CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

1,2-Dichloroethane, also called ethylene dichloride, is a colorless oily liquid. It is primarily used in the production of vinyl chlorides, which are used to make a variety of plastic and vinyl products including polyvinyl chloride (PVC) pipes and other construction materials. 1,2-Dichloroethane is also used as a solvent in organic synthesis. 1,2-Dichloroethane is produced by chlorination of ethylene using a catalyst.

1,2-Dichloroethane is released to the environment during its production and use, with the vast majority of the fugitive emissions going into the air. Vapor-phase 1,2-dichloroethane goes through photochemical degradation in the atmosphere, with an estimated reaction half-life of 65–73 days; the primary degradation products are carbon dioxide and hydrochloric acid (Arnts et al. 1989; Atkinson 1986; Kwok and Atkinson 1995). If released to soil, 1,2-dichloroethane is not expected to adsorb strongly and may leach into groundwater. Volatilization is expected to be an important environmental fate process for 1,2-dichloroethane in soil and bodies of water due to its Henry's law constant of 1.18×10^{-3} atm-m^3/mol at 25°C. Biodegradation is expected to occur slowly in both water and soil surfaces. Hydrolysis and photolysis are not expected to be important fate processes in aqueous and soil environments, and the potential for bioconcentration in aquatic organisms appears to be low.

The general population is exposed to 1,2-dichloroethane primarily from inhalation of ambient air, particularly near point sources. Other potential routes of exposure for the general population include ingestion of 1,2-dichloroethane in contaminated drinking water or food items and dermal absorption. In addition, inhalation exposure may occur from 1,2-dichloroethane that has volatilized from water during activities such as cooking, bathing, showering, and dishwashing, if 1,2-dichloroethane is in the water supply. Children are expected to be exposed to 1,2-dichloroethane by the same routes as adults. In the past, 1,2-dichloroethane was detected in human milk, but more recent data showing 1,2-dichloroethane in breast milk were not located. Occupational exposure to 1,2-dichloroethane occurs through inhalation and dermal contact with the compound at workplaces where it is produced or used.

Median daily atmospheric concentrations of 1,2-dichloroethane are typically in the 0.01–0.1 ppb range for urban, suburban, rural, and remote sites, and higher near point sources such as factories, wastewater treatment plants, and hazardous waste sites. Populations residing near hazardous waste disposal sites or municipal landfills may be subject to higher-than-average levels of 1,2-dichloroethane in ambient air and drinking water since 1,2-dichloroethane is volatile and is mobile in soil and may leach into drinking water supplies.

1.2 SUMMARY OF HEALTH EFFECTS

Acute (1–14 days), intermediate (15–364 days), and chronic (≥365 days) health effects can result from inhalation, oral, or dermal contact with 1,2-dichloroethane. There are a limited number of epidemiological studies on the health effects in humans, as well as numerous case reports of people who died following acute-duration exposure to high levels by inhalation or ingestion. Studies in animals exposed by inhalation, oral, and dermal routes were evaluated. As illustrated in Figure 1-1, reproductive, respiratory, neurological, hepatic, immunological, and cancer endpoints are the most sensitive targets of 1,2-dichloroethane inhalation exposure. As shown in Figure 1-2, renal, gastrointestinal, body weight, immunological, and cancer endpoints are the most sensitive targets of 1,2-dichloroethane oral exposure. Animals exposed to 1,2-dichloroethane for chronic durations also had high mortality.

Figure 1-1 identifies the sensitive targets of inhalation exposure to 1,2-dichloroethane in animals and Figure 1-2 identifies the sensitive targets of oral exposure in animals. For oral exposure studies in animals, there are differences between gavage exposure and drinking water/feed exposure. Generally, effects are observed at lower doses in gavage studies compared to drinking water or feed studies. For example, in intermediate-duration studies, the lowest gavage dose producing death was 240 mg/kg/day (NTP 1991), compared to 4,926 mg/kg/day in a drinking water study (NTP 1991). The differences in response may be due to saturation of the detoxification/excretion mechanism due to bolus gavage dosing. When biotransformation processes are saturated, higher levels of 1,2-dichloroethane circulate throughout the body and conjugate with glutathione resulting in reactive intermediates and toxic effects rather than being detoxified and eliminated.

