CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

1,1-Dichloroethene (Chemical Abstracts Service [CAS] Registry Number 75-35-4; synonyms include 1,1-dichloroethylene and vinylidene chloride) is a human-made chemical that does not occur naturally in the environment. The major use for 1,1-dichloroethene is as a chemical intermediate to make other products. 1,1-Dichloroethene is used to make various plastics, such as packaging materials and flexible films and as flame retardant coatings for fiber and carpet backing. 1,1-Dichloroethene is a colorless liquid that evaporates quickly at room temperature, has a mild, sweet smell, is flammable, and burns quickly.

Occupational exposure to 1,1-dichloroethene is most likely to occur through inhalation and dermal routes. The general population is most likely exposed to 1,1-dichloroethene by inhalation of contaminated air and ingestion of contaminated food and drinking water.

1.2 SUMMARY OF HEALTH EFFECTS

Information on the toxicity of 1,1-dichloroethene primarily comes from studies conducted in experimental animals. Three limited studies evaluated the toxicity of 1,1-dichloroethene in humans. Approximately 90 experiments conducted in animals were available for review. Two-thirds of the studies employed inhalation exposure; one-third of the studies employed oral exposure. Results from selected oral studies indicated species and sex differences in 1,1-dichloroethene toxicity, as well as differences related to nutritional status (i.e., fasted animals were more sensitive than fed animals). Limited information was available regarding 1,1-dichloroethene toxicity following dermal exposure. As illustrated in Figures 1-1 and 1-2, the most sensitive effects appear to be depressed body weight, nasal tissue damage, liver damage, kidney damage, and delayed skeletal development. A systematic review of respiratory, hepatic, and renal endpoints conducted by ATSDR resulted in the following hazard identification conclusions (see Appendix C for details):

- Upper respiratory tract toxicity is a presumed health effect for humans
- Liver toxicity is a presumed health effect for humans
- Kidney toxicity is a presumed health effect for humans

Figure 1-1. Health Effects Found in Animals Following Inhalation Exposure to 1,1-Dichloroethene

