

Appendix A. Background Information for Chloroform

This appendix was written based primarily on the *Toxicological Profile for Chloroform* (ATSDR 2024a). Primary references are cited for the reader's convenience in identifying pertinent studies. For additional information beyond what is presented here, the reader is referred to the toxicological profile.

A.1 Toxicokinetic

Following inhalation exposure, absorption of chloroform appears to be rapid and extensive. Numerous studies in humans have demonstrated that inhaled chloroform is absorbed into the blood and extra-respiratory tissues (Aggazzotti et al. 1993; Cammann and Hübner 1995; Lévesque et al. 1994; Nashelsky et al. 1995). Quantitative measurement of inhalation absorption fraction or rate is limited to one study. In six adult subjects inhaling chloroform present in shower water and protected from dermal exposure, Xu and Weisel (2005) estimated the percent chloroform absorbed as 71% (range of 40–80%) using a one-compartment model. Animal toxicity studies of inhaled chloroform have provided evidence for absorption, but quantitative estimates have not been reported (see ATSDR 2024a). A study of absorption of an oral dose of ¹³C-labeled chloroform (0.5 g in a gelatin capsule) in volunteers revealed that absorption was both rapid and complete, with nearly 100% of the dose absorbed and peak blood levels in 1 hour after exposure (Fry et al. 1972). Experiments in mice, rats, and monkeys indicate that oral doses (up to 60 mg/kg) of ¹⁴C-labeled chloroform in olive oil were almost completely absorbed, as indicated by an 80–96% recovery of radioactivity in expired air, urine, and carcass (Brown et al. 1974; Taylor et al. 1974). Absorption in mice and monkeys was rapid; the peak blood levels were reached 1 hour after oral administration of 60 mg/kg chloroform in olive oil. Oral absorption of chloroform from an aqueous vehicle has been shown to be more rapid than from an oil vehicle (Pereira 1994; Withey et al. 1983), although absorption is complete from both vehicles.

Due to its lipophilic character, chloroform accumulates to a greater extent in tissues of high lipid content. Following absorption, the relative concentrations of chloroform in various tissues generally decrease as follows: adipose tissue > brain > liver > kidney > blood. The chloroform levels in seven patients who died after excessive administration during chloroform anesthesia were: brain, 372–480 mg/kg; lungs, 355–485 mg/kg; and liver, 190–275 mg/kg tissue wet weight (Gettler and Blume 1931); chloroform levels in patients under anesthesia who died from other causes were: brain, 120–182 mg/kg; lungs, 92–145 mg/kg; and liver, 65–88 mg/kg tissue wet weight. After whole-body autoradiography to study the distribution of inhaled ¹⁴C-labeled chloroform in mice, most of the radioactivity was found in fat

immediately after exposure, while the concentration of radioactivity in the liver increased during the postanesthetic period, most likely due to covalent binding to lipid and protein in the liver (Cohen and Hood 1969). Radioactivity from ^{14}C -labeled chloroform was detected in the placenta and fetuses of mice shortly after inhalation exposure (Danielsson et al. 1986). Studies of distribution of chloroform in humans following oral exposure are not available. Following oral exposure in animal studies, distribution of chloroform appears to be similar to distribution following inhalation exposure, with the primary concentrations in lipophilic tissues (Brown et al. 1974; Pfaffenberger et al. 1980; Taylor et al. 1974; Take et al. 2010).

Metabolism of chloroform occurs primarily by cytochrome P450-dependent pathways, with CYP2E1 (ethanol-inducible) being the primary isozyme responsible (Wang et al. 1994). The initial reaction results in the formation of a reactive intermediate, which gives off hydrochloric acid to form phosgene, which is then free to react with cellular macromolecules (including GSH, proteins, and nucleic acids) or conjugate with water to form carbon dioxide and hydrochloric acid (Ade et al. 1994; Branchflower et al. 1984; Pohl et al. 1981; Smith et al. 1984; Stevens and Anders 1981). On the basis of pharmacokinetic results obtained in rats and mice exposed to chloroform by inhalation, and of enzymatic studies in human tissues *in vitro*, *in vivo* metabolic rate constants ($V_{\max}\text{C} = 15.7 \text{ mg/hour/kg}$, $K_m = 0.448 \text{ mg/L}$) were defined for humans (Corley et al. 1990). Interspecies differences in the rate of chloroform conversion were observed in mice, rats, and squirrel monkeys, with species differences in metabolism being highly dose-dependent. The conversion of chloroform to carbon dioxide was highest in mice (80%) and lowest in squirrel monkeys (18%) (Brown et al. 1974). Similarly, chloroform metabolism was calculated to be slower in humans than in rodents.

Regardless of the route of exposure, chloroform is excreted from the body primarily as expired carbon dioxide, although at higher concentrations, where metabolism is saturated, appreciable levels of parent compound may be exhaled as well (Brown et al. 1974; Corley et al. 1990; Taylor et al. 1974). Only small amounts of chloroform or metabolites are excreted in the urine (Brown et al. 1974; Mink et al. 1986). The calculated biological half-time for chloroform in humans following inhalation exposure is on the order of 8 hours (Gordon et al. 1988). Nearly all of a single inhaled dose of chloroform is eliminated within 48 hours in rats and mice (Corley et al. 1990). In humans given a single oral dose of chloroform, most of the dose was exhaled as parent compound and carbon dioxide (Fry et al. 1972). Very little was excreted in the urine. Results in mice and rats given single oral doses of chloroform (Brown et al. 1974; Mink et al. 1986; Taylor et al. 1974) were similar to those seen from single inhalation exposures.

Numerous PBPK models exist for chloroform in both humans and animals. While a detailed discussion of these models is beyond the scope of this document (a complete discussion of the models can be found in ATSDR 2024a), the models, in general, are structured as multicompartment models with up to eight compartments, not including arterial and venous blood, and inputs for inhalation, oral, and dermal exposure. Models have been developed in mice, rats, and humans (Chinery and Gleason 1993; Corley et al. 1990, 2000; Evans et al. 2020; Gearhart et al. 1993; Reitz et al. 1990) and have been used to predict blood and tissue concentrations for multiple routes of exposure.

A.2 Health Effects

Hepatic Effects. Chloroform inhalation has been demonstrated to induce hepatic effects in both humans and animals. Acute, high-dose inhalation exposure to chloroform, such as in chloroform anesthesia, has been shown to cause jaundice, necrosis, liver enlargement and tenderness, and increased sulfobromophthalein retention in humans (ATSDR 2024a). Workers exposed to 14–400 ppm chloroform for 1–6 months developed toxic hepatitis and other effects including jaundice, nausea, and vomiting, without fever (Phoon et al. 1983). Toxic hepatitis (with hepatomegaly, enhanced serum ALT, and serum AST activities, and hypergammaglobulinemia) was observed in workers exposed chronically to 2–205 ppm chloroform (Bomski et al. 1967). Exposure of swimmers to lower levels of chloroform (18–24 ppm) did not result in detectable hepatic changes (Aiking et al. 1994). Animal studies of inhaled chloroform have also identified hepatic effects as a sensitive target, including altered liver enzymes, fatty changes, centrilobular degeneration, and necrosis (ATSDR 2024a).

The liver is a primary target of oral chloroform toxicity in humans, with some evidence that suggests the damage may be reversible (Wallace 1950). Hepatic injury occurred in patients within 1–3 days following chloroform ingestion (Piersol et al. 1933; Schroeder 1965; Storms 1973), which included jaundice and liver enlargement and tenderness, as well as several altered blood biochemical parameters (increased ALT, AST, and lactate dehydrogenase (LDH) activities and increased bilirubin levels). At autopsy, fatty degeneration and extensive centrilobular necrosis were observed (Dettling et al. 2016; Piersol et al. 1933). Increased sulfobromophthalein retention indicated impaired liver function in an individual who ingested 21 mg/kg/day chloroform in a cough medicine for 10 years (Wallace 1950); the changes resolved after exposure was discontinued. Biochemical tests indicate that liver function in male and female humans was not affected by the use of mouthwash providing 0.96 mg/kg/day chloroform for ≤ 5 years (De Salva et al. 1975).

The liver is also a target organ for oral chloroform toxicity in animals. Following acute-duration oral doses of ≥ 34 mg/kg, hepatic effects included increased liver weight, fatty changes, and necrosis (ATSDR 2024a). A no-observed-adverse-effect level (NOAEL) of 26 mg/kg/day (4 days) was identified in mice (Larson et al. 1994). Liver effects in animals have been reported in numerous oral studies of intermediate duration (Chu et al. 1982a; Eschenbrenner and Miller 1945; Larson et al. 1995a). Hepatic changes from intermediate-duration oral studies have included increased liver weight, increased levels of liver enzymes in serum, histological changes in hepatocytes, increased cell proliferation, and necrosis (ATSDR 2024a). The early effects of oral chloroform exposure appear to be reversible (EPA 1980). The lowest intermediate-duration exposure at which hepatic effects were seen was 30 mg/kg/day, with a NOAEL of 15 mg/kg/day, in dogs (Heywood et al. 1979). Results of chronic-duration oral studies have also identified hepatic effects as a sensitive effect of chloroform exposure, with effects including altered liver enzymes, hyperplasia, fatty liver, and fibrosis (Heywood et al. 1979; NCI 1976a; Tumasonis et al. 1985, 1987); the lowest level at which chronic effects were seen was 15 mg/kg/day, the lowest exposure tested, in dogs (Heywood et al. 1979). Hepatic effects served as the basis for the derivation of acute-, intermediate-, and chronic-duration oral MRLs for chloroform (see Section A.4).