Figure 1-1. Health Effects Found in Animals Following Inhalation Exposure to 1,2-Dichloroethane

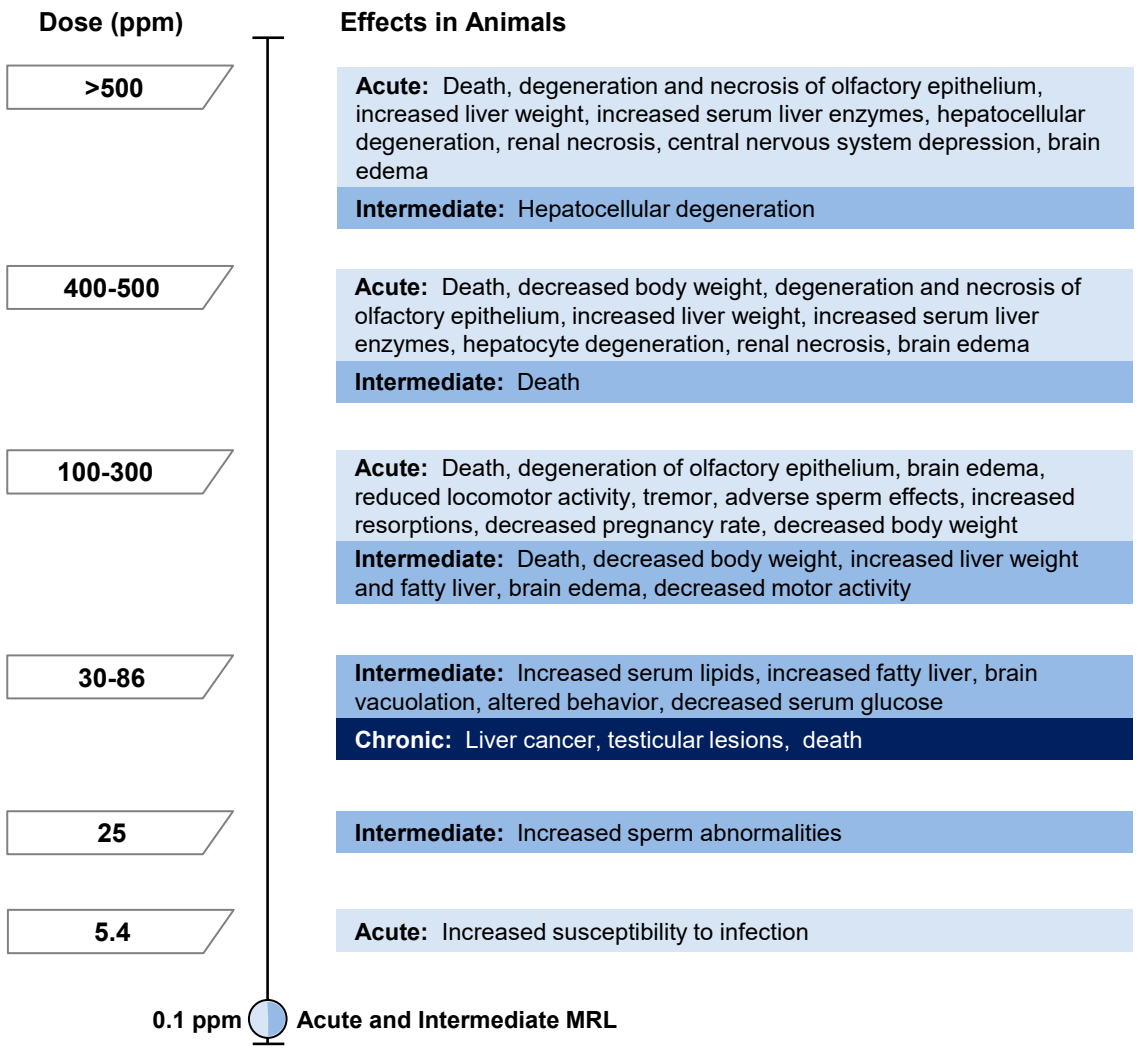
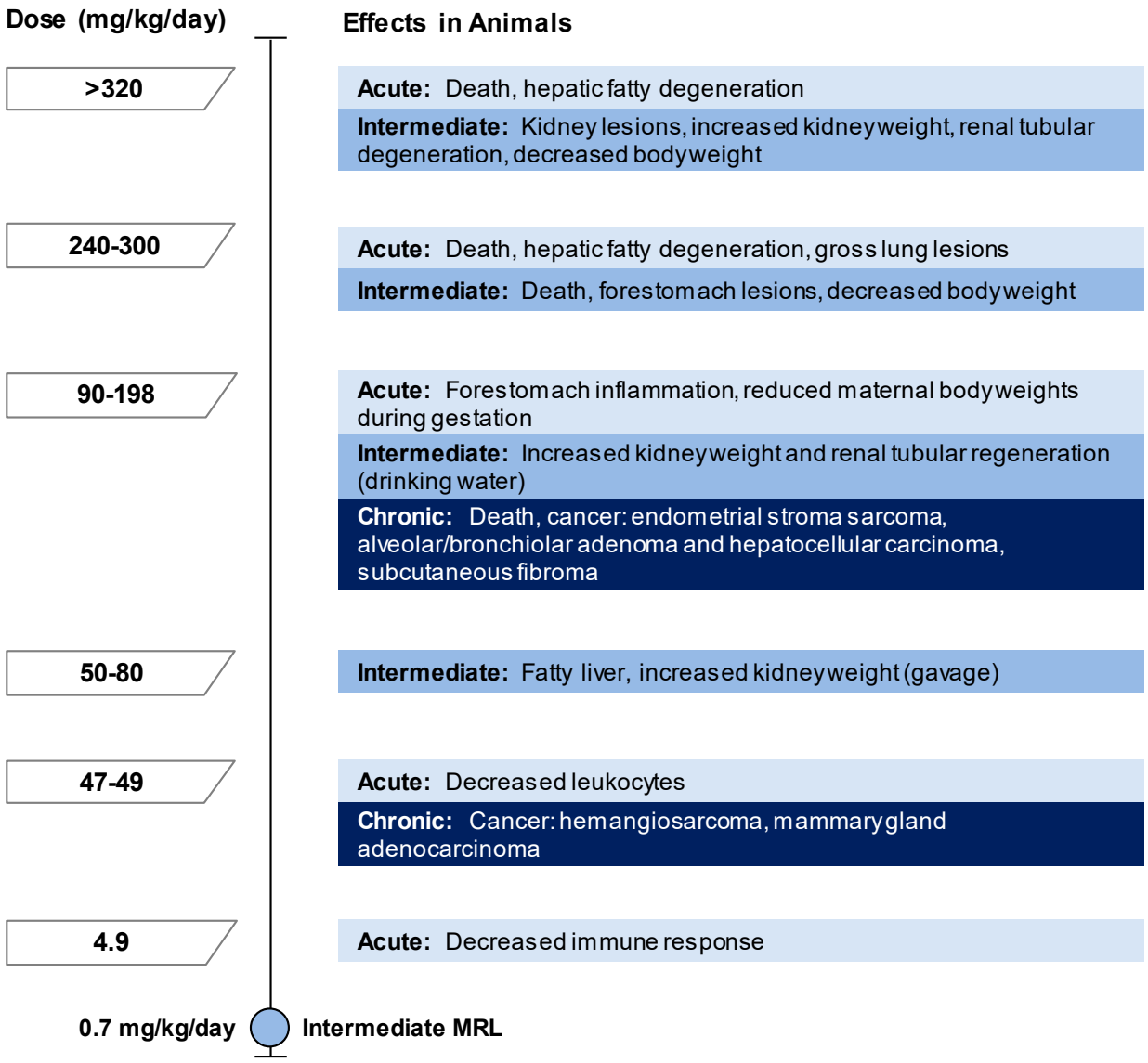