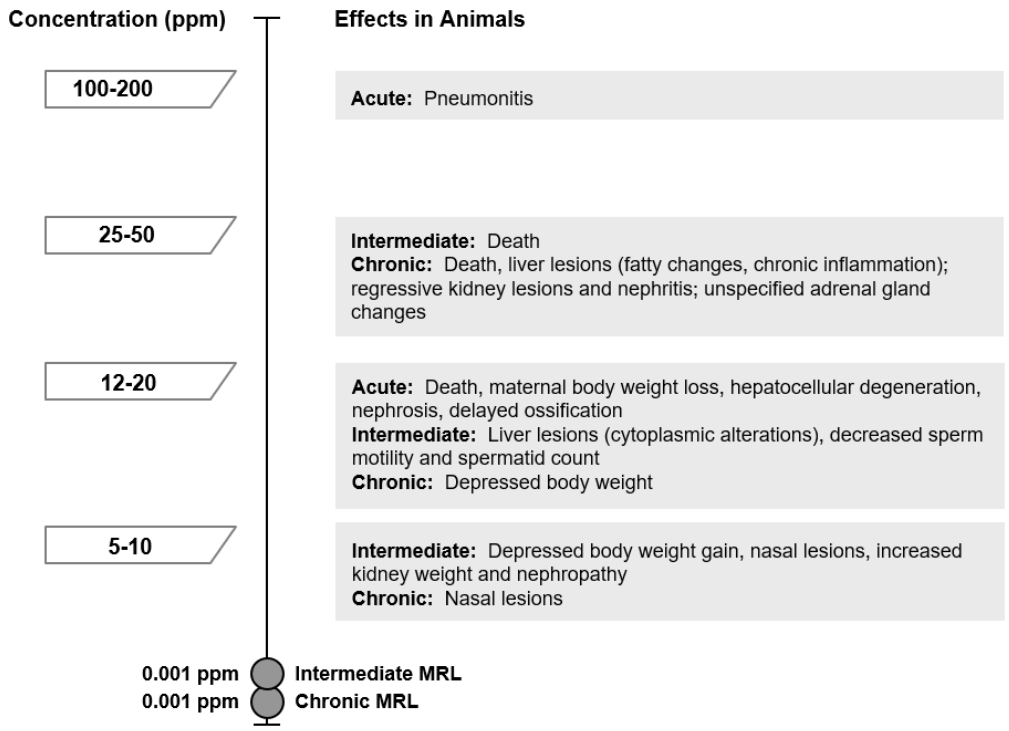
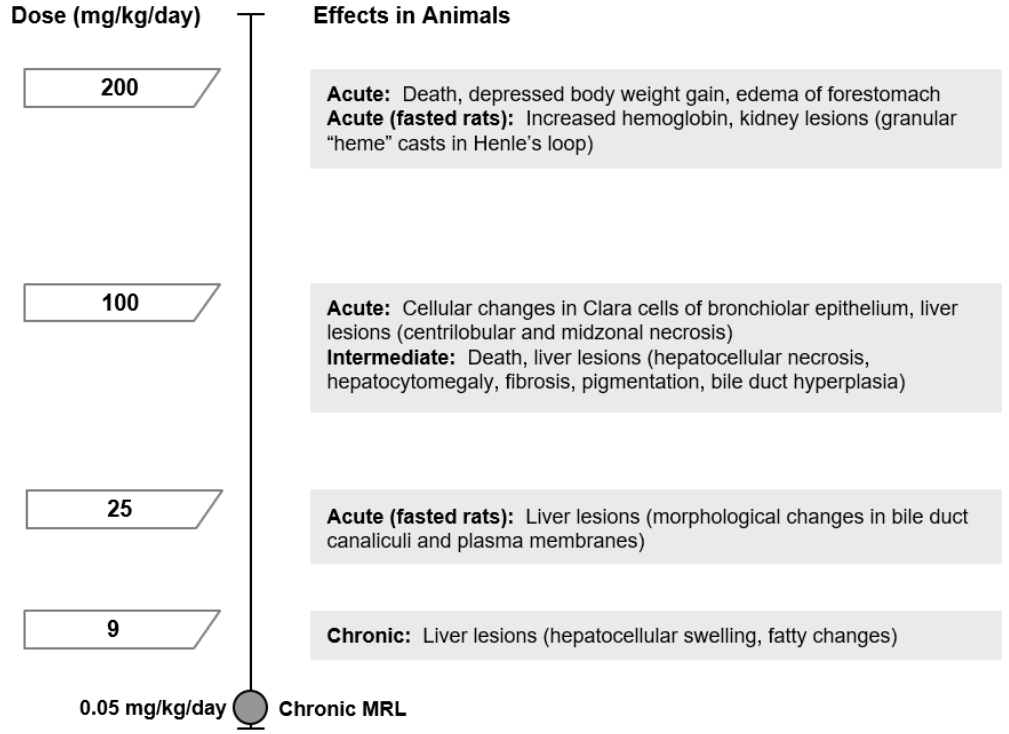


Figure 1-2. Health Effects Found in Animals Following Oral Exposure to 1,1-Dichloroethene



Body Weight Effects. Depressed body weight or body weight loss were reported among maternal rats intermittently exposed to 1,1-dichloroethene vapor during major portions of gestation at exposure levels as low as 15–56 ppm (EPA 1977a) and rabbits exposed at 160 ppm (Murray et al. 1979). Adverse body weight effects were observed in other inhalation studies that employed repeated or continuous exposure of rats, mice, or rabbits at concentrations in the range of 6.25–500 ppm (Gage 1970; Henck et al. 1979; Maltoni et al. 1985; NTP 2015a; Prendergast et al. 1967).

In a series of oral studies of rats and mice repeatedly gavaged with 1,1-dichloroethene (NTP 1982), depressed body weight gain was noted in male rats treated for 14 days at 500 mg/kg/day and similarly treated female rats at 100 mg/kg/day. Depressed body weight gains were observed in male and female rats treated for 90 days at 250 mg/kg/day. There were no apparent treatment-related effects on body weight among similarly treated mice.