Renal Effects. Studies of the effects of inhaled chloroform in humans have not clearly identified the kidney as a sensitive target of chloroform toxicity, although acute-duration, high-dose exposure has been shown to result in renal effects (Aiking et al. 1994; Li et al. 1993; Royston 1924). Acute- and intermediate-duration animal inhalation studies have suggested renal effects of chloroform, particularly tubular cell proliferation and necrosis (ATSDR 2024a). Acute, high-dose oral exposure to chloroform in humans results in albuminuria, urinary casts, epithelial swelling, and fatty degeneration of kidney tubules (Piersol et al. 1933; Schroeder 1965), while similar urinary symptoms were seen in one subject who ingested 21 mg/kg/day chloroform in cough medicine for 10 years (Wallace 1950). No indications of renal effects were observed in humans who ingested estimated doses of 0.34–0.96 mg/kg/day chloroform in mouthwash for 5 years (De Salva et al. 1975). Acute-duration, high-dose animal studies of oral chloroform exposure have also identified renal effects, including cytoplasmic vacuolization, swelling, and necrosis of proximal tubule cells (ATSDR 2024a). Intermediate-duration animal studies have also identified renal changes, including increased kidney weight, inflammation, renal cell proliferation, and proximal tubular necrosis (ATSDR 2024a). The lowest lowest-observed-adverse-effect level (LOAEL) reported by ATSDR (2024a) for renal effects of intermediate-duration oral exposure was 27 mg/kg/day for increased incidences of both hyperplasia and atypical tubules in male rats given chloroform in their drinking water for 10 months (Hooth et al. 2002; McDorman et al. 2003a, 2003b). In chronic-duration oral studies in rodents, the lowest LOAEL for renal effects was 45 mg/kg/day based on increased

incidences of both tubular lumen dilation and cytoplasmic basophilia in the proximal tubule identified in rats given chloroform in their drinking water for 104 weeks (Nagano et al. 2006). In dogs, fat deposition in renal glomeruli was observed at a dose of 30 mg/kg/day chloroform for 7.5 years, but not at 15 mg/kg/day (Heywood et al. 1979).

Respiratory Effects. As presented in case reports, humans exposed to high levels of chloroform via inhalation exhibited depressed respiratory rates and/or respiratory arrest (Jayaweera et al. 2017; Storms 1973; Whitaker and Jones 1965), effects that were likely secondary to depression of the central nervous system (CNS). Results of animal studies indicate that the nasal epithelium and the underlying nasal bones are targets of chloroform toxicity in rodents following acute-, intermediate-, and chronic-duration inhalation exposures (ATSDR 2024a). The acute-, intermediate-, and chronic-duration inhalation MRLs for chloroform were based on nasal lesions in rodents following exposures for 4 days (Larson et al. 1996; Templin et al. 1996a), 13 weeks (Templin et al. 1996b), and 104 weeks (Yamamoto et al. 2002), respectively. Similar effects were observed following acute- and intermediate-duration gavage dosing in rodents (Dorman et al. 1997; Larson et al. 1995a; Templin et al. 1996a, 1996b). Chloroform-induced damage to the lower respiratory tract was generally only detected in animals following exposure to lethal concentrations (Bowman et al. 1978; Kasai et al. 2002; NCI 1976a), although there is limited evidence in mice of lung inflammatory responses following inhalation exposure to low chloroform concentrations (de Oliveira et al. 2015).

Neurological Effects. The neurological effects of high-dose inhaled chloroform are well-documented; chloroform was once used as an anesthetic in humans. Levels of 3,000–30,000 ppm were used to induce anesthesia (Featherstone 1947; Smith et al. 1973; Whitaker and Jones 1965), while concentrations of \approx 40,000 ppm, if continued for several minutes, could result in death (Featherstone 1947). Concentrations $<$ 1,500 ppm are insufficient to induce anesthesia, while concentrations of 1,500–2,000 ppm cause light anesthesia (Goodman and Gilman 1980). Following occupational exposures to chloroform at 223–1,163 ppm, workers with long-term (mean of 5.4 years) employment self-reported slowness, decreased concentration, irritability, and depression, which were not reported by workers with short-term (mean of 15 months) employment service (Challen et al. 1958). In formal neurological testing, workers exposed to chloroform at a mean concentration of 6.04 ppm for an average of 7.8 years exhibited significant deficits in visual retention, simple visual reaction time, symbol-digit substitution, digit span, and pursuit aiming relative to controls (Li et al. 1993). Workers exposed to chloroform at a mean concentration of 2.79 ppm exhibited deficits in pursuit aiming only. Case reports of neurological effects following oral exposure to chloroform identified abolished reflexes, unconsciousness, and coma (ATSDR 2024a). Following

regaining consciousness, most patients recovered fully. One patient experienced mild cerebellar damage characterized by intention tremor and gait instability but full recovery occurred within two weeks (Storms 1973). CNS depression has been observed in inhalation and oral studies in animals (ATSDR 2024a), with overt signs generally seen only at very high exposure levels. The NOAEL and LOAEL values for neurobehavioral effects were 31.1 mg/kg/day (up to 90 days) and 100 mg/kg/day (60 days), respectively, as determined by a battery of behavioral tests in mice administered the chemical by gavage in aqueous emulphor (Balster and Borzelleca 1982).

Developmental Effects. Data on the developmental effects of chloroform in humans following inhalation exposure are limited to a single case-control study (Swartz et al. 2015a, 2015b); exposure to chloroform via ambient outdoor air was not associated with incidences of spina bifida. Results of epidemiological studies evaluating relationships between developmental effects and ingestion of chloroform in chlorinated water are mixed; some studies reported associations between chloroform exposure and impaired *in utero* growth (Botton et al. 2015; Grazuleviciene et al. 2011; Summerhayes et al. 2012; Sun et al. 2020) but are confounded by co-exposure to numerous other substances, while other studies reported no associations between chloroform exposure and neurodevelopmental outcomes (Villanueva et al. 2018) or birth defects (Grazuleviciene et al. 2013; Kaufman et al. 2018, 2020; Zaganjor et al. 2020).

Animal studies of chloroform inhalation have consistently identified developmental effects, including growth retardation, decreased crown-rump length, altered ossification, cleft palate, and fetal resorption (ATSDR 2024a), generally beginning at 30 ppm chloroform or greater. Oral exposure of rats to ≥ 316 mg/kg/day on gestation days (GDs) 6–15 resulted in decreased pup body weight and increased resorptions, but not in increased frequency of malformations (Ruddick et al. 1983; Thompson et al. 1974). The NOAEL and LOAEL values for decreased fetal weight were 50 and 126 mg/kg/day, respectively, on GDs 6–15 in the rat (Thompson et al. 1974). Thompson et al. (1974) also identified an oral LOAEL for decreased fetal weight of 20 mg/kg/day in rabbits dosed on GDs 6–18. The potential developmental toxicity of intermediate-duration oral exposure to chloroform is even less well-characterized in animals. No neurobehavioral effects were reported in offspring of mice treated with 31.1 mg/kg/day for 6–10 weeks (Burkhalter and Balster 1979). In a continuous breeding study in mice, F1 males had increased epididymal weights and degeneration of the epididymal epithelium and F1 females had increased liver weight and hepatocellular degeneration at 41 mg/kg/day for 105 days (NTP 1988a).

Cancer. One occupational study of workers with “substantial” exposure to chloroform identified an increased risk of pancreatic cancer but no associations with other forms of cancer (Christensen et al.

2013). Epidemiology studies suggest an association between cancer in humans and the consumption of chlorinated drinking water (Bove et al. 2007; Font-Ribera et al. 2018; Gao et al. 2014; Jones et al. 2019), but the results are not conclusive at this time. Such an association implicates chloroform because chloroform is a known animal carcinogen and is the predominant trihalomethane in chlorinated drinking water; however, it is important to note that some of the many chemicals produced in the process of water chlorination are highly mutagenic and/or carcinogenic, and human data have not been able to adequately control for these co-exposures.

In animals, chronic-duration inhalation exposure to chloroform produced renal tumors in mice (Yamamoto et al. 2002). Evidence of chloroform carcinogenicity is mixed following intermediate-duration oral exposure in animals, with some studies suggesting no increase in tumor formation following exposures of <52 weeks to <250 mg/kg/day (Klaunig et al. 1986; Stoner et al. 1986), but one study reported that a 30-day exposure to 594 mg/kg/day in mice resulted in increased formation of hepatomas (Eschenbrenner and Miller 1945). Chloroform has been shown to be carcinogenic in numerous chronic-duration animal studies, resulting in tumors of the liver and kidney (ATSDR 2024a). In general, studies of exposure levels ≥ 60 mg/kg/day resulted in increased incidence of tumors, while carcinogenicity at lower exposure levels was less clear.

A.3 Mechanisms of Action

Chloroform is widely distributed to many tissues of the body in laboratory animals and, presumably, in humans; however, many studies have demonstrated that chloroform does not tend to accumulate in the body for extended periods. Chloroform may accumulate to some degree in the body fat stores; however, it quickly partitions out of the fat and is excreted by the normal routes and mechanisms. The liver, respiratory tract, and kidneys are considered to be the target organs for chloroform toxicity in both humans and laboratory animals.

Chloroform is largely metabolized in many tissues (particularly the liver and kidney) to carbon dioxide in humans and animals (Brown et al. 1974; Corley et al. 1990; Fry et al. 1972; Liu et al. 2013). Chloroform metabolism is catalyzed by cytochrome P450, isozyme CYP2E1 in particular, initiating an oxidative cleavage of the C-H bond producing trichloromethanol. Trichloromethanol is unstable and is rapidly transformed to phosgene (COCl_2). Phosgene may react with water to form CO_2 , which can be exhaled by the lung or excreted in the urine as carbonate or bicarbonate, and hydrochloric acid. Phosgene can also react with other molecules such as cysteine, deplete hepatic GSH (Docks and Krishna 1976; Pohl et al.