Figure 1-2. Health Effects Found in Animals Following Oral Exposure to 1,2-Dichloroethane



Respiratory Effects. 1,2-Dichloroethane produces adverse respiratory effects in humans following both inhalation and ingestion. Respiratory effects observed in individuals who died following acute high-level oral exposure were respiratory distress, lung congestion, pulmonary edema, dyspnea, and bronchitis (Hubbs and Prusmack 1955; Hueper and Smith 1935; Lochhead and Close 1951; Martin et al. 1969; Nouchi et al. 1984; Yodaiken and Babcock 1973). Experimental animal studies demonstrated nasal olfactory degeneration/necrosis and regeneration, pulmonary congestion, and pulmonary edema after acute-duration inhalation or gavage exposure (Heppel et al. 1945; Hotchkiss et al. 2010; Salovsky et al. 2002). Intermediate- and chronic-duration inhalation and oral studies did not result in respiratory effects

(Daniel et al. 1994; Morgan et al. 1990; NCI 1978; NTP 1991; van Esch et al. 1977). A 26-week dermal study (using transgenic mice susceptible to early tumorigenesis) produced hyperplasia and tumors in the lungs of female mice (Suguro et al. 2017).

Hepatic Effects. Liver effects have been observed in cases of humans who died following acute-duration inhalation or ingestion of 1,2-dichloroethane. Hepatotoxicity was indicated by elevated serum markers used to assess liver injury, enlarged liver, and vacuolation and extensive centrilobular necrosis at autopsy in case studies (Chen et al. 2015; Cheng et al. 1999; Hubbs and Prusmack 1955; Martin et al. 1969; Przezdziak and Bakula 1975; Schönborn et al. 1970). Evidence from animal studies supports the conclusion that the liver is a target organ for inhalation exposure to 1,2-dichloroethane. Hepatic effects in animals exposed via inhalation included increased levels of serum markers of liver injury, increased liver weight, and histopathological changes of macrophage aggregation and hepatocellular degeneration (Brondeau et al. 1983; Heppel et al. 1946; Hotchkiss et al. 2010; Pang et al. 2018; Spencer et al. 1951; Wang et al. 2017). No hepatic effects were observed after chronic-duration inhalation exposure; however, liver tumors were observed (Cheever et al. 1990; Nagano et al. 2006). Studies of animals exposed orally have not shown adverse hepatic effects of 1,2-dichloroethane (Alumot et al. 1976; Aragno et al. 1992; Daniel et al. 1994; Danni et al. 1992; Munson et al. 1982; NCI 1978; NTP 1991).

Renal Effects. 1,2-Dichloroethane is acutely nephrotoxic in humans following both inhalation and ingestion. Renal effects observed in individuals who died following acute-duration, high-level exposure were diffuse necrosis, tubular necrosis, and kidney failure (Hubbs and Prusmack 1955; Hueper and Smith 1935; Lochhead and Close 1951; Nouchi et al. 1984; Schönborn et al. 1970; Yodaiken and Babcock 1973). Renal effects seen in experimental animals include increased kidney weight and tubular degeneration and regeneration with oral (Daniel et al. 1994; Morgan et al. 1990; NTP 1991; van Esch et al. 1977) and dermal exposure (Suguro et al. 2017). No renal effects were observed following chronic-duration oral exposure (NCI 1978). Inhalation studies have shown renal effects only at high concentrations (Heppel et al. 1946; Hotchkiss et al. 2010; Spencer et al. 1951).

Gastrointestinal Effects. 1,2-Dichloroethane induced nausea and vomiting in case studies of humans exposed by inhalation (McNally and Fostvedt 1941; Nouchi et al. 1984; Wirtschafter and Schwartz 1939) and in occupational studies (Liu et al. 2010; Zhan et al. 2011; Zhou et al. 2015). Gastrointestinal effects including nausea, vomiting, diarrhea, gastritis, and hemorrhages of the gastrointestinal tract have been noted in humans after ingestion of 1,2-dichloroethane (Garrison and Leadingham 1954; Hubbs and Prusmack 1955; Hueper and Smith 1935; Lochhead and Close 1951; Martin et al. 1969; Schönborn et al.

1970; Yodaiken and Babcock 1973). Animal studies of oral exposure have reported gastrointestinal inflammation and hyperplasia (Daniel et al. 1994; Morgan et al. 1990; NCI 1978; NTP 1991). The gastrointestinal effects were observed in gavage studies; in studies in which 1,2-dichloroethane was administered via drinking water, no gastrointestinal effects were noted at much higher doses (NTP 1991).

Immunological and Lymphoreticular Effects. Information pertaining to immunological effects in humans exposed to 1,2-dichloroethane is limited to a report of splenic congestion and hemorrhage in one case report of ingestion (Hubbs and Prusmack 1955). In mice, immunosuppressive effects were observed following both acute-duration inhalation exposure and acute-duration oral exposure. A single 3-hour inhalation exposure to low levels of 1,2-dichloroethane increased susceptibility of mice to bacterial infection, although no changes in bactericidal activity or other immune function endpoints were found in rats after single inhalation exposures with longer durations and higher concentrations (Sherwood et al. 1987). Effects observed in mice following acute-duration gavage administration of 1,2-dichloroethane included reduced humoral immunity (immunoglobulin response to sheep red blood cells) and decreased cell-mediated immunity (delayed-type hypersensitivity response to sheep erythrocytes) (Munson et al. 1982). However, an intermediate-duration oral study of drinking water exposure failed to corroborate the results of the gavage study by the same study authors (Munson et al. 1982). Leukocyte counts were not affected in intermediate-duration drinking water and gavage studies in rats, and intermediate- and chronic-duration oral exposures did not produce histological changes in immune system tissues in rats and mice (Daniel et al. 1994; Morgan et al. 1990, NCI 1978; NTP 1991). Immune function has not been evaluated in intermediate- or chronic-duration inhalation studies nor in chronic-duration oral studies of 1,2-dichloroethane.