Respiratory Effects. Well-conducted inhalation studies in rats and mice support the identification of the upper respiratory system as a presumed target in humans. Effects in animals exposed to 1,1-dichloroethene by inhalation include increased lung weight; chronic active inflammation; hyperostosis; nasal turbinate atrophy; and/or olfactory epithelial mineralization, necrosis, atrophy, and/or metaplasia at repeated exposure levels as low as 6.25–25 ppm (NTP 2015a). In intermediate-duration inhalation studies, rats appear to be more sensitive than mice. Single oral dosing of mice resulted in damage and disruption of Clara cells (club cells) in the lung and increased lung weight (Forkert et al. 1985).

Hepatic Effects. Results from inhalation and oral animal studies support the identification of the liver as a presumed target in humans. Animal studies identify the liver as a major target organ of 1,1-dichloroethene toxicity associated with acute-, intermediate-, and chronic-duration inhalation and oral routes of exposure. Hepatotoxicity is evident by the appearance of both biochemical changes such as alterations in serum enzyme levels indicative of liver injury and induction of hepatic enzymes (e.g., Jaeger 1977; Jaeger et al. 1974; Jenkins and Andersen 1978; Short et al. 1977d) and marked histological changes (e.g., midzonal and centrilobular swelling of liver, degeneration and necrosis of hepatocytes) (e.g., Henck et al. 1979; Jenkins and Andersen 1978; Maltoni et al. 1985; NTP 1982, 2015a). Acute-duration inhalation and oral studies have demonstrated that fasted animals are more susceptible than nonfasted animals to 1,1-dichloroethene hepatotoxicity.

Renal Effects. Results from inhalation and oral animal studies support the identification of the kidney as a presumed target in humans. Adverse effects have been observed in the kidneys of experimental animals

following acute-, intermediate-, and chronic-duration inhalation exposure to 1,1-dichloroethene. These effects are manifested as enzyme changes (decreases in kidney monooxygenase and epoxide hydrolase levels) (Oesch et al. 1983), tubular alterations (hemoglobinuria) (McKenna et al. 1978a), increased kidney weight (Henck et al. 1979; NTP 2015a; Quast et al. 1986), and histological changes (nephropathy; tubular swelling, degeneration, and necrosis; granular casts in renal tubules of males) (e.g., Jackson and Conolly 1985; NTP 2015a; Short et al. 1977a). Male mice appear to be more susceptible than female mice to the acute nephrotoxic effects of inhaled 1,1-dichloroethene and more susceptible than both sexes of rats. Acute-duration inhalation and oral studies have demonstrated that fasted animals are more susceptible than nonfasted animals to 1,1-dichloroethene renal toxicity.

Developmental Effects. Available human data are restricted to population-based, cross-sectional studies conducted in northern New Jersey for the years 1985–1988; these studies provide only suggestive evidence of impaired orofacial and nervous system development associated with total dichloroethylenes in public drinking water (Bove et al. 1995). Delayed ossification of selected bones was reported for fetuses from maternal mice exposed to 1,1-dichloroethene vapor during gestation (EPA 1977a).

Cancer. Limited human data have not found associations between exposure to 1,1-dichloroethene and risk of cancer. Only two studies (Ott et al. 1976; Waxweiler 1981) were available for analysis and neither study was large enough to demonstrate a relationship between cancer and 1,1-dichloroethene unless there was an overt causality.

The carcinogenicity of 1,1-dichloroethene following inhalation, oral, dermal, or subcutaneous exposure has been evaluated in mice (Hong et al. 1981; Lee et al. 1978; Maltoni et al. 1985; Van Duuren et al. 1979), rats (Hong et al. 1981; Maltoni et al. 1982, 1985; NTP 1982; Ponomarkov and Tomatis 1980; Quast et al. 1983, 1986; Rampy et al. 1977; Viola and Caputo 1977), and Chinese hamsters (Maltoni et al. 1985).