1981), and form adducts with microsomal proteins (Corley et al. 1990). Experiments performed with a CYP2E1 inhibitor or CYP2E1 knockout mice have demonstrated that chloroform's toxic effects to nasal, hepatic, and renal tissues are mediated by metabolites (Constan et al. 1999).

Chloroform toxicity can be attributed to the presence of both the parent compound and the formation of phosgene in most instances of toxicosis. High doses of inhaled chloroform have been reported to cause death (due to respiratory depression), ataxia, narcosis, and CNS depression, and due to the direct effects of the parent compound. Lower doses of chloroform in the air, feed, or water, or administered by gavage, with variable exposure times, may induce toxicity due to the presence of the parent compound or to production of phosgene during metabolism. It appears that the metabolite is responsible for hepatocellular damage, resulting in the ultimate leakage of hepatic enzymes (AST, ALT, gamma-glutamyl transferase [GGT], etc.) into the serum and cellular damage/necrosis. The accumulation of chloroform in the renal cortex of mice with the subsequent metabolism to phosgene most likely contributes to the renal toxicity of chloroform seen in male mice. Tubular necrosis, calcification, nephritis, increased kidney weight, alterations in Na/K excretion, and other cellular anomalies were observed in response to one or both of these toxicants.

A.4 Health Guidelines

ATSDR (2024a) derived an acute-duration inhalation MRL of 0.001 ppm for chloroform, based on a NOAEL of 2 ppm (human equivalent concentration NOAEL [NOAEL_{HEC}] of 0.04 ppm) for respiratory effects (nasal lesions) in rats and mice exposed for 4 days (Larson et al. 1996; Templin et al. 1996a) and an uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustment and 10 for human variability).

ATSDR (2024a) derived an intermediate-duration inhalation MRL of 0.0008 ppm for chloroform, based on a LOAEL of 2 ppm for respiratory effects (nasal lesions) in rats exposed for 13 weeks (Templin et al. 1996b) and an uncertainty factor of 90 (3 for extrapolation from a LOAEL to a NOAEL, 3 for extrapolation from animals to humans with dosimetric adjustment, and 10 for human variability).

ATSDR (2024a) derived a chronic-duration inhalation MRL of 0.0004 ppm for chloroform, based on a LOAEL of 5 ppm (human equivalent concentration LOAEL [LOAEL_{HEC}] of 0.11 ppm) for respiratory effects (nasal lesions) in mice exposed for 104 weeks (Yamamoto et al. 2002) and an uncertainty factor of

300 (10 for use of a LOAEL, 3 for extrapolation from animals to humans with dosimetric adjustment, and 10 for human variability).

ATSDR (2024a) derived an acute-duration oral MRL of 0.3 mg/kg/day for chloroform, based on a NOAEL of 26 mg/kg/day in the drinking water for 4 days for hepatic effects (hepatic lesions) in mice (Larson et al. 1994) and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

ATSDR (2024a) derived an intermediate-duration oral MRL of 0.1 mg/kg/day for chloroform, based on a NOAEL of 15 mg/kg/day (adjusted NOAEL [NOAEL_{ADJ}] of 13 mg/kg/day) for hepatic effects (increased serum ALT) in dogs dosed with chloroform in a capsule 1 time/day, 6 days/week for 6 weeks (Heywood et al. 1979) and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

ATSDR (2024a) derived a chronic-duration oral MRL of 0.02 mg/kg/day for chloroform, based on a 10% benchmark dose lower confidence limit (BMDL₁₀) of 2.15 mg/kg/day (adjusted benchmark lower confidence limit [BMDL_{ADJ}] of 1.84 mg/kg/day) for hepatic effects (fatty cysts) in dogs dosed with chloroform 6 days/week for 7.5 years (Heywood et al. 1979) and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

EPA (2001) has not derived a reference concentration (RfC) for chloroform.

EPA (2001) derived a reference dose (RfD) of 0.01 mg/kg/day for chloroform based on a BMDL₁₀ of 1.2 mg/kg/day (BMDL_{ADJ} of 1.0 mg/kg/day) for hepatic effects in dogs dosed with chloroform 6 days/week for 7.5 years (Heywood et al. 1979) and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

HHS's *Fifteenth Report on Carcinogens* (NTP 2021a) states that chloroform is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity in experimental animals.

Under EPA's *Proposed Guidelines for Carcinogen Risk Assessment* (EPA 1996), EPA (2001) determined that chloroform is *likely to be carcinogenic to humans* by all routes of exposure under high-exposure conditions that lead to cytotoxicity and regenerative hyperplasia in susceptible tissues.

IARC (1999) classifies chloroform as *possibly carcinogenic to humans* (Group 2B) based on inadequate evidence in humans and sufficient evidence in experimental animals.

A.5 Derivation of Target-Organ Toxicity Dose(s)

The noncancer endpoints of concern for chloroform in this mixture are hepatic, renal, respiratory, neurological, and developmental. For endpoints that are not the basis of the MRL, TTDS are derived below, using the methods described by ATSDR (2018). The derivations are based primarily on data provided in ATSDR (2024a) and, in particular, the Levels of Significant Exposure (LSE) tables.

Inhalation TTDS

The human equivalent concentration point of departure (POD_{HEC}) for an extra-respiratory effect is calculated by multiplying the duration-adjusted point of departure by the ratio of the blood:gas partition coefficients in animals and humans $[(Hb/g)_A / (Hb/g)_H]$. Since the partition coefficient for chloroform in rodents is greater than in humans (see ATSDR 2024a), a default value of 1 is used for the ratio.

Hepatic Effects, Intermediate Inhalation. Templin et al. (1998) identified a NOAEL of 5 ppm and a LOAEL of 17 ppm for increased relative liver weight and centrilobular swelling in mice exposed to chloroform for 6 hours/day, 5 days/week, for 7 weeks. Similar NOAEL and LOAEL values of 5 and 23–30 ppm, respectively, were identified based on hepatocytic swelling in mice exposed to chloroform for 6 hours/day, 5 days/week, for 13 weeks. The NOAEL of 5 ppm was duration-adjusted to 0.9 ppm for a continuous exposure scenario and converted to a $NOAEL_{HEC}$ of 0.9 ppm. Application of an uncertainty factor of 30 (3 for animal to human extrapolations with dosimetric adjustments and 10 for human variability) yields an intermediate-duration $TTD_{HEPATIC}$ of 0.03 ppm.

Renal Effects, Intermediate Inhalation. Larson et al. (1996) identified a LOAEL of 10 ppm for renal cell proliferation in the proximal convoluted tubules of male mice exposed to chloroform for 6 hours/day, 5 days/week, for 13 weeks; 10 ppm was the lowest concentration evaluated. Similarly, Templin et al. (1998) identified NOAEL and LOAEL values of 5 and 23 ppm, respectively, for cellular proliferation and regenerative lesions in the proximal convoluted tubule of mice exposed to chloroform for 6 hours/day, 5 days/week, for 13 weeks. Based on the similar study design, the NOAEL of 5 ppm was selected as the point of departure (POD) for the TTD. The NOAEL of 5 ppm was duration-adjusted to 0.9 ppm for a continuous exposure scenario and converted to a $NOAEL_{HEC}$ of 0.9 ppm. Application of an uncertainty

factor of 30 (3 for animal to human extrapolations for dosimetric adjustments and 10 for human variability) yields an intermediate-duration TTD_{RENAL} of 0.03 ppm.

Respiratory Effects, Intermediate Inhalation. The intermediate-duration inhalation MRL for chloroform is 0.0008 ppm based on respiratory effects.

Neurological Effects, Intermediate Inhalation. Adequate studies of the neurological effects of chloroform following intermediate-duration inhalation exposure are not available. Two studies (Larson et al. 1996; Templin et al. 1996b) evaluated chloroform's neurotoxicity in rodents following intermediate-duration exposures but failed to identify treatment-related effects. A chronic-duration TTD_{NEURO} of 0.006 ppm was derived based on impaired hand-eye coordination in workers exposed to 2.76 ppm for 1–15 years (Li et al. 1993). This TTD is higher than the intermediate-duration inhalation MRL and was adopted as the intermediate-duration TTD_{NEURO} .

Developmental Effects, Intermediate Inhalation. No intermediate-duration inhalation studies evaluated the developmental toxicity of chloroform. In an acute-duration study, Schwetz et al. (1974) reported a LOAEL of 30 ppm for delayed ossification and wavy ribs in the offspring of rats exposed for 7 hours/day on GDs 6–15. Since developmental toxicity is dependent on exposure during sensitive timepoints and not duration of exposure, results of the Schwetz et al. (1974) study were used to derive the intermediate-duration inhalation TDD for developmental effects. The LOAEL of 30 ppm was adjusted to 8.75 ppm for a continuous exposure scenario. Application of an uncertainty factor of 300 (10 for use of a LOAEL, 3 for animal to human extrapolation using a dosimetric adjustment, and 10 for human variability) yields a TTD_{DEVEL} of 0.03 ppm.

Hepatic Effects, Chronic Inhalation. Yamamoto et al. (2002) identified a NOAEL of 29.1 ppm and a less serious LOAEL of 85.8 ppm for fatty liver changes in mice exposed for 6 hours/day, 5 days/week, for 104 weeks. The NOAEL of 29.1 ppm was duration-adjusted to 5.2 ppm for a continuous exposure scenario and converted to a $NOAEL_{\text{HEC}}$ of 5.2 ppm. Application of an uncertainty factor of 30 (3 for animal to human extrapolations using a dosimetric adjustment and 10 for human variability) yields a chronic-duration TTD_{HEPATIC} of 0.2 ppm. As this is greater than the intermediate-duration TTD_{HEPATIC} of 0.03 ppm, the lower value of 0.03 ppm is adopted as the chronic-duration TTD_{HEPATIC} .

