

## 2. RELEVANCE TO PUBLIC HEALTH

### 2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO 1,2-DICHLOROETHANE IN THE UNITED STATES

1,2-Dichloroethane, also called ethylene dichloride, is a volatile, clear, manufactured liquid that is not found naturally in the environment. It has a pleasant smell and a sweet taste and burns with a smoky flame. 1,2-Dichloroethane is readily soluble in water and several organic solvents such as alcohol, chloroform, and ether. 1,2-Dichloroethane is one of the most widely produced chemicals in the world. Its predominant use is in the manufacture of vinyl chloride. 1,2-Dichloroethane was formerly used in varnish and finish removers, soaps and scouring compounds, organic synthesis for extraction and cleaning purposes, metal degreasers, ore flotation, and paints, coatings, and adhesives.

1,2-Dichloroethane is a widespread contaminant 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 is photochemically degraded in the atmosphere with an estimated reaction half-life of about 73 days. 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. Biodegradation is expected to occur slowly in both water and soil surfaces. Hydrolysis and photolysis are not expected to be important fate processes, 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. Occupational exposure to 1,2-dichloroethane occurs through inhalation and dermal contact with the compound at workplaces where it is produced or used. Children are expected to be exposed to 1,2-dichloroethane by the same routes as adults. 1,2-Dichloroethane has been detected in human milk, indicating that infants could possibly be exposed to 1,2-dichloroethane from breast-feeding mothers. The importance of this route of child exposure is unclear because current data on the concentration of 1,2-dichloroethane in breast milk are not available.

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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 slightly higher near point sources such as factories, treatment plants, and hazardous waste sites. The estimated daily intake of 1,2-dichloroethane in Japan attributed to food ingestion is 0.004 mg/day, a level well below ATSDR's intermediate oral MRL of 0.2 mg/kg/day for 1,2-dichloroethane. Since the levels of 1,2-dichloroethane in food products of Japan are similar to those in the United States, the daily intake value may also be similar.

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-Dichloroethane is included in the priority list of hazardous substances identified by ATSDR and the Environmental Protection Agency (EPA), and has been found in at least 570 of the 1,585 current or former National Priorities List (NPL) sites. However, the total number of NPL sites evaluated for 1,2-dichloroethane is not known. As more sites are evaluated, the sites at which 1,2-dichloroethane is found may increase.

### 2.2 SUMMARY OF HEALTH EFFECTS

Short-, intermediate-, and long-term health effects can result from inhalation or ingestion of, or dermal contact to, 1,2-dichloroethane. Main targets of mammalian toxicity include the liver, kidneys, and neurological, cardiovascular, and immune systems. A limited amount of information is available regarding effects in humans, most coming from case reports of people who died following acute exposure to high levels by inhalation or ingestion. Symptoms and signs in these people included central nervous system depression, nausea and vomiting, corneal opacity, bronchitis, respiratory distress, lung congestion, myocardial lesions, hemorrhagic gastritis and colitis, increased blood clotting time, hepatocellular damage, renal necrosis, and histopathological changes in brain tissue. Death was most often attributed to cardiac arrhythmia. Inhalation and oral studies in animals have found similar effects, as well as immunological, genotoxic, and carcinogenic effects not reported in humans. Animal data further indicate that 1,2-dichloroethane is unlikely to cause reproductive or developmental toxicity at doses below those that are maternally toxic.

Route-related differences in some toxic and carcinogenic responses have been observed between gavage and drinking water or inhalation exposure in animal studies of 1,2-dichloroethane. The differences in response may be due to saturation of the detoxification/excretion mechanism due to bolus gavage dosing. As discussed in Chapter 3 (Section 3.5, Mechanisms of Action), effects of 1,2-dichloroethane in various

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tissues appear to be largely mediated by reactive intermediates formed by conjugation with glutathione. The reaction of 1,2-dichloroethane and glutathione is unusual in that it results in activation rather than detoxification (i.e., the typical consequence of conjugation of xenobiotics with glutathione). Toxicity may occur when the biotransformation processes are saturated, thereby allowing higher levels of 1,2-dichloroethane to circulate throughout the body and conjugate with glutathione instead of being detoxified and eliminated. Therefore, even though certain health effects might be expected in humans ingesting sufficient doses of 1,2-dichloroethane, it is uncertain whether the effects would occur following typical drinking water and inhalation exposures.