Neurological Effects. Neurological symptoms and signs in people exposed to high levels of 1,2-dichloroethane by inhalation or ingestion included headache, dizziness, irritability, drowsiness, tremors, partial paralysis, and coma (Chen et al. 2015; Dang et al. 2019; Hubbs and Prusmack 1955; Liu et al. 2010; Lochhead and Close 1951; Nouchi et al. 1984; Wirtschafter and Schwartz 1939; Yodaiken and Babcock 1973; Zhan et al. 2011). Autopsies of people who died after acute-duration exposure revealed effects in the brain including hyperemia, hemorrhage, myelin degeneration, diffuse changes in the cerebellum, shrunken appearance and pyknotic nuclei in the Purkinje cell layer of the cerebellum, and parenchymatous changes in the brain and spinal cord (Nouchi et al. 1984). Toxic encephalopathy, primarily characterized by cerebral edema, has been observed in workers exposed to 1,2-dichloroethane for longer periods of time (Chen et al. 2015; Dang et al. 2019; Liu et al. 2010; Zhan et al. 2011). Additionally, neuronal necrosis, demyelination and toxic leukoencephalopathy were noted in case studies

(Zhan et al. 2011; Zhou et al. 2015), and neuropsychological impairment was reported in workers in an occupational study (Bowler et al. 2003).

The results of experimental animal inhalation studies confirm that the central nervous system is a target of 1,2-dichloroethane, with exposure leading to clinical signs such as tremors, abnormal posture, uncertain gait, and narcosis, along with brain edema and increased brain water weight (Heppel et al. 1945; Jin et al. 2018a; Spencer et al. 1951; Zhang et al. 2011; Zhong et al. 2020). Neurobehavioral changes indicative of central nervous system depression have been observed in animals after inhalation exposure to 1,2-dichloroethane (Hotchkiss et al. 2010; Wang et al. 2013). In addition, clinical signs of neurotoxicity and mild necrosis in the cerebellum were found in rats administered 1,2-dichloroethane by gavage for 13 weeks (Morgan et al. 1990; NTP 1991). In contrast, no clinical signs or neurological lesions were seen in rats or mice exposed through their drinking water at higher concentrations for 13 weeks (NTP 1991), and no brain lesions were seen in rats exposed orally for 2 years (NCI 1978). The effects seen in the gavage study might be attributable to the method of dosing. As noted above, the differences in response may be due to saturation of the detoxification/excretion mechanism due to bolus gavage dosing.

Reproductive Effects. A single epidemiological study on reproductive effects of exposure to 1,2-dichloroethane in humans is suggestive of a reduction in gestation duration, but co-exposure to other chemicals occurred in most cases, and the adequacy of the study design could not be evaluated because of reporting deficiencies (Zhao et al. 1989). A study in mice reported reproductive toxicity after intermediate-duration inhalation exposure to 1,2-dichloroethane; effects included significant pathological changes in the testes; vacuolar degeneration of germ cells in the testes; decreased sperm concentration, motility, and progressive motility; and increased abnormalities of the sperm head, body, and tail (Zhang et al. 2017). A well-designed study of reproductive toxicity found no adverse effects on the fertility, gestation, or survival of the pups of rats exposed by inhalation to 150 ppm of 1,2-dichloroethane for 60 days pre-mating, then throughout mating, gestation, and lactation in a one-generation reproduction study (Rao et al. 1980). One- and two-generation reproductive toxicity studies found no chemical-related effects on fertility indices in long-term oral studies in mice and rats, but exposure to higher oral doses caused increases in non-surviving implants and resorptions in rats that also experienced maternal toxicity (Lane et al. 1982; Payan et al. 1995). Histological examinations of the testes, ovaries, and other male and female reproductive system tissues were performed in other intermediate- and chronic-duration inhalation and oral animal studies with negative results, but reproductive function was not evaluated (Alumot et al. 1976; Cheever et al. 1990; Daniel et al. 1994; Morgan et al. 1990; NCI 1978; NTP 1991; van Esch et al. 1977).