Renal Effects, Chronic Inhalation. Yamamoto et al. (2002) identified NOAEL and LOAEL values of 5 and 29.1 ppm, respectively, based on renal tubular lesions in male mice exposed for 6 hours/day,

5 days/week, for 104 weeks. The NOAEL of 5 ppm was duration-adjusted to 0.89 ppm for a continuous exposure scenario and converted to a NOAEL_{HEC} of 0.89 ppm. Application of an uncertainty factor of 30 (3 for animal to human extrapolations with dosimetric adjustment and 10 for human variability) yields a chronic-duration TTD_{RENAL} of 0.03 ppm.

Respiratory Effects, Chronic Inhalation. The chronic-duration inhalation MRL for chloroform is 0.0004 ppm based on respiratory effects.

Neurological Effects, Chronic Inhalation. Li et al. (1993) reported neurological effects, including impaired hand-eye coordination, in workers exposed to 2.79 ppm chloroform for 1–15 years. The LOAEL of 2.79 ppm was duration-adjusted for a continuous exposure scenario assuming that the workers were exposed 8 hours/day, 5 days/week, resulting in a LOAEL_{ADJ} of 0.66 ppm. An uncertainty factor of 100 (10 for use of a LOAEL and 10 for human variability) was applied to derive the TTD_{NEURO} of 0.006 ppm.

Developmental Effects, Chronic Inhalation. No chronic-duration inhalation studies evaluated the developmental toxicity of chloroform. Schwetz et al. (1974) reported a less serious developmental LOAEL of 30 ppm in rats exposed for 7 hours/day on GDs 6–15. Because developmental toxicity is dependent on exposure during sensitive timepoints and not duration of exposure, results of the Schwetz et al. (1974) study were used to derive the chronic-duration inhalation TDD for developmental effects. The LOAEL of 30 ppm was adjusted to 8.75 ppm for a continuous exposure scenario. Application of an uncertainty factor of 300 (10 for use of a LOAEL, 3 for animal to human extrapolation using a dosimetric adjustment, and 10 for human variability) yields a TTD_{DEVEL} of 0.03 ppm.

Oral TTDs

As discussed in ATSDR (2024a), rodents are more susceptible to chloroform's toxic effects via gavage or other bolus dosing than continual exposure via drinking water. This difference may be due to saturation of detoxification pathways following gavage dosing and/or adaptive changes following drinking water exposures at environmentally relevant concentrations. Therefore, results of drinking water studies are more relevant to human health effects resulting from environmental exposure levels and scenarios. For these reasons, the oral TTDs discussed below are derived solely from results of drinking water or capsule-based studies.

Hepatic Effects, Intermediate Oral. The intermediate-duration oral MRL for chloroform is 0.1 mg/kg/day, based on hepatic effects.

Renal Effects, Intermediate Oral. Only one intermediate-duration study identified renal effects of chloroform in animals exposed via drinking water: McDorman et al. (2003a) identified an increased incidence of atypical tubules and hyperplasia in the kidneys of Eker rats exposed to chloroform at 27 mg/kg/day for 10 months. Since the Eker rat is a model for hereditary renal cancer, the results of this study are not suitable to derive a TTD for renal effects. In additional intermediate-duration drinking water studies, no renal effects were identified in rats exposed to ≤ 106 mg/kg/day for 3 weeks (Larson et al. 1995b), ≤ 193 mg/kg/day for 28 days (Chu et al. 1982b), or ≤ 200 mg/kg/day for 90 days (Chu et al. 1982a; EPA 1980), or in mice exposed to ≤ 329 mg/kg/day for 3 weeks (Larson et al. 1994) or ≤ 435 mg/kg/day for 90 days (EPA 1980). Additionally, dogs dosed with ≤ 30 mg/kg/day via capsules for up to 42 weeks did not develop renal effects (Heywood et al. 1979). The highest dose tested for each of these studies is the NOAEL for renal effects. Since a free-standing NOAEL is not suitable for MRL or TTD development, the intermediate-duration oral MRL of 0.1 mg/kg/day is adopted as the TTD_{RENAL}.

Neurological Effects, Intermediate Oral. No intermediate-duration study identified neurological effects of chloroform in animals exposed via drinking water. No neurological effects were identified in rats exposed to ≤ 193 mg/kg/day for 28 days (Chu et al. 1982b) or ≤ 200 mg/kg/day for 90 days (Chu et al. 1982a). The highest dose tested for each of these studies is the NOAEL for neurological effects. Since a free-standing NOAEL is not suitable for MRL or TTD development, the intermediate-duration oral MRL of 0.1 mg/kg/day is adopted as the TTD_{NEURO}.

Developmental Effects, Intermediate Oral. No intermediate-duration oral studies evaluated the developmental toxicity of chloroform. The available acute-duration oral developmental toxicity studies administered chloroform via gavage. Therefore, the intermediate-duration oral MRL of 0.1 mg/kg/day is adopted as the TTD_{DEVEL}.

Hepatic Effects, Chronic Oral. The chronic-duration oral MRL for chloroform is 0.02 mg/kg/day, based on hepatic effects.

Renal Effects, Chronic Oral. Heywood et al. (1979) identified a NOAEL of 15 mg/kg/day and a LOAEL of 30 mg/kg/day for renal effects (fat deposition in the glomeruli) in dogs given chloroform in a capsule 6 days/week for 7.5 years. The NOAEL of 15 mg/kg/day was adjusted for intermittent exposure,

resulting in a $\text{NOAEL}_{\text{ADJ}}$ of 13 mg/kg/day. An uncertainty factor of 100 (10 for animal to human extrapolations and 10 for human variability) applied to the $\text{NOAEL}_{\text{ADJ}}$ results in a $\text{TTD}_{\text{RENAL}}$ of 0.1 mg/kg/day for chronic-duration oral exposure.

Neurological Effects, Chronic Oral. No chronic-duration oral study of sensitive endpoints for neurological effects was available for chloroform. Further, no chronic-duration oral studies evaluated neurological effects of chloroform in animals exposed via drinking water. No neurological effects were identified in dogs dosed with ≤ 30 mg/kg/day via capsule 6 days/week for 7.5 years (Heywood et al. 1979). Because the highest dose tested is the NOAEL for neurological effects and a free-standing NOAEL is not suitable for MRL or TTD development, the chronic-duration oral MRL of 0.02 mg/kg/day is adopted as the $\text{TTD}_{\text{NEURO}}$.

Developmental Effects, Chronic Oral. No chronic-duration oral studies evaluated the developmental toxicity of chloroform. The available acute-duration oral developmental toxicity studies administered chloroform via gavage. Therefore, the chronic-duration oral MRL of 0.02 mg/kg/day is adopted as the $\text{TTD}_{\text{DEVEL}}$.

Summary (TTD for Chloroform)

Intermediate-Duration Inhalation TTDs:

$$\text{TTD}_{\text{HEPATIC}} = 0.03 \text{ ppm}$$

$$\text{TTD}_{\text{RENAL}} = 0.03 \text{ ppm}$$

$$\text{MRL}_{\text{RESP}} = 0.0008 \text{ ppm}$$

$$\text{TTD}_{\text{NEURO}} = 0.006 \text{ ppm}$$

$$\text{TTD}_{\text{DEVEL}} = 0.03 \text{ ppm}$$

Chronic-Duration Inhalation TTDs:

$$\text{TTD}_{\text{HEPATIC}} = 0.03 \text{ ppm}$$

$$\text{TTD}_{\text{RENAL}} = 0.03 \text{ ppm}$$

$$\text{MRL}_{\text{RESP}} = 0.0004 \text{ ppm}$$

$$\text{TTD}_{\text{NEURO}} = 0.006 \text{ ppm}$$

$$\text{TTD}_{\text{DEVEL}} = 0.03 \text{ ppm}$$

Intermediate-Duration Oral TTDs:

$MRL_{HEPATIC} = 0.1 \text{ mg/kg/day}$

$TTD_{RENAL} = 0.1 \text{ mg/kg/day}$

$TTD_{NEURO} = 0.1 \text{ mg/kg/day}$

$TTD_{DEVEL} = 0.1 \text{ mg/kg/day}$

Chronic-Duration Oral TTDs:

$MRL_{HEPATIC} = 0.02 \text{ mg/kg/day}$

$TTD_{RENAL} = 0.1 \text{ mg/kg/day}$

$TTD_{NEURO} = 0.02 \text{ mg/kg/day}$

$TTD_{DEVEL} = 0.02 \text{ mg/kg/day}$

A.6 References

- Ade P, Guastadisegni C, Testai E, et al. 1994. Multiple activation of chloroform in kidney microsome from male and female DBA/2J mice. *J Biochem Toxicol* 9(6):289-295. <https://doi.org/10.1002/jbt.2570090603>.
- Aggazzotti G, Fantuzzi G, Righi E, et al. 1993. Chloroform in alveolar air of individuals attending indoor swimming pools. *Arch Environ Health* 48(4):250-254. <https://doi.org/10.1080/00039896.1993.9940368>.
- Aiking H, van Acker MB, Scholten RJPM, et al. 1994. Swimming pool chlorination: A health hazard? *Toxicol Lett* 72(1-3):375-380. [https://doi.org/10.1016/0378-4274\(94\)90051-5](https://doi.org/10.1016/0378-4274(94)90051-5).
- ATSDR. 2018. Framework for assessing health impacts of multiple chemicals and other stressors (Update). Agency for Toxic Substances and Disease Registry. <https://www.atsdr.cdc.gov/interaction-profiles/media/pdfs/ipga-p.pdf>. January 26, 2025.
- ATSDR. 2024a. Toxicological profile for chloroform. Agency for Toxic Substances and Disease Registry. <https://www.atsdr.cdc.gov/ToxProfiles/tp6.pdf>. December 16, 2024.
- Balster RL, Borzelleca JF. 1982. Behavioral toxicity of trihalomethane contaminants of drinking water in mice. *Environ Health Perspect* 46:127-136. <https://doi.org/10.1289/ehp.8246127>.
- Bomski H, Sobolewaka A, Strakowski A. 1967. [Toxic damage of the liver by chloroform in chemical industry workers]. *Int Arch Arbeitsmed* 24(2):127-134. <https://doi.org/10.1007/BF00369015>. (German)
- Botton J, Kogevinas M, Gracia-Lavedan E, et al. 2015. Postnatal weight growth and trihalomethane exposure during pregnancy. *Environ Res* 136:280-288. <https://doi.org/10.1016/j.envres.2014.09.035>.
- Bove GE, Rogerson PA, Vena JE. 2007. Case-control study of the effects of trihalomethanes on urinary bladder cancer risk. *Arch Environ Occup Health* 62(1):39-47. <https://doi.org/10.3200/AEOH.62.1.39-47>.
- Bowman FJ, Borzelleca JF, Munson AE. 1978. The toxicity of some halomethanes in mice. *Toxicol Appl Pharmacol* 44(1):213-215. [https://doi.org/10.1016/0041-008X\(78\)90300-9](https://doi.org/10.1016/0041-008X(78)90300-9).
- Branchflower RV, Nunn DS, Highet RJ, et al. 1984. Nephrotoxicity of chloroform: Metabolism to phosgene by the mouse kidney. *Toxicol Appl Pharmacol* 72:159-168. [https://doi.org/10.1016/0041-008X\(84\)90260-6](https://doi.org/10.1016/0041-008X(84)90260-6).

- Brown DM, Langley PF, Smith D, et al. 1974. Metabolism of chloroform. I. The metabolism of ^{14}C -chloroform by different species. *Xenobiotica* 4(3):151-163. <https://doi.org/10.3109/00498257409049355>.
- Burkhalter JE, Balster RL. 1979. Behavioral teratology evaluation of trichloromethane in mice. *Neurobehav Toxicol* 1(3):199-205.
- Cammann K, Hübner K. 1995. Trihalomethane concentrations in swimmers' and bath attendants' blood and urine after swimming or working in indoor swimming pools. *Arch Environ Health* 50(1):61-65. <https://doi.org/10.1080/00039896.1995.9955013>.
- Challen PJR, Hickish DE, Bedford J. 1958. Chronic chloroform intoxication. *Br J Ind Med* 15(4):243-249. <https://doi.org/10.1136/oem.15.4.243>.
- Chinery RL, Gleason AK. 1993. A compartmental model for the prediction of breath concentration and absorbed dose of chloroform after exposure while showering. *Risk Anal* 13(1):51-62. <https://doi.org/10.1111/j.1539-6924.1993.tb00728.x>.
- Christensen KY, Vizcaya D, Richardson H, et al. 2013. Risk of selected cancers due to occupational exposure to chlorinated solvents in a case-control study in Montreal. *J Occup Environ Med* 55(2):198-208. <https://doi.org/10.1097/JOM.0b013e3182728eab>.
- Chu I, Villeneuve DC, Secours VE, et al. 1982a. Trihalomethanes: II. Reversibility of toxicological changes produced by chloroform, bromodichloromethane, chlorodibromomethane and bromoform in rats. *J Environ Sci Health B* 17(3):225-240. <https://doi.org/10.1080/03601238209372315>.
- Chu I, Villeneuve DC, Secours VE, et al. 1982b. Toxicity of trihalomethanes: I. The acute and subacute toxicity of chloroform, bromodichloromethane, chlorodibromomethane and bromoform in rats. *J Environ Sci Health B* 17(3):205-224. <https://doi.org/10.1080/03601238209372314>.
- Cohen EN, Hood N. 1969. Application of low-temperature autoradiography to studies of the uptake and metabolism of volatile anesthetics in the mouse. *Anesthesiology* 30:306-314.
- Constan AA, Sprankle CS, Peters JM, et al. 1999. Metabolism of chloroform by cytochrome P450 2E1 is required for induction of toxicity in the liver, kidney, and nose of male mice. *Toxicol Appl Pharmacol* 160(2):120-126. <https://doi.org/10.1006/taap.1999.8756>.
- Corley RA, Mendrala AL, Smith FA, et al. 1990. Development of a physiologically based pharmacokinetic model for chloroform. *Toxicol Appl Pharmacol* 103:512-527. [https://doi.org/10.1016/0041-008X\(90\)90324-N](https://doi.org/10.1016/0041-008X(90)90324-N).
- Corley RA, Gordon SM, Wallace LA. 2000. Physiologically based pharmacokinetic modeling of the temperature-dependent dermal absorption of chloroform by humans following bath water exposures. *Toxicol Sci* 53(1):13-23. <https://doi.org/10.1093/toxsci/53.1.13>.
- Danielsson BRG, Ghantous H, Dencker L. 1986. Distribution of chloroform and methyl chloroform and their metabolites in pregnant mice. *Biol Res Pregnancy* 7(2):77-83.
- de Oliveira TH, Campos KK, Soares NP, et al. 2015. Influence of sexual dimorphism on pulmonary inflammatory response in adult mice exposed to chloroform. *Int J Toxicol* 34(3):250-257. <https://doi.org/10.1177/1091581815580172>.
- De Salva S, Volpe A, Leigh G, et al. 1975. Long-term safety studies of a chloroform-containing dentifrice and mouth-rinse in man. *Food Cosmet Toxicol* 13(5):529-532. [https://doi.org/10.1016/0015-6264\(75\)90007-3](https://doi.org/10.1016/0015-6264(75)90007-3).
- Dettling A, Stadler K, Eisenbach C, et al. 2016. Systemic inflammatory response due to chloroform intoxication-an uncommon complication. *Int J Legal Med* 130(2):401-404. <https://doi.org/10.1007/s00414-015-1156-8>.
- Docks EL, Krishna G. 1976. The role of glutathione in chloroform-induced hepatotoxicity. *Exp Mol Pathol* 24:13-22. [https://doi.org/10.1016/0014-4800\(76\)90053-8](https://doi.org/10.1016/0014-4800(76)90053-8).
- Dorman DC, Miller KL, D'Antonio A, et al. 1997. Chloroform-induced olfactory mucosal degeneration and osseous ethmoid hyperplasia are not associated with olfactory deficits in Fischer 344 rats. *Toxicology* 122(1-2):39-50. [https://doi.org/10.1016/s0300-483x\(97\)00076-0](https://doi.org/10.1016/s0300-483x(97)00076-0).

- EPA. 1980. Effects of chloroform in the drinking water of rats and mice: Ninety-day subacute toxicity study. Cincinnati, OH: U.S. Environmental Protection Agency. EPA600180030. <https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=9100SIV9.txt>. February 21, 2023.
- EPA. 1996. Proposed guidelines for carcinogen risk assessment. U.S. Environmental Protection Agency. EPA600P92003C. <https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=55868>. June 29, 2021.
- EPA. 2001. Chloroform. Integrated Risk Information System (IRIS). Cincinnati, OH: U.S. Environmental Protection Agency. https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=25. October 19, 2001.
- Eschenbrenner AB, Miller E. 1945. Induction of hepatomas in mice by repeated oral administration of chloroform, with observations on sex differences. *J Natl Cancer Inst* 5:251-255. <https://doi.org/10.1093/jnci/5.4.251>.
- Evans MV, Eklund CR, Williams DN, et al. 2020. Global optimization of the Michaelis-Menten parameters using physiologically-based pharmacokinetic (PBPK) modeling and chloroform vapor uptake data in F344 rats. *Inhal Toxicol* 32(3):97-109. <https://doi.org/10.1080/08958378.2020.1742818>.
- Featherstone HW. 1947. Chloroform. *Anesthesiology* 8:362-371.
- Font-Ribera L, Gracia-Lavedan E, Aragonés N, et al. 2018. Long-term exposure to trihalomethanes in drinking water and breast cancer in the Spanish multicase-control study on cancer (MCC-SPAIN). *Environ Int* 112:227-234. <https://doi.org/10.1016/j.envint.2017.12.031>.
- Fry BJ, Taylor R, Hathaway DE. 1972. Pulmonary elimination of chloroform and its metabolite in man. *Arch Int Pharmacodyn* 196:98-111.
- Gao Y, Zhang Y, Kamijima M, et al. 2014. Quantitative assessments of indoor air pollution and the risk of childhood acute leukemia in Shanghai. *Environ Pollut* 187:81-89. <https://doi.org/10.1016/j.envpol.2013.12.029>.
- Gearhart JM, Seckel C, Vinegar A. 1993. In vivo metabolism of chloroform in B6C3F1 mice determined by the method of gas uptake: the effects of body temperature on tissue partition coefficients and metabolism. *Toxicol Appl Pharmacol* 119(2):258-266. <https://doi.org/10.1006/taap.1993.1067>.
- Gettler AO, Blume H. 1931. Chloroform in the brain, lungs, and liver. Quantitative recovery and determination. *Arch Pathol* 11:554-560.
- Goodman LS, Gilman A. 1980. Trichloroethylene and chloroform. In: *The pharmacological basis of therapeutics*. 6th ed. New York, NY: MacMillan Publishing, 291-292, 1646.
- Gordon SM, Wallace LA, Pellizzari ED, et al. 1988. Human breath measurements in a clean-air chamber to determine half-lives for volatile organic compounds. *Atmos Environ* 22(10):2165-2170. [https://doi.org/10.1016/0004-6981\(88\)90126-6](https://doi.org/10.1016/0004-6981(88)90126-6).
- Grazuleviciene R, Nieuwenhuijsen MJ, Vencloviene J, et al. 2011. Individual exposures to drinking water trihalomethanes, low birth weight and small for gestational age risk: a prospective Kaunas cohort study. *Environ Health* 10:32. <https://doi.org/10.1186/1476-069X-10-32>.
- Grazuleviciene R, Kapustinskiene V, Vencloviene J, et al. 2013. Risk of congenital anomalies in relation to the uptake of trihalomethane from drinking water during pregnancy. *Occup Environ Med* 70(4):274-282. <https://doi.org/10.1136/oemed-2012-101093>.
- Heywood R, Sortwell RJ, Noel PRB, et al. 1979. Safety evaluation of toothpaste containing chloroform. III. Long-term study in beagle dogs. *J Environ Pathol Toxicol* 2(3):835-851.
- Hooth MJ, McDorman KS, Hester SD, et al. 2002. The carcinogenic response of Tsc2 mutant Long-Evans (Eker) rats to a mixture of drinking water disinfection by-products was less than additive. *Toxicol Sci* 69(2):322-331. <https://doi.org/10.1093/toxsci/69.2.322>.
- IARC. 1999. Some chemicals that cause tumours of the kidney or urinary bladder in rodents and some other substances. IARC Monographs on the evaluation of carcinogenic risks to humans. Vol. 73. Lyon, France: International Agency for Research on Cancer. <https://publications.iarc.fr/91>. May 26, 2021.