**Hepatic Effects.** Liver effects have been observed in cases of humans who died following acute inhalation or ingestion of 1,2-dichloroethane. Hepatotoxicity was indicated by an increase in levels of serum markers of liver dysfunction, an enlarged liver, and extensive centrilobular necrosis in a man who was exposed to concentrated 1,2-dichloroethane vapors for 30 minutes and subsequently died. Necrosis and cirrhosis were reported in people following acute high-level oral exposure to 570 mg/kg/day. Evidence from animal studies supports the conclusion that the liver is a target organ for 1,2-dichloroethane. Hepatic effects in exposed animals were not limited to any specific route or duration of exposure and included increased levels of serum markers of liver dysfunction, increased liver weight, and fatty degeneration. For inhalation exposure, the lowest concentrations producing hepatic effects were 400 ppm for acute-duration exposure and 100 ppm for intermediate-duration exposure. As discussed in Section 2.3, liver histopathology is the basis of the chronic-duration minimal risk level (MRL) for inhalation oral exposure. For oral exposure, the lowest dose producing hepatic effects was 18 mg/kg/day for intermediate-duration exposure.

**Renal Effects.** 1,2-Dichloroethane is acutely nephrotoxic in humans following both inhalation and ingestion. Renal effects observed in individuals who died following acute high-level exposure were diffuse necrosis, tubular necrosis, and kidney failure. Renal effects seen in experimental animals include increased kidney weight, cloudy swelling of the tubular epithelium, tubular degeneration and regeneration, karyomegaly, dilatation, protein casts, and mineralization. The effects in animals were not limited to any specific route or duration of exposure and support the conclusion that the kidney is a target organ for 1,2-dichloroethane. For inhalation exposure, the lowest concentration reported to produce renal effects was 400 ppm for durations of 8–12 days and 8 months. For oral exposure, the lowest dose producing renal effects was 58 mg/kg/day for 13 weeks. Increased kidney weight, considered to be an early-stage adverse effect because it leads to histopathological changes at higher doses, was used to derive the intermediate-duration MRL for oral exposure to 1,2-dichloroethane as discussed in Section 2.3.

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**Immunological and Lymphoreticular Effects.** Immunological effects have not been reported in humans exposed to 1,2-dichloroethane. In mice, however, this chemical had immunosuppressive effects following both acute inhalation exposure and acute oral exposure. A single 3-hour inhalation exposure to 5–11 ppm increased susceptibility of mice to bacterial infection, although no changes in bactericidal activity or other immune function end points were found in rats after a single 5-hour exposure to 200 ppm or 12 5-hour exposures to 100 ppm. Effects observed in mice following gavage administration of 4.9 or 49 mg/kg/day for 14 days included reduced humoral immunity (immunoglobulin response to sheep red blood cells) and cell-mediated immunity (delayed-type hypersensitivity response to sheep erythrocytes). The immune system was the most sensitive target for short-term exposure to 1,2-dichloroethane by both the inhalation and oral routes in mice. Because of the apparent interspecies differences in immunotoxicity; however, it is unclear whether the immune system could be a target of 1,2-dichloroethane in humans following acute exposure by inhalation or ingestion.

Immune function has not been evaluated in intermediate- or chronic-duration inhalation studies of 1,2-dichloroethane. Immune function also has not been evaluated after chronic oral exposure, although mice given up to 189 mg/kg/day of 1,2-dichloroethane in drinking water for 90 days had no treatment-related effects on either the antibody-forming cell response or the delayed-type hypersensitivity response after immunization with sheep erythrocyte antigens. Leucocyte counts were not affected in intermediate-duration drinking water and gavage studies in rats, and intermediate and chronic oral exposures did not produce histological changes in immune system tissues in rats and mice. Although immunological effects might be expected in humans ingesting sufficient doses of undiluted 1,2-dichloroethane, it is uncertain whether the effects would occur in people exposed via drinking water from wells located near hazardous waste sites.

**Neurological Effects.** Neurological symptoms and signs in people acutely exposed to high levels of 1,2-dichloroethane by inhalation or ingestion included headache, irritability, drowsiness, tremors, partial paralysis, and coma. Autopsies of people who died 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 parenchymous changes in the brain and spinal cord.