Cancer. Epidemiological studies that have investigated associations between occupational or oral exposure to 1,2-dichloroethane and increased incidences of cancer are inadequate for assessing carcinogenicity in humans because studies did not adequately assess confounding by co-exposures to various other chemicals (Austin and Schnatter 1983a, 1983b; Benson and Teta 1993; Goldberg et al. 1995; Hansen 2000; Hogstedt et al. 1979; Isacson et al. 1985; Reeve et al. 1983; Teta et al. 1989; Waxweiler et al. 1983). There have been mixed results in animal studies of tumor incidence after 1,2-dichloroethane exposure via inhalation. While Cheever et al. (1990) and Maltoni et al. (1980) failed to find carcinogenic effects after chronic-duration exposure, Nagano et al. (2006) found dose-dependent increases in benign and malignant tumors in rats of both sexes and female mice after chronic-duration inhalation exposure to 1,2-dichloroethane. The former studies were limited by use of a single exposure concentration (that was lower than the concentration resulting in tumors in the study by Nagano et al. [2006]) and by early mortality, respectively. 1,2-Dichloroethane induced a clear positive carcinogenic response in animals after gavage administration, resulting in statistically significant increases in forestomach squamous cell carcinomas, hemangiosarcomas, and subcutaneous fibromas in male rats; mammary gland adenocarcinomas and hemangiosarcomas in female rats; hepatocellular carcinomas and alveolar/bronchiolar adenomas in male mice; and alveolar/bronchiolar adenomas, mammary carcinomas, and endometrial tumors in female mice (NCI 1978). Other animal bioassays provide supportive evidence for the carcinogenicity of dermal contact with 1,2-dichloroethane. Van Duuren et al. (1979) showed compound-related increases in lung tumors following lifetime dermal exposure of female mice, and Suguro et al. (2017) reported an increase in bronchioloalveolar adenomas and adenocarcinomas in transgenic (genetically modified for increased susceptibility to cancer) mice after intermediate-duration dermal exposure.

The Department of Health and Human Services (HHS) has determined that 1,2-dichloroethane may reasonably be anticipated to be a human carcinogen. The International Agency Research on Cancer (IARC) has placed 1,2-dichloroethane in Group 2B (possibly carcinogenic to humans), and the U.S. Environmental Protection Agency (EPA) has classified 1,2-dichloroethane as a Group B2 carcinogen (probable human carcinogen).

1.3 MINIMAL RISK LEVELS (MRLs)

The inhalation database was considered adequate for derivation of an acute- and intermediate-duration inhalation MRL for 1,2-dichloroethane. A chronic-duration inhalation MRL was not derived because

available studies identified effect levels (LOAELs and NOAELs) for noncancer effects that are higher than both the point of departure (POD) for the acute-duration inhalation MRL (36.28 ppm) and the serious LOAEL for intermediate-duration inhalation exposure (25 ppm), precluding derivation of an MRL. It is ATSDR's practice to not derive MRLs from serious LOAELs. The respiratory tract was the most sensitive target following acute-duration inhalation exposure to 1,2-dichloroethane. Other sensitive endpoints of inhalation exposure include immunological, neurological, and reproductive effects, as demonstrated in Figure 1-3. The oral database was considered adequate for derivation of an intermediate-duration oral MRL for 1,2-dichloroethane, and inadequate for derivation of acute- and chronic-duration oral MRLs. Data were insufficient to derive an acute-duration oral MRL due to uncertainty about the validity of results at the lowest effect level based on differences in effect between gavage doses and drinking water doses. Briefly, there is a notable difference in toxicokinetics between gavage and drinking water administration. With gavage administration, bolus dosing leads to saturation of the detoxification/ excretion mechanism and exacerbates toxicity (see Section 3.1). This is described in more detail in Appendix A. Data were insufficient for the derivation of a chronic-duration oral MRL as the most sensitive endpoint was represented by a serious effect. As presented in Figure 1-4, immunological, gastrointestinal, body weight changes, and the kidney are sensitive targets of 1,2-dichloroethane toxicity. In the figure, LOAELs obtained from gavage studies are shown as circles, while LOAELs obtained from drinking water or dietary studies are shown as squares. The MRL values are summarized in Table 1-1 and discussed in greater detail in Appendix A.

Figure 1-3. Summary of Sensitive Targets of 1,2-Dichloroethane – Inhalation

Reproductive, respiratory, neurological, hepatic, immunological, and cancer endpoints are the most sensitive targets of 1,2-dichloroethane inhalation exposure.
Numbers in circles are the lowest LOAELs for all health effects in animals.
No reliable dose-response data were available for humans.