In a chronic toxicity/carcinogenicity study of rats that employed the inhalation exposure route, significantly increased incidences of malignant mesothelioma and nasal respiratory epithelium adenoma were observed in males and significantly increased incidences of C-cell tumors, mononuclear cell leukemia, and malignant mammary gland tumors were observed in females (NTP 2015a). In a study of mice intermittently exposed for 52 weeks, significantly increased incidences of tumors included kidney adenocarcinoma in males, pulmonary tumors in males and females, and mammary gland tumors in females (Maltoni et al. 1985).

Negative findings of various other inhalation studies may be partially explained by inadequate test conditions. Study limitations for many of these investigations included less-than-lifetime exposure, use of concentrations well below or above the maximum tolerated dose, small numbers of animals, and/or limited gross or microscopic examinations (Hong et al. 1981; Lee et al. 1977, 1978; Maltoni et al. 1982, 1985; Quast et al. 1986; Rampy et al. 1977; Viola and Caputo 1977).

1,1-Dichloroethene was inactive as a complete carcinogen upon repeated application to the skin of mice for a lifetime and did not induce local malignancies when administered chronically by subcutaneous injection. However, a statistically significant increase in the incidence of skin papillomas was noted in Swiss mice treated dermally initially with 1,1-dichloroethene and subsequently with the tumor-promoting agent, phorbol myristate acetate (Van Duuren et al. 1979).

Several chronic studies in rats and mice evaluated the potential carcinogenicity of 1,1-dichloroethene by oral exposure. Administration was by gavage (Maltoni et al. 1982, 1985; NTP 1982; Ponomarkov and Tomatis 1980) or via the drinking water (Quast et al. 1983; Rampy et al. 1977). Trends toward increased incidences of malignant and nonmalignant tumors in 1,1-dichloroethene-treated animals were reported in some oral studies, although incidences for most tumor types were not statistically significantly increased by pairwise comparison (NTP 1982; Ponomarkov and Tomatis 1980; Quast et al. 1983).

1,1-Dichloroethene (vinylidene chloride) is not listed in the 14th Report on Carcinogens (NTP 2016). EPA (2002) reviewed available human and animal data and concluded that 1,1-dichloroethene "exhibits *suggestive evidence* of carcinogenicity but not sufficient evidence to assess human carcinogenic potential following inhalation exposure in studies of rodents." EPA (2002) also noted "the data for 1,1-dichloroethene are *inadequate* for an assessment of human carcinogenic potential by the oral route." IARC recently assigned 1,1-dichloroethene to Group 2B, based on "sufficient evidence of carcinogenicity in experimental animals" and no data or "inadequate evidence" in humans (Grosse et al. 2017).