The results of animal inhalation studies confirm that the central nervous system is a target of high concentrations of 1,2-dichloroethane. Symptoms similar to those reported in humans, such as tremors, abnormal posture, uncertain gait, and narcosis were observed after high-level acute vapor exposures. In

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addition, clinical signs of neurotoxicity and mild necrosis in the cerebellum were found in rats administered 240–300 mg/kg/day of 1,2-dichloroethane by gavage for 13 weeks. In contrast, no clinical signs or neurological lesions were seen in rats exposed through their drinking water up to 492 mg/kg/day or mice exposed up to 4,210 mg/kg/day for 13 weeks, and no brain lesions were seen in rats intermittently exposed to 50 ppm for 2 years. The effects seen in the gavage study at a level lower than the NOAEL in the drinking water study might be attributable to the method of dosing. These data do not sufficiently characterize the potential for 1,2-dichloroethane to induce more subtle neurotoxic effects following low-level prolonged exposure by inhalation, oral, or dermal exposure. Acute exposure levels high enough to produce neurological effects would not be expected to occur at hazardous waste sites or in the workplace, but might result from accidental occupational exposure or accidental or intentional ingestion.

**Cardiovascular Effects.** Cardiac arrhythmia was given as the cause of death of a man briefly exposed to 1,2-dichloroethane as a concentrated vapor. Autopsy revealed diffuse degenerative changes in the myocardium (fragmentation, interstitial edema, loss of nuclei from myocardial fibers). In addition, cardiovascular insufficiency and hemorrhage were major factors contributing to death in people following acute high-level oral exposure to 570 mg/kg/day. In laboratory animals, myocardial inflammation was reported following acute inhalation of lethal concentrations, and fatty infiltration of the myocardium was observed in guinea pigs that died following exposure to 200 ppm for 25 weeks and in monkeys that survived the same exposure regimen. These findings in animals were based upon a very limited number of observations and in some cases did not include comparison to controls. More complete animal studies did not report cardiovascular histopathologic effects following high-level intermediate-duration oral exposure or low-level chronic-duration inhalation exposure. Overall, the data suggest that the heart could be a target of 1,2-dichloroethane following acute high-level exposure and possibly longer-term inhalation exposure as well. Levels that might produce cardiovascular effects are not likely to be found at hazardous waste sites or a well-regulated workplace.

**Developmental Effects.** The only studies regarding developmental effects in humans are epidemiologic investigations of adverse birth outcomes that found increased odds ratios for exposure to 1,2-dichloroethane in public drinking water and major cardiac defects (but not neural tube defects), and for residence within the census tract of NPL sites contaminated with 1,2-dichloroethane and neural tube defects (but not heart defects). Primary routes of exposure in these epidemiologic studies may have been both oral and inhalation, including inhalation of 1,2-dichloroethane volatilized from household water. It has been previously shown that taking a 10-minute shower is equivalent to drinking 1–3 liters of the same water contaminated with some volatile organic compounds. In these studies, the study populations were

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also simultaneously exposed to elevated levels of other contaminants. Because of the mixed chemical exposure, lack of dose-response information, and inconsistency between the findings of the two studies, the associations with 1,2-dichloroethane are only suggestive and do not establish a cause-and-effect relationship.

The weight of evidence from available inhalation and oral studies in rats, mice, and rabbits indicates that 1,2-dichloroethane is not fetotoxic or teratogenic, although indications of embryoletality at maternally toxic doses have been reported. (There are reports of increased embryo and pup mortality following intermediate-duration inhalation of lower [not maternally toxic] concentrations of 1,2-dichloroethane, but the reliability of the results is uncertain due to the lack of statistical analysis and inadequate description of methods.) The possibility of induction of cardiac malformations in human offspring by 1,2-dichloroethane, as suggested by the epidemiologic data, was not confirmed in available animal studies because the teratology protocols did not include detailed examinations of dissected hearts. Studies of dichloroethylene and trichloroethylene, which are metabolized to some of the same reactive intermediates as 1,2-dichloroethane, have also shown evidence of heart malformations in humans as well as animal cardiac teratogenicity. Overall, the available information does not indicate that 1,2-dichloroethane is a developmental toxicant in animals at doses below those that cause other toxic effects.

