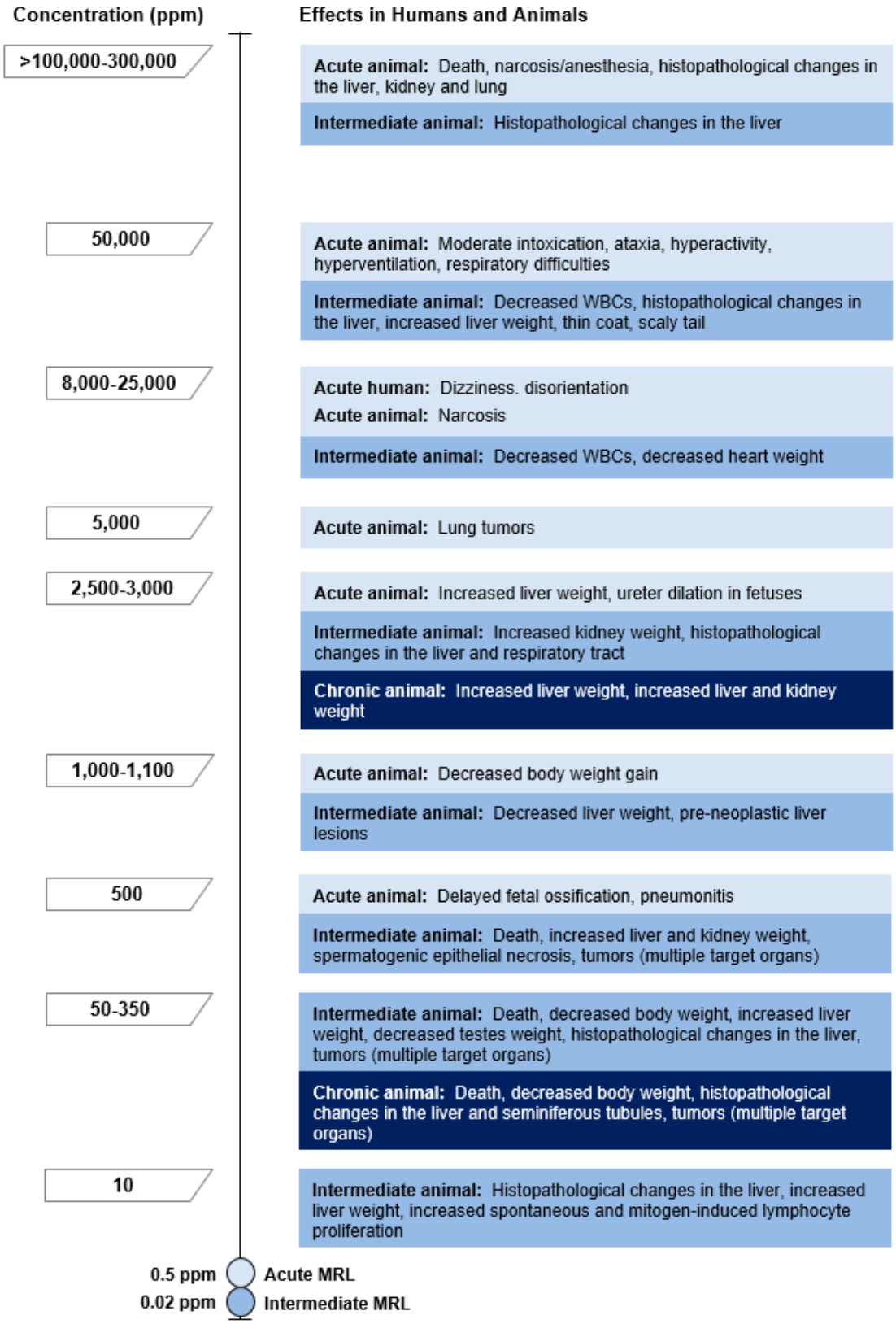