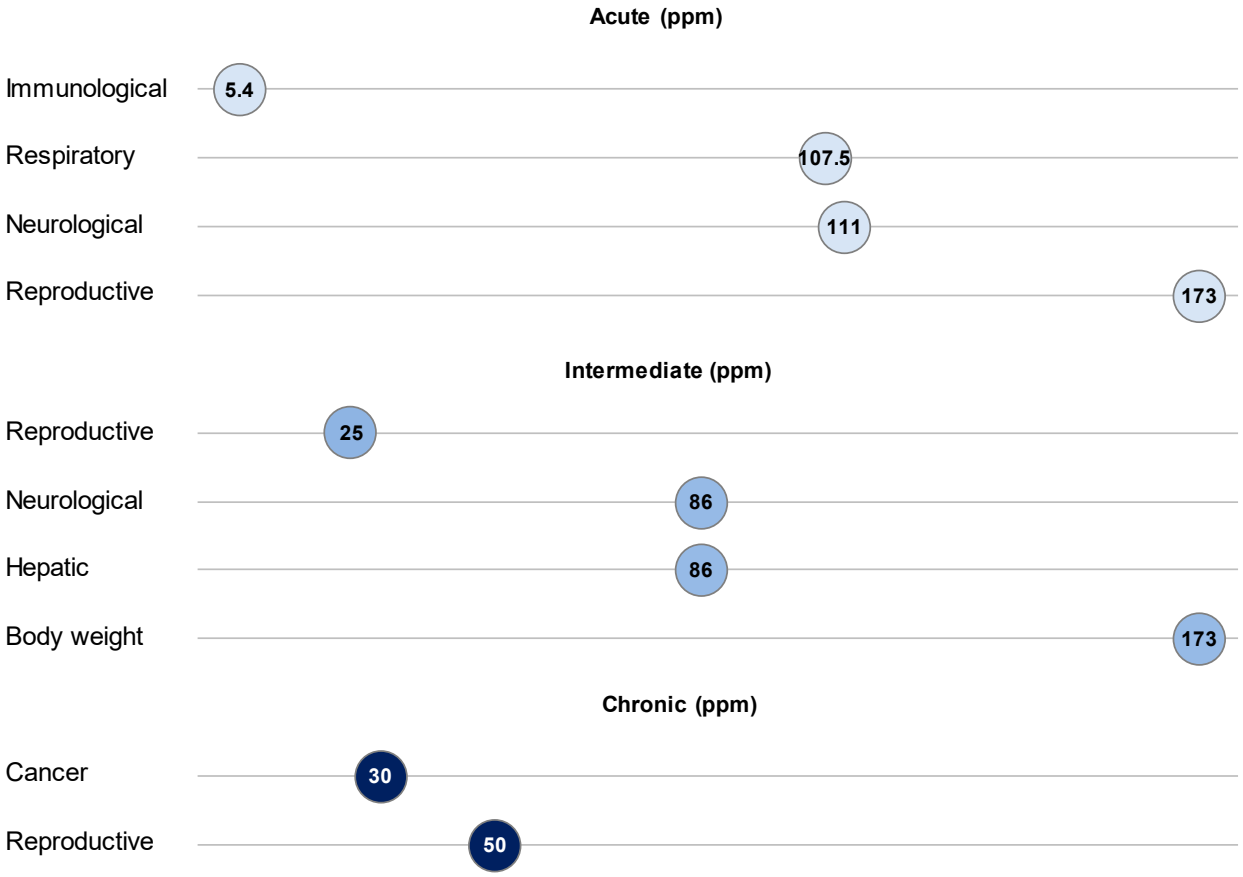


Figure 1-4. Summary of Sensitive Targets of 1,2-Dichloroethane – Oral

Renal, gastrointestinal, body weight, immunological, mortality, and cancer endpoints are the most sensitive targets of 1,2-dichloroethane oral exposure.

Numbers in circles are the lowest LOAELs from gavage studies for all health effects in animals.
Numbers in squares are the lowest LOAELs from drinking water or dietary studies.
No reliable dose-response data were available for humans.