- Jayaweera D, Islam S, Gunja N, et al. 2017. Chloroform ingestion causing severe gastrointestinal injury, hepatotoxicity and dermatitis confirmed with plasma chloroform concentrations. *Clin Toxicol* 55(2):147-150. <https://doi.org/10.1080/15563650.2016.1249795>.
- Jones RR, DellaValle CT, Weyer PJ, et al. 2019. Ingested nitrate, disinfection by-products, and risk of colon and rectal cancers in the Iowa Women's Health Study cohort. *Environ Int* 126:242-251. <https://doi.org/10.1016/j.envint.2019.02.010>.
- Kasai T, Nishizawa T, Arito H, et al. 2002. Acute and subchronic inhalation toxicity of chloroform in rats and mice. *J Occup Health* 44(4):193-202. <https://doi.org/10.1539/joh.44.193>.
- Kaufman JA, Wright JM, Evans A, et al. 2018. Associations between disinfection by-product exposures and craniofacial birth defects. *J Occup Environ Med* 60(2):109-119. <https://doi.org/10.1097/jom.0000000000001191>.
- Kaufman JA, Wright JM, Evans A, et al. 2020. Disinfection by-product exposures and the risk of musculoskeletal birth defects. *Environ Epidemiol* 4(1):e081. <https://doi.org/10.1097/ee9.0000000000000081>.
- Klaunig JE, Ruth RJ, Pereira MA. 1986. Carcinogenicity of chlorinated methane and ethane compounds administered in drinking water to mice. *Environ Health Perspect* 69:89-95. <https://doi.org/10.1289/ehp.866989>.
- Larson JL, Wolf DC, Butterworth BE. 1994. Induced cytotoxicity and cell proliferation in the hepatocarcinogenicity of chloroform in female B6C3F1 mice: comparison of administration by gavage in corn oil vs ad libitum in drinking water. *Fundam Appl Toxicol* 22(1):90-102. <https://doi.org/10.1006/faat.1994.1012>.
- Larson JL, Wolf DC, Méry S, et al. 1995a. Toxicity and cell proliferation in the liver, kidneys and nasal passages of female F-344 rats, induced by chloroform administered by gavage. *Food Chem Toxicol* 33(6):443-456. [https://doi.org/10.1016/0278-6915\(95\)00013-r](https://doi.org/10.1016/0278-6915(95)00013-r).
- Larson JL, Wolf DC, Butterworth BE. 1995b. Induced regenerative cell proliferation in livers and kidneys of male F-344 rats given chloroform in corn oil by gavage or ad libitum in drinking water. *Toxicology* 95(1-3):73-86. [https://doi.org/10.1016/0300-483x\(94\)02886-y](https://doi.org/10.1016/0300-483x(94)02886-y).
- Larson JL, Templin MV, Wolf DC, et al. 1996. A 90-day chloroform inhalation study in female and male B6C3F1 mice: implications for cancer risk assessment. *Fundam Appl Toxicol* 30(1):118-137. <https://doi.org/10.1006/faat.1996.0049>.
- Lévesque B, Ayotte P, LeBlanc A, et al. 1994. Evaluation of dermal and respiratory chloroform exposure in humans. *Environ Health Perspect* 102(12):1082-1087. <https://doi.org/10.1289/ehp.102-1567469>.
- Li LH, Jiang XZ, Liang YX, et al. 1993. Studies on the toxicity and maximum allowable concentration of chloroform. *Biomed Environ Sci* 6(2):179-186.
- Liu S, Yao Y, Lu S, et al. 2013. The role of renal proximal tubule P450 enzymes in chloroform-induced nephrotoxicity: utility of renal specific P450 reductase knockout mouse models. *Toxicol Appl Pharmacol* 272(1):230-237. <https://doi.org/10.1016/j.taap.2013.05.022>.
- McDorman KS, Hooth MJ, Starr TB, et al. 2003a. Analysis of preneoplastic and neoplastic renal lesions in Tsc2 mutant Long-Evans (Eker) rats following exposure to a mixture of drinking water disinfection by-products. *Toxicology* 187(1):1-12. [https://doi.org/10.1016/s0300-483x\(03\)00004-0](https://doi.org/10.1016/s0300-483x(03)00004-0).
- McDorman KS, Chandra S, Hooth MJ, et al. 2003b. Induction of transitional cell hyperplasia in the urinary bladder and aberrant crypt foci in the colon of rats treated with individual and a mixture of drinking water disinfection by-products. *Toxicol Pathol* 31(2):235-242. <https://doi.org/10.1080/01926230390183733>.
- Mink FL, Brown TJ, Rickabaugh J. 1986. Absorption, distribution and excretion of C-trihalomethanes in mice and rats. *Bull Environ Contam Toxicol* 37:752-758. <https://doi.org/10.1007/BF01607835>.
- Nagano K, Kano H, Arito H, et al. 2006. Enhancement of renal carcinogenicity by combined inhalation and oral exposures to chloroform in male rats. *J Toxicol Environ Health* 69(20):1827-1842. <https://doi.org/10.1080/15287390600630146>.

- Nashelsky MB, Dix JD, Adelstein EH. 1995. Homicide facilitated by inhalation of chloroform. *J Forensic Sci* 40(1):134-138. <https://doi.org/10.1520/JFS13778J>.
- NCI. 1976a. Report on carcinogenesis bioassay of chloroform. Bethesda, MD: National Cancer Institute. PB264018. <https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/PB264018.xhtml>. February 21, 2023.
- NTP. 1988a. Chloroform: reproduction and fertility assessment in CD 1 mice when administered by gavage. Research Triangle Park, NC: National Toxicology Program. PB89148639. NTP-89-018. <https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/PB89148639.xhtml>. January 28, 2025.
- Pereira MA. 1994. Route of administration determines whether chloroform enhances or inhibits cell proliferation in the liver of B6C3F1 mice. *Fundam Appl Toxicol* 23(1):87-92. <https://doi.org/10.1006/faat.1994.1083>.
- Pfaffenberger CD, Peoples AJ, Enos HF. 1980. Distribution of volatile halogenated organic compounds between rat blood serum and adipose tissue. *Int J Environ Anal Chem* 8(1):55-65. <https://doi.org/10.1080/03067318008071879>.
- Phoon WH, Goh KT, Lee LT, et al. 1983. Toxic jaundice from occupational exposure to chloroform. *Med J Malaysia* 38(1):31-34.
- Piersol GM, Tumen HJ, Kau LS. 1933. Fatal poisoning following the ingestion of chloroform. *Med Clin North Am* 17:587-601.
- Pohl LR, Branchflower RV, Highet RJ, et al. 1981. The formation of diglutathionyl dithiocarbonate as a metabolite of chloroform, bromotrichloromethane, and carbon tetrachloride. *Drug Metab Dispos* 9(4):334-339. [https://doi.org/10.1016/S0090-9556\(25\)06157-4](https://doi.org/10.1016/S0090-9556(25)06157-4).
- Reitz RH, Mendrala AL, Corley RA, et al. 1990. Estimating the risk of liver cancer associated with human exposures to chloroform using physiologically based pharmacokinetic modeling. *Toxicol Appl Pharmacol* 105:443-459. [https://doi.org/10.1016/0041-008X\(90\)90148-N](https://doi.org/10.1016/0041-008X(90)90148-N).
- Royston GD. 1924. Delayed chloroform poisoning following delivery. *Am J Obstet Gynecol* 10:808-814. [https://doi.org/10.1016/S0002-9378\(25\)90451-6](https://doi.org/10.1016/S0002-9378(25)90451-6).
- Ruddick JA, Villeneuve DC, Chu I, et al. 1983. A teratological assessment of four trihalomethanes in the rat. *J Environ Sci Health B* 18(3):333-349. <https://doi.org/10.1080/03601238309372373>.
- Schroeder HG. 1965. Acute and delayed chloroform poisoning. *Br J Anaesth* 37:972-975. <https://doi.org/10.1093/bja/37.12.972>.
- Schwetz BA, Leong BK, Gehring PJ. 1974. Embryo- and fetotoxicity of inhaled chloroform in rats. *Toxicol Appl Pharmacol* 28(3):442-451. [https://doi.org/10.1016/0041-008x\(74\)90229-4](https://doi.org/10.1016/0041-008x(74)90229-4).
- Smith AA, Volpitto PP, Gramling ZW, et al. 1973. Chloroform, halothane, and regional anesthesia: A comparative study. *Anesth Analg* 52(1):1-11.
- Smith JH, Maita K, Sleight SD, et al. 1984. Effect of sex hormone status on chloroform nephrotoxicity and renal mixed function oxidases in mice. *Toxicology* 30:305-316. [https://doi.org/10.1016/0300-483X\(84\)90141-0](https://doi.org/10.1016/0300-483X(84)90141-0).
- Stevens JL, Anders MW. 1981. Effect of cysteine, diethyl maleate, and phenobarbital treatments on the hepatotoxicity of [1H]- and [2H]chloroform. *Chem Biol Interact* 37:207-217. [https://doi.org/10.1016/0009-2797\(81\)90178-2](https://doi.org/10.1016/0009-2797(81)90178-2).
- Stoner GD, Conran PB, Greisiger EA, et al. 1986. Comparison of two routes of chemical administration on the lung adenoma response in strain A/J mice. *Toxicol Appl Pharmacol* 82:19-31. [https://doi.org/10.1016/0041-008X\(86\)90433-3](https://doi.org/10.1016/0041-008X(86)90433-3).
- Storms WW. 1973. Chloroform parties. *J Am Med Assoc* 225(2):160. <https://doi.org/10.1001/jama.1973.03220290048012>.
- Summerhayes RJ, Morgan GG, Edwards HP, et al. 2012. Exposure to trihalomethanes in drinking water and small-for-gestational-age births. *Epidemiology* 23(1):15-22. <https://doi.org/10.1097/EDE.0b013e31823b669b>.