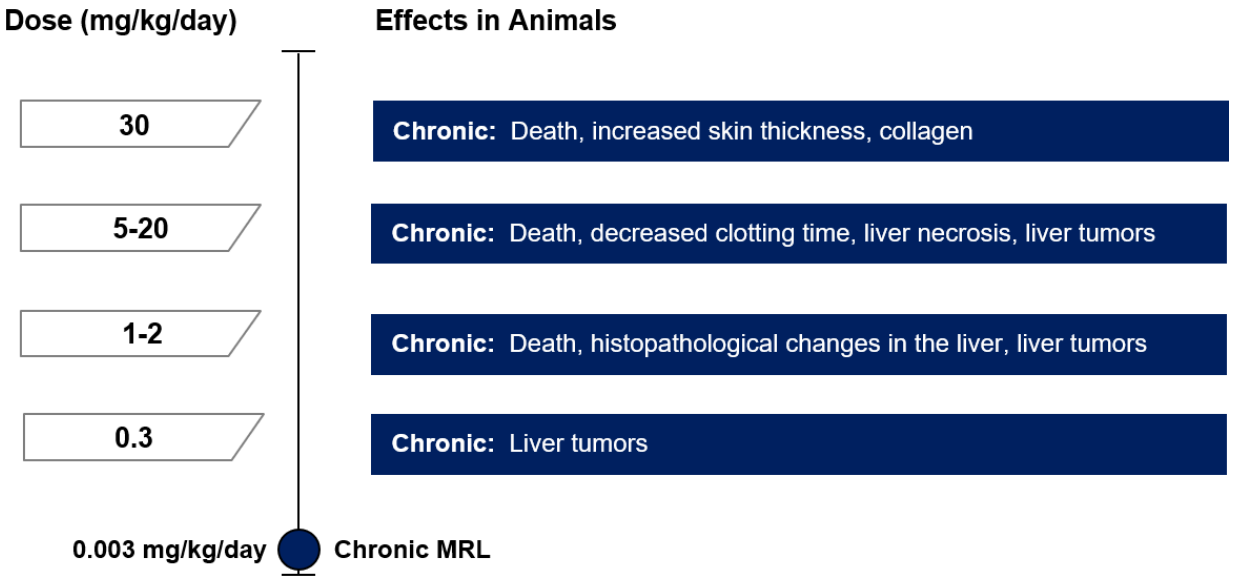