**Reproductive Effects.** A single 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. Results of animal studies indicate that 1,2-dichloroethane is unlikely to cause reproductive impairment at doses that are not maternally toxic. Some inhalation studies found that exposure of dams to 1,2-dichloroethane prior to mating and continuing into gestation caused pre-implantation loss and embryoletality in rats, although the study methods were not well reported and the reliability of the data is uncertain. In contrast to these findings, a well-designed study of reproductive toxicity found no adverse effects on the fertility of rats exposed by inhalation to 10-fold higher concentrations of 1,2-dichloroethane in a one-generation reproduction study. One- and two-generation reproduction 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 nonsurviving implants and resorptions in rats that also experienced maternal toxicity. Histological examinations of the testes, ovaries, and other male and female reproductive system tissues were performed in intermediate- and chronic-duration inhalation and oral animal studies with negative results, but reproductive function was not evaluated in these studies. Although 1,2-dichloroethane appears to have induced embryotoxic effects in some animal studies, the

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overall indication of the data is that this chemical is unlikely to impair reproduction at doses that do not also cause other toxic manifestations.

**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, due to complicating co-exposures to various other chemicals. In animals, no tumors were produced in rats and mice exposed to 1,2-dichloroethane via inhalation. The inhalation data are limited by use of a single, subthreshold exposure level in one study, and exceedance of the maximum tolerated dose in rats, less-than-lifetime study duration, and poor survival in mice in the other study.

1,2-Dichloroethane induced a clear positive carcinogenic response in animals after gavage administration, causing 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. Other animal bioassays provide supportive or suggestive evidence for the carcinogenicity of 1,2-dichloroethane. One study showed compound-related lung papillomas following lifetime dermal exposure of female mice. Two additional studies found that pulmonary adenomas were induced in mice by intraperitoneal injection.

The positive and suggestive carcinogenicity results from animal bioassays, along with data indicating that 1,2-dichloroethane and some metabolites are mutagenic and capable of forming DNA adducts (see Chapter 3, Section 3.3), provide sufficient evidence to suggest that 1,2-dichloroethane is a probable human carcinogen. Because oral, dermal, and intraperitoneal exposure of experimental animals to 1,2-dichloroethane is associated with the induction of tumors remote from the site of administration, 1,2-dichloroethane should be considered potentially carcinogenic by the inhalation route of exposure as well. The Department of Health and Human Services (DHHS) 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 EPA has classified 1,2-dichloroethane as a Group B2 carcinogen (probable human carcinogen).

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**2.3 MINIMAL RISK LEVELS***Inhalation MRLs*

An acute-duration inhalation MRL has not been derived for 1,2-dichloroethane. The lowest effect level for acute inhalation exposure is 5.4 ppm for significantly increased mortality in mice from streptococcal (*Streptococcus zooepidemicus*) bacterial challenge following a single 3-hour exposure to 1,2-dichloroethane. Significantly increased mortality from streptococcal challenge in addition to decreased bactericidal activity after challenge with *Klebsiella pneumoniae* were seen in mice at 10.8 ppm. The no-observed-adverse-effect-level (NOAEL) for susceptibility to streptococcal challenge in mice was 2.3 ppm after a single 3-hour exposure or five 3-hour exposures on consecutive days. In the same study, rats did not show decreased bactericidal activity from *K. pneumoniae* challenge following single exposures of up to 200 ppm, or multiple 5-hour exposures of up to 100 ppm of 1,2-dichloroethane. Sherwood et al. indicated that the clear interspecies difference in immunotoxic susceptibility suggests against extrapolating from animals to humans. The MRL Workgroup concluded that the massive streptococcal challenge to mice, consisting of whole-body, 30-minute exposures to aerosols of bacteria for an estimated challenge exposure of  $2 \times 10^4$  inhaled viable streptococci, is unlikely to be relevant to normal human immunological challenge and that, therefore, the increased mortality in mice observed in the Sherwood et al. study is not a suitable basis for an acute inhalation MRL. Immune function has not been evaluated in intermediate- or chronic-duration inhalation studies of 1,2-dichloroethane, although immunosuppressive effects have been reported in mice that were orally exposed to 1,2-dichloroethane for 14 days.

- C An MRL of 0.6 ppm has been derived for chronic-duration inhalation exposure (>365 days) to 1,2-dichloroethane. This chronic MRL is also expected to be protective for intermediate-duration inhalation exposure (15–364 days).