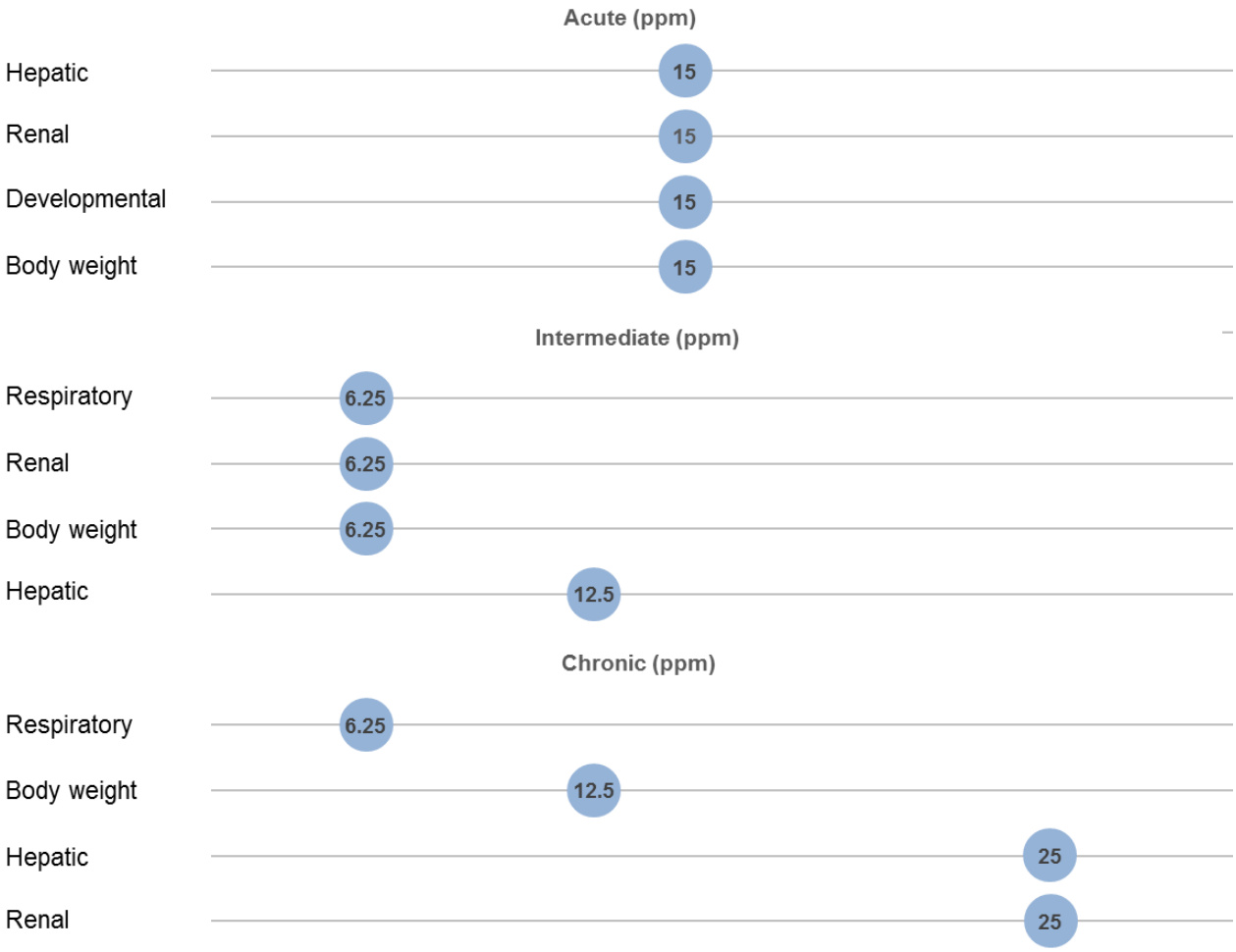
1.3 MINIMAL RISK LEVELS (MRLs)

The inhalation database was considered adequate for derivation of intermediate- and chronic-duration inhalation MRLs for 1,1-dichloroethene. As discussed in Appendix A, the inhalation database was not considered adequate for derivation of an acute-duration inhalation MRL. As presented in Figure 1-3, the available inhalation data for 1,1-dichloroethene suggest that the respiratory tract, liver, and kidney are sensitive targets of toxicity following inhalation exposure.

Figure 1-3. Summary of Sensitive Targets of 1,1-Dichloroethene – Inhalation

The upper respiratory tract and kidney are the most sensitive targets of 1,1-dichloroethene inhalation exposure.