Figure 1-2. Health Effects Found in Animals Following Oral Exposure to Vinyl Chloride



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 hepatic effects increased with increasing vinyl chloride concentration, ranging from cellular hypertrophy and sinusoidal compression, to vacuolization, hepatic hyperplasia, fibrosis, and necrosis (Jia et al. 2022; 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) and exposed to vinyl chloride experienced 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; Jia et al. 2022; Lang et al. 2018, 2020; Liang et al. 2018; Liu et al. 2023; Wahlang et al. 2020). Chronic-duration 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 (a condition in which the fingers blanch and become numb with discomfort upon exposure to the cold), 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, orosomucoid) were elevated in highly exposed male vinyl chloride workers (Bencko et al. 1988; Bogdanikowa and Zawilska 1984; Wagnerova et al. 1988), 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), increased thymus weight in immunized rabbits (Sharma et al. 1980), and an increase in spontaneous and/or mitogen-stimulated lymphocyte proliferation in mice and immunized rabbits (Sharma and Gehring 1979; Sharma et al. 1980).

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 12,000 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, decreased reflexes, 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-duration 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 2021). 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 classified as *carcinogenic 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

Available data indicate that 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.

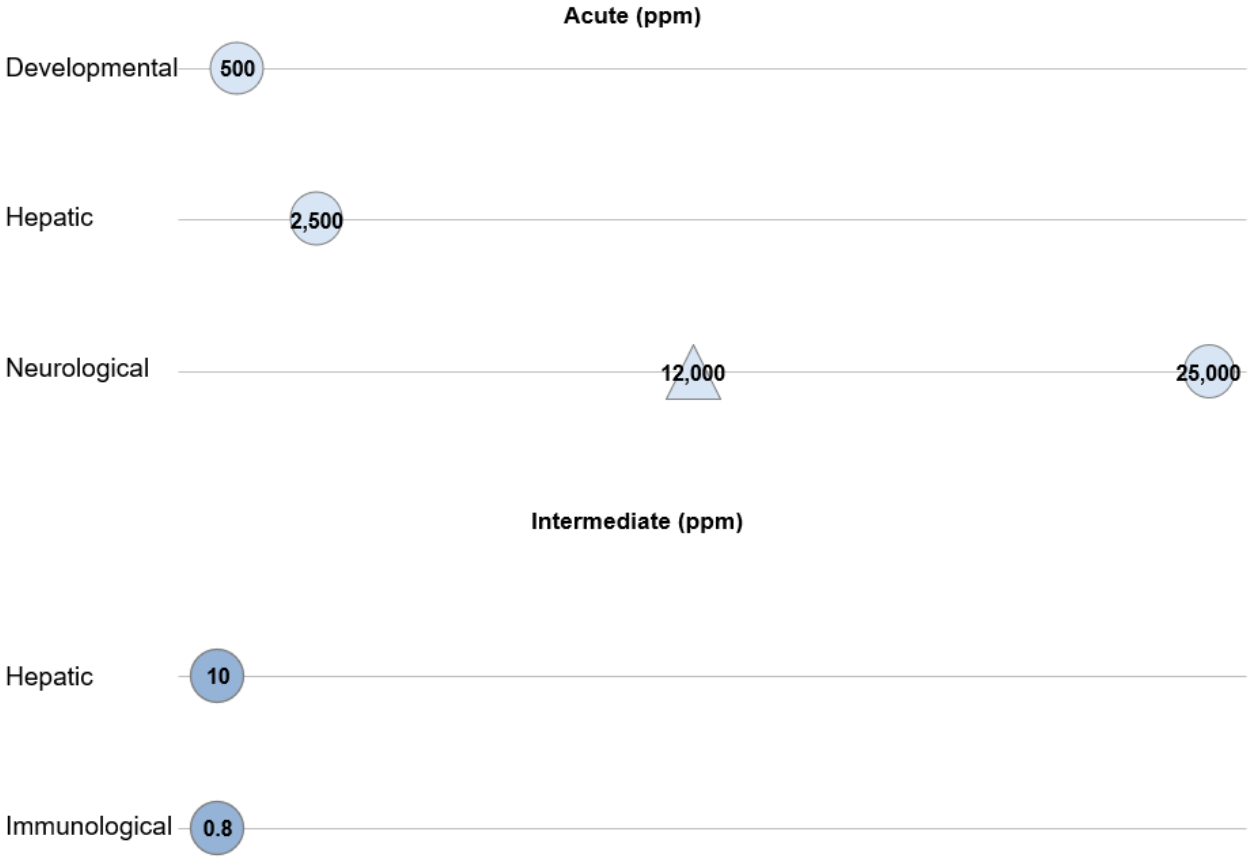


Figure 1-4. Summary of Sensitive Targets of Vinyl Chloride – Oral

Available data indicate that 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 route	Exposure duration	Provisional MRL	Critical effect	POD type	POD value	Uncertainty/ modifying factor	Reference
Inhalation	Acute	**0.5 ppm** (1.3 mg/m^3)	Delayed ossification	$NOAEL_{HEC}$	15 ppm	UF: 30	John et al. 1977, 1981
	Intermediate	**0.02 ppm** (0.05 mg/m^3)	Increased incidence of centrilobular hypertrophy	$BMCL_{HEC}$	0.5 ppm	UF: 30	Thornton et al. 2002
	Chronic	None	–	–	–	–	–
Oral	Acute	None	–	–	–	–	–
	Intermediate	None	–	–	–	–	–
	Chronic	**0.003 mg/kg/day**	Liver cell polymorphism	$NOAEL_{HED}$	0.09 mg/kg/day	UF: 30	Til et al. 1983, 1991

[a]See Appendix A for additional information.

BMCL = benchmark concentration lower confidence limit; HEC = human equivalent concentration; HED = human equivalent dose; NOAEL = no-observed-adverse-effect level; POD = point of departure; UF = uncertainty factor