- Sun Y, Wang YX, Liu C, et al. 2020. Trimester-specific blood trihalomethane and urinary haloacetic acid concentrations and adverse birth outcomes: Identifying windows of vulnerability during pregnancy. *Environ Health Perspect* 128(10):107001. <https://doi.org/10.1289/EHP7195>.
- Swartz MD, Cai Y, Chan W, et al. 2015a. Air toxics and birth defects: a Bayesian hierarchical approach to evaluate multiple pollutants and spina bifida. *Environ Health* 14:16. <https://doi.org/10.1186/1476-069X-14-16>.
- Swartz MD, Cai Y, Chan W, et al. 2015b. Supplemental material: Air toxics and birth defects: a Bayesian hierarchical approach to evaluate multiple pollutants and spina bifida. *Environ Health* 14 <https://doi.org/10.1186/1476-069X-14-16>.
- Take M, Yamamoto S, Ohnishi M, et al. 2010. Chloroform distribution and accumulation by combined inhalation plus oral exposure routes in rats. *J Environ Sci Health A Toxic Hazard Subst Environ Eng* 45(12):1616-1624. <https://doi.org/10.1080/10934529.2010.506121>.
- Taylor DC, Brown DM, Keeble R, et al. 1974. Metabolism of chloroform. II. A sex difference in the metabolism of [¹⁴C]chloroform in mice. *Xenobiotica* 4(3):165-174. <https://doi.org/10.3109/00498257409049356>.
- Templin MV, Jamison KC, Wolf DC, et al. 1996a. Comparison of chloroform-induced toxicity in the kidneys, liver, and nasal passages of male Osborne-Mendel and F-344 rats. *Cancer Lett* 104(1):71-78. [https://doi.org/10.1016/0304-3835\(96\)04234-6](https://doi.org/10.1016/0304-3835(96)04234-6).
- Templin MV, Larson JL, Butterworth BE, et al. 1996b. A 90-day chloroform inhalation study in F-344 rats: profile of toxicity and relevance to cancer studies. *Fundam Appl Toxicol* 32(1):109-125. <https://doi.org/10.1006/faat.1996.0113>.
- Templin MV, Constan AA, Wolf DC, et al. 1998. Patterns of chloroform-induced regenerative cell proliferation in BDF1 mice correlate with organ specificity and dose-response of tumor formation. *Carcinogenesis* 19(1):187-193. <https://doi.org/10.1093/carcin/19.1.187>.
- Thompson DJ, Warner SD, Robinson VB. 1974. Teratology studies on orally administered chloroform in the rat and rabbit. *Toxicol Appl Pharmacol* 29(3):348-357. [https://doi.org/10.1016/0041-008x\(74\)90107-0](https://doi.org/10.1016/0041-008x(74)90107-0).
- Tumasonis CF, McMartin DN, Bush B. 1985. Lifetime toxicity of chloroform and bromodichloromethane when administered over a lifetime in rats. *Ecotoxicol Environ Saf* 9(2):233-240. [https://doi.org/10.1016/0147-6513\(85\)90026-0](https://doi.org/10.1016/0147-6513(85)90026-0).
- Tumasonis CF, McMartin DN, Bush B. 1987. Toxicity of chloroform and bromodichloromethane when administered over a lifetime in rats. *J Environ Pathol Toxicol Oncol* 7(4):55-64.
- Villanueva CM, Gracia-Lavedan E, Julvez J, et al. 2018. Drinking water disinfection by-products during pregnancy and child neuropsychological development in the INMA Spanish cohort study. *Environ Int* 110:113-122. <https://doi.org/10.1016/j.envint.2017.10.017>.
- Wallace CJ. 1950. Hepatitis and nephrosis due to cough syrup containing chloroform. *Calif Med* 73(5):442-443.
- Wang PY, Kaneko T, Tsukada H, et al. 1994. Dose and route dependency of metabolism and toxicity of chloroform in ethanol-treated rats. *Arch Toxicol* 69:18-23. <https://doi.org/10.1007/s002040050131>.
- Whitaker AM, Jones CS. 1965. Report of 1500 chloroform anesthetics administered with a precision vaporizer. *Anesth Analg* 44(1):60-65.
- Withey JR, Collins BT, Collins PG. 1983. Effect of vehicle on the pharmacokinetics and uptake of four halogenated hydrocarbons from the gastrointestinal tract of the rat. *J Appl Toxicol* 3(5):249-253. <https://doi.org/10.1002/jat.2550030506>.
- Xu X, Weisel CP. 2005. Human respiratory uptake of chloroform and halo ketones during showering. *J Expo Anal Environ Epidemiol* 15(1):6-16. <https://doi.org/10.1038/sj.jea.7500374>.
- Yamamoto S, Kasai T, Matsumoto M, et al. 2002. Carcinogenicity and chronic toxicity in rats and mice exposed to chloroform by inhalation. *J Occup Health* 44(5):283-293. <https://doi.org/10.1539/joh.44.283>.

Zaganjor I, Luben TJ, Desrosiers TA, et al. 2020. Maternal exposure to disinfection by-products and risk of hypospadias in the National Birth Defects Prevention Study (2000-2005). *Int J Environ Res Public Health* 17(24):9564. <https://doi.org/10.3390/ijerph17249564>.

Appendix B. Background Information for 1,1-Dichloroethene

This appendix was written based primarily on the *Toxicological Profile for 1,1-Dichloroethene* (ATSDR 2022c). Primary references are cited for the reader's convenience in identifying pertinent studies. For additional information beyond what is presented here, the reader is referred to the toxicological profile.

B.1 Toxicokinetics

No studies evaluating the absorption of 1,1-dichloroethene in humans following inhalation or oral exposure were located. Animal studies have demonstrated that 1,1-dichloroethene is rapidly absorbed following inhalation exposure (Dallas et al. 1983; McKenna et al. 1978b), being detectable in blood following as little as 2 minutes of exposure (Dallas et al. 1983), and is linear up to concentrations of 150 ppm (Dallas et al. 1983). Animal studies of oral exposure of 1,1-dichloroethene have similarly demonstrated rapid and near-complete absorption (Reichert et al. 1979). Doses of 1,1-dichloroethene ranging from 10 to 100 mg/kg were rapidly and almost completely absorbed from the gastrointestinal tract of rats and mice following oral administration in corn oil (Jones and Hathway 1978a; Putcha et al. 1986). Rapid absorption likewise occurred following oral administration of 200 mg/kg in an aqueous emulsion, as evidenced by the observation that the largest percentage of the dose was exhaled during the initial 15-minute period (Chieco et al. 1981). After oral administration to rats of 1,1-dichloroethene labeled with radioactive carbon (^{14}C), 81–99.8% of the administered radioactivity was recovered within 72 hours (Reichert et al. 1979), indicating very rapid and near-complete absorption.

No studies evaluating the distribution of 1,1-dichloroethene in humans following inhalation or oral exposure were located. Following inhalation exposure of rats to 10 or 200 ppm of ^{14}C -labeled 1,1-dichloroethene, the highest level of radioactivity was found in the liver and kidneys after 72 hours, with only very small amounts present in other tissues (McKenna et al. 1978b). Preferential accumulation of radioactivity was reported in the kidney and liver of rats exposed to 2,000 ppm radiolabeled 1,1-dichloroethene for 2 hours (Jaeger et al. 1977); fasted animals showed a higher accumulation of radiolabel than unfasted animals. 1,1-Dichloroethene was rapidly distributed to all tissues examined following a single oral dose of the ^{14}C -labeled compound to rats (Jones and Hathway 1978b). The highest amount of radioactivity was found in the liver and kidneys within 30 minutes of administration, although more general redistribution throughout the soft tissues of the body followed.

The metabolism of 1,1-dichloroethene following oral administration in rats has been extensively studied (Jones and Hathway 1978a, 1978b; McKenna et al. 1978a; Reichert et al. 1979). The primary biotransformation pathway is believed to involve the metabolism by CYP2E1 to a reactive epoxide, 1,1-dichloroethene oxide (Jones and Hathway 1978b; McKenna et al. 1977; Reichert et al. 1979). This metabolite may react with cellular molecules, may be conjugated to GSH, or may rearrange to chloroacetyl chloride and eventually to monochloroacetic acid. It is believed that metabolism of 1,1-dichloroethene is saturable based on studies demonstrating that at high exposure levels, a greater amount of unchanged compound is eliminated in the expired air (Dallas et al. 1983; Jones and Hathway 1978b; McKenna et al. 1978a, 1978b; Reichert et al. 1979).