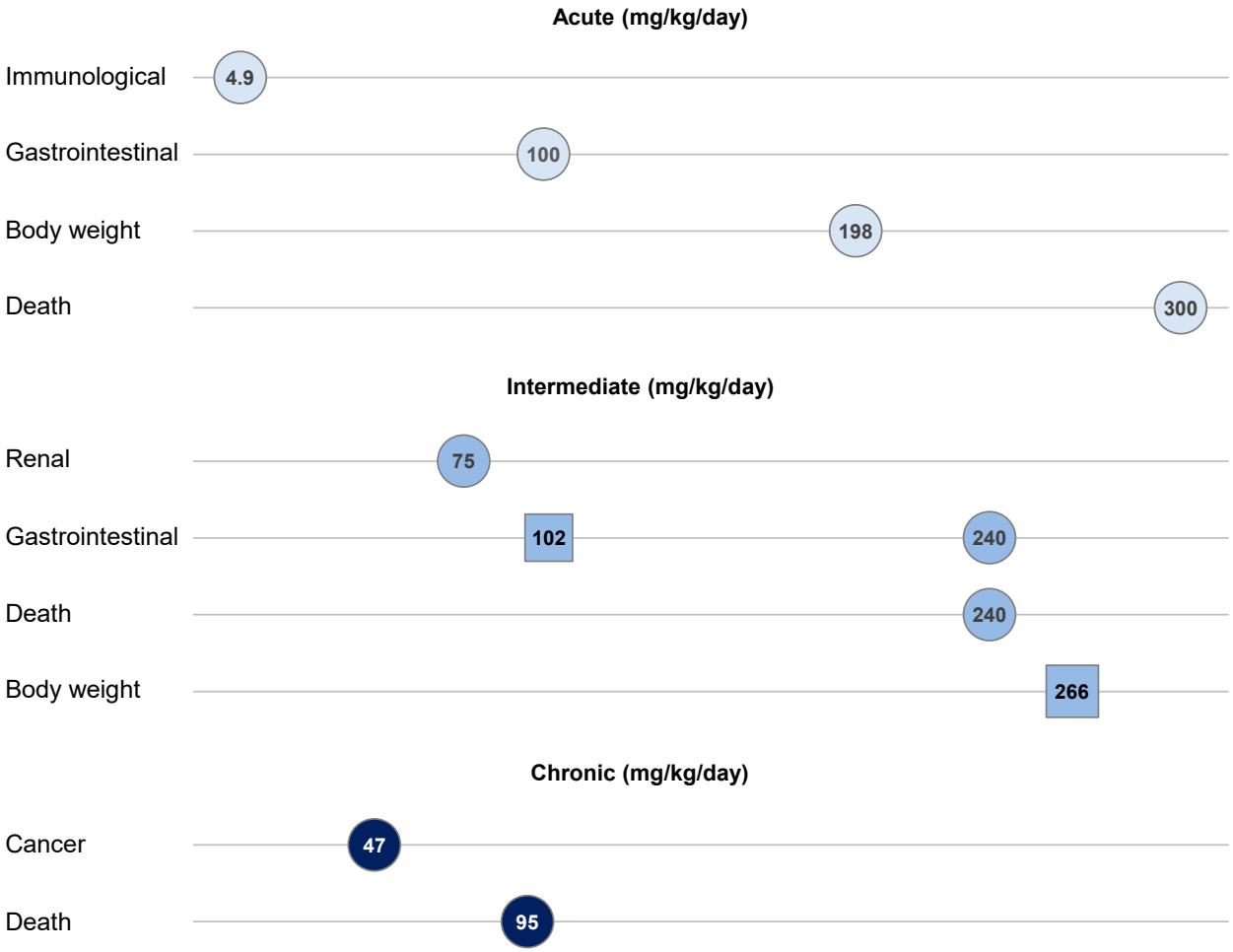


Table 1-1. Minimal Risk Levels (MRLs) for 1,2-Dichloroethane[a]

Exposure route	Exposure duration	MRL	Critical effect	POD type	POD value	Uncertainty/ modifying factor	Reference
Inhalation	Acute	**0.1 ppm** (0.4 mg/m^3)	Degeneration with necrosis of olfactory epithelium	$BMCL_{HEC}$	3.84 ppm	UF: 30	Hotchkiss et al. 2010
	Intermediate	**0.1 ppm** (0.4 mg/m^3)	Neurobehavioral changes (altered performance in open field test)	$BBMCL_{1SD\text{-}HEC}$	3.70 ppm	UF: 30	Zhong et al. 2022
	Chronic	None	–	–	–	–	–
Oral	Acute	None	–	–	–	–	–
	Intermediate	**0.7 mg/kg/day**	Kidney tubule regeneration, increased kidney weight	$BMDL_{10}$	70.1 mg/kg/day	UF: 100	Morgan et al. 1990; NTP 1991
	Chronic	None	–	–	–	–	–

[a]See Appendix A for additional information.

$BBMCL_{1SD}$ = Bayesian benchmark response of 1 standard deviation; BMCL = 95% lower confidence limit on the benchmark concentration; $BMDL_{10}$ = benchmark dose lower confidence limit for 10% extra risk benchmark response; HEC = human equivalent concentration; LOAEL = lowest-observed-adverse-effect level; POD = point of departure; UF = uncertainty factor