The MRL was derived by dividing a NOAEL of 50 ppm for liver histopathology in rats exposed for 7 hours/day, 5 days/week for 2 years by an uncertainty factor of 90 (3 for interspecies extrapolation after dosimetric adjustment; 10 for human variability; and 3 as a modifying factor for database deficiencies). Although other concentrations of 1,2-dichloroethane were not tested, confidence in the NOAEL is high due to the group size (50 of each sex) and scope of the study. Additionally, the liver is a documented target of 1,2-dichloroethane toxicity in several acute- and intermediate-duration inhalation studies, as well as in a number of studies of orally exposed animals. Limitations in the acute and intermediate inhalation studies preclude considering them as the basis for MRL derivation, but the weight of evidence indicates



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that NOAELs for hepatotoxicity in the intermediate-duration studies are higher than the chronic liver NOAEL. Consequently, the chronic-duration inhalation MRL of 0.6 ppm is also expected to be protective of toxic effects after intermediate-duration inhalation exposures to 1,2-dichloroethane.

*Oral MRLs*

An MRL has not been derived for acute-duration oral exposure (#14 days) to 1,2-dichloroethane. The lowest effect level that can be identified for acute oral toxicity is a lowest-observed-adverse-effect level (LOAEL) of 4.9 mg/kg/day for immunosuppression from a mouse study. Doses lower than 4.9 mg/kg/day were not tested, precluding identification of a NOAEL. Male mice that were treated with 4.9 or 49 mg/kg/day by gavage for 14 days showed a significant dose-related reduction in humoral immune response (IgM response to sheep erythrocytes). The number of antibody-forming cells (AFCs) was dose-related and statistically significantly reduced at both dose levels; when adjusted to AFC/10<sup>6</sup> cells, there was an apparent negative trend with dose, but a significant reduction occurred only in the high-dose group. The cell-mediated immune response (delayed-type hypersensitivity response to sheep erythrocytes) was significantly reduced in both dose groups, but not in a dose-related manner. There was also a depression in leukocytes in the high dose group. However, because administration of 1,2-dichloroethane in the drinking water at doses as high as 189 mg/kg/day for 90 days failed to induce immunosuppressive effects in mice, it was determined that it may not be appropriate to base an MRL on an effect level from a gavage oil study due to toxicokinetic considerations (e.g., possible bolus saturation of the detoxification/excretion mechanism).

- C An MRL of 0.2 mg/kg/day was derived for intermediate-duration oral exposure (15–364 days) to 1,2-dichloroethane.

This MRL was derived by dividing a LOAEL of 58 mg/kg/day for increased absolute and relative kidney weights in rats that were exposed to 1,2-dichloroethane in drinking water for 13 weeks by an uncertainty factor of 300 (3 for use of minimal LOAEL; 10 for interspecies extrapolation; and 10 for human variability). Doses lower than 58 mg/kg/day were not tested, precluding identification of a NOAEL. The increases in kidney weight were dose-related and were considered to be an early-stage adverse effect in a known target organ, because histopathological changes were manifested in the kidney at higher doses in the rats as well as in similarly exposed mice in the same study. Tissue examinations showed dose-related, increased incidences of minimal-to-moderate renal regeneration in rats at \$102 mg/kg/day and mice at \$249 mg/kg/day. These changes are indicative of previous tubular injury with subsequent repair. More

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severe kidney effects including karyomegaly, dilatation, protein casts, and mineralization occurred in male mice exposed to 4,210 mg/kg/day. Observations of increased relative kidney weight in rats that were treated with 75 or 90 mg/kg/day by gavage for 90 days are supportive of the 58 mg/kg/day LOAEL.

An MRL has not been derived for chronic oral exposure (365 days) to 1,2-dichloroethane, because an appropriate study was not identified. The only chronic oral study tested rats and mice that were treated by gavage 5 days/week for up to 78 weeks. This study had several limitations such as dosage adjustments, possible contamination by other chemicals tested in the same laboratory, poor survival, and small numbers of control animals. Additionally, it may not be appropriate, in this case, to base an MRL on an effect level from a gavage oil study due to toxicokinetic considerations (e.g., possible bolus saturation of the detoxification/excretion mechanism).