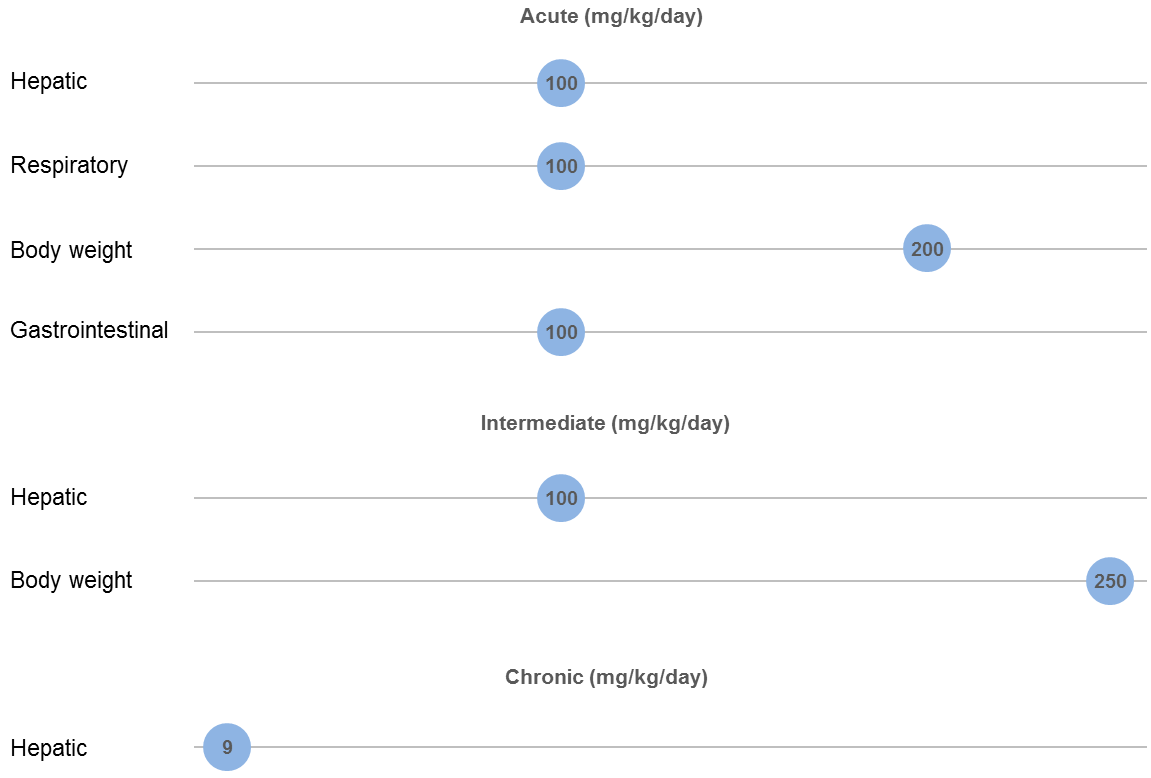
Numbers in circles are the lowest LOAELs for all health effects in animals; no exposure-response human data were identified.



The oral database was considered adequate for derivation of a chronic-duration oral MRL for 1,1-dichloroethene. The data were not considered adequate for derivation of acute- or intermediate-duration oral MRLs. As presented in Figure 1-4, the liver is the most sensitive target of toxicity following oral exposure.

Figure 1-4. Summary of Sensitive Targets of 1,1-Dichloroethene – Oral

The liver is the most sensitive target of 1,1-dichloroethene oral exposure.
Numbers in circles are the lowest LOAELs for all health effects in animals; no reliable dose-response data were available for humans.



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

Table 1-1. Minimal Risk Levels (MRLs) for 1,1-Dichloroethene[a]

Exposure duration	MRL	Critical effect	Point of departure/ human equivalent concentration	Uncertainty factor	Reference
Inhalation exposure (ppm)					
Acute	Insufficient data for MRL derivation				
Intermediate	0.001 (1 ppb)	Nasal olfactory epithelium necrosis	$BMCL_{10}$: 1.59 ($BMCL_{HEC}$: 0.036)	30	NTP 2015a
Chronic	0.001 (1 ppb)	Intermediate inhalation MRL adopted for chronic inhalation MRL			
Oral exposure (mg/kg/day)					
Acute	Insufficient data for MRL derivation				
Intermediate	Insufficient data for MRL derivation				
Chronic	0.05	Hepatic midzonal fatty change	$BMDL_{10}$: 4.51	100	Humiston et al. 1978; Quast et al. 1983

[a]See Appendix A for additional information.

$BMCL_{10}$ = upper 95% confidence limit on the benchmark concentration (BMC) associated with benchmark response rate of 10%; $BMDL_{10}$ = upper 95% confidence limit on the benchmark dose (BMD) associated with benchmark response rate of 10%; HEC = human equivalent concentration.