Regardless of route of exposure, elimination of 1,1-dichloroethene is rapid and accomplished primarily in the form of metabolites in the urine, with elimination of the parent compound in the expired air becoming more prevalent as the exposure levels increase. At low doses (<150 ppm by inhalation or ≤ 1 mg/kg/day orally), very little (≤ 1) of the parent compound is eliminated in the expired air, while at higher concentrations, the percentage eliminated as the parent compound increases (Dallas et al. 1983; Jones and Hathway 1978b; McKenna et al. 1978a; Reichert et al. 1979).

D'Souza and Andersen (1988) reported a PBPK model for 1,1-dichloroethene in rats, based on the model for styrene developed by Ramsey and Andersen (1984). The model consists of four compartments (liver, slowly perfused, richly perfused, and fat) as well as blood, and contains inputs for both oral and inhalation exposure. Metabolism is assumed to occur in the liver compartment and consists of an initial oxidation followed by conjugation with GSH. Values for organ volume and blood flow were taken from previous modeling efforts (Gargas et al. 1986). The model simulations were optimized using data from McKenna et al. (1978b) and Jones and Hathway (1978a, 1978b). Models for species other than the rat are not available.

B.2 Health Effects

Hepatic Effects. Following both inhalation and oral exposure, the most sensitive effects of 1,1-dichloroethene appear to be on the liver. Numerous studies in animals have identified hepatic effects, including both biochemical changes (e.g., alterations in serum enzyme levels indicative of liver injury) and marked histological changes (e.g., midzonal and centrilobular swelling of liver, degeneration, and necrosis of hepatocytes). These effects have been reported at acute-duration exposure concentrations as low as 15 ppm for 23 hours/day for 5 days, or at higher concentrations for shorter durations (ATSDR

2022c). 1,1-Dichloroethene's hepatotoxic effects are greater in fasted animals compared to nonfasted animals administered the same dose for the same exposure time. The hepatotoxic effects of 1,1-dichloroethene following intermediate- or chronic-duration inhalation exposure in animals are similar to those described above for acute-duration exposure. Two chronic-duration inhalation studies of 1,1-dichloroethene in animals have reported similar hepatic changes (Lee et al. 1977; Quast et al. 1986), including fatty changes in the liver, but the studies provide only suggestive evidence because of the poor presentation of the data. Similar effects on the liver are seen when 1,1-dichloroethene is given orally, with acute-duration effects at doses of 25–100 mg/kg including changes in liver serum enzymes, bile canalicular injury, and histological changes in liver cells (ATSDR 2022c). Chronic-duration oral exposure studies in animals have identified minor hepatic effects at exposure levels between 9 and 20 mg/kg/day (Nitschke et al. 1983; Quast et al. 1983; Rampy et al. 1977); the chronic-duration oral MRL of 0.05 mg/kg/day for 1,1-dichloroethene is based on a BMDL₁₀ of 4.51 mg/kg/day for hepatocellular changes in rats exposed *in utero* and throughout adulthood (Humiston et al. 1978; Quast et al. 1983).

Renal Effects. Adverse effects have been observed in the kidneys of laboratory 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), tubular alterations (hemoglobinuria), gross changes (increase in organ weight), and histological changes (tubular swelling, degeneration, and necrosis) (ATSDR 2022c). Effects have been reported in animals exposed by inhalation acutely to 10–300 ppm or chronically to 25–75 ppm. Similar renal effects have been reported following acute-duration oral exposure to 200–400 mg/kg (Chieco et al. 1981; Jenkins and Andersen 1978), but no renal effects were noted in animals following intermediate-duration oral exposure to 25 mg/kg/day, an exposure level that did not produce any adverse effects (Quast et al. 1983) or chronic-duration oral exposure to 30 mg/kg/day, an exposure level that resulted in mild hepatic effects (Rampy et al. 1977).

Respiratory Effects. Results of high-quality inhalation toxicity studies in rodents indicate that the upper respiratory system may be a sensitive target for exposed humans. After repeated inhalation exposures to 1,1-dichloroethene at concentrations as low as 6.25–25 ppm, rats and mice exhibited increased lung weights; hyperostosis; chronic active inflammation; nasal turbinate atrophy; and/or olfactory epithelial mineralization, necrosis, atrophy, and/or metaplasia (NTP 2015). Rats appeared to be more sensitive than mice based on the results of intermediate-duration studies. The intermediate- and chronic-duration inhalation MRLs for 1,1-dichloroethene are based on necrosis of the rat olfactory epithelium.

Developmental Effects. Following inhalation exposure in mice, rats, and rabbits, 1,1-dichloroethene has been shown to produce effects on the developing organism, but generally only at exposure levels (15–160 ppm) that also produced maternal effects (EPA 1977; Murray et al. 1979); observed effects in the offspring included increased skeletal and soft tissue anomalies and fetal resorptions. One oral study of neural tube defects in human newborns after maternal exposure to 1,1-dichloroethene via contaminated water has been published (NJDH 1992a, 1992b), but it provided only suggestive evidence of an association of 1,1-dichloroethene with developmental effects. A single study reported no developmental effects from oral exposure of 40 mg/kg/day of 1,1-dichloroethene in rats, an exposure level that produced no effects (on body weight gain, liver weight, food or water consumption) in the dams (Murray et al. 1979). A 3-generation reproductive study in rats (Nitschke et al. 1983) reported no dose-related changes at up to 30 mg/kg/day in the limited pup indices that were investigated. Mild liver effects (hepatocellular fatty change) were reported in the adults at 9–30 mg/kg/day.

Neurological Effects. CNS depression has been observed in humans after acute exposure to high concentrations of 1,1-dichloroethene, typically $\geq 4,000$ ppm (ATSDR 2022c). Evidence of CNS toxicity has also been identified in experimental animals acutely exposed to 1,1-dichloroethene via inhalation at or above concentrations associated with lethality (ATSDR 2022c). Symptoms included lethargy, hunched posture, dyspnea, CNS depression, narcosis, and, eventually, death following exposure to $\geq 2,000$ ppm for 4 hours (Klimisch and Freisberg 1979; Zeller et al. 1979). Increased sympathetic activity leading to cardiac arrhythmia has been identified in rats exposed to 25,600 ppm for 10 minutes (Siletnik and Carlson 1974). No evidence of neurotoxicity was identified in experimental animals following oral exposure to 1,1-dichloroethene (ATSDR 2022c).

Cancer. Chronic-duration occupational exposure to 1,1-dichloroethene was not associated with the occurrence of angiosarcoma in rubber-plant workers (Waxweiler 1981). Similarly, no association was found between occupational exposure and cancer mortality in 1,1-dichloroethene production and polymerization plant workers (Ott et al. 1976). The carcinogenicity of 1,1-dichloroethene in laboratory animals following inhalation exposure has been evaluated in intermediate- and chronic-duration studies with rats, mice, and Chinese hamsters (ATSDR 2022c). Exposure concentrations of 1,1-dichloroethene in these studies ranged from 10 to 200 ppm. Of the long-term inhalation bioassays conducted in laboratory animals to date, Maltoni et al. (1985) identified increased incidences of renal, pulmonary, and mammary gland tumors in mice, and NTP (2015) reported increased incidences of nasal respiratory epithelium adenoma and mesothelioma in male rats and increased incidences of leukemia, mammary gland tumors, and thyroid (C-cell) tumors in female rats.

No studies were located regarding cancer in humans after oral exposure to 1,1-dichloroethene. A number of chronic-duration studies in rats and mice have evaluated the carcinogenicity of 1,1-dichloroethene by oral exposure at dose levels of 0.5–150 mg/kg/day (ATSDR 2022c); a trend toward increased incidence of malignant and nonmalignant tumors in 1,1-dichloroethene-treated animals has been reported (NTP 1982; Ponomarev and Tomatis 1980; Quast et al. 1983), but in the majority of cases, the increase in tumor frequencies has not been statistically significant. Reported tumor types have included meningiomas, mammary gland fibroadenomas and adenofibromas, and liver cell adenomas and carcinomas; tumor types have not been consistent across studies.

B.3 Mechanisms of Action

The toxicity of 1,1-dichloroethene is the result of biotransformation reactions and not to the parent compound (Andersen et al. 1978, 1980; Jaeger et al. 1977; Jones and Hathway 1978c).

1,1-Dichloroethene is initially oxidized by the hepatic cytochrome P450 system, primarily CYP2E1, resulting in the formation of reactive and electrophilic products such as epoxides, acyl chlorides, and halogenated aldehydes, which are responsible for the liver toxicity via alkylation of macromolecules (Forkert et al. 1986). These reactive intermediates form GSH S-conjugates by the action of GSTs located in the hepatic cytosol and microsomes. GSH S-conjugates that are primarily secreted from the hepatocytes into plasma and S-conjugates entering the circulation after reabsorption from the small intestine are ultimately delivered to the kidney where they undergo glomerular filtration (Dekant et al. 1989). In the kidney, GSH S-conjugates may be metabolized to the corresponding cysteine S-conjugate, which may be acetylated to form the corresponding mercapturic acid and excreted in the urine (Vamvakas and Anders 1990). However, cysteine S-conjugates may also be metabolized by β -lyase, an enzyme located in the renal proximal tubule cells; the resulting unstable thiols in turn yield electrophilic products whose interactions with macromolecules are associated with nephrotoxicity. In summary, GSH S-conjugate formation of nephrotoxic haloalkenes competes with hepatic cytochrome P450 for substrates. The relative extent of these reactions *in vivo* appears to be decisive for the initiation of adverse effects either in the liver (via oxidation products generated by P450 system) or in the kidney (via formation and renal processing of S-conjugates).

B.4 Health Guidelines

ATSDR (2022c) did not derive an acute-duration inhalation MRL for 1,1-dichloroethene.

ATSDR (2022c) derived an intermediate-duration inhalation MRL of 0.001 ppm for 1,1-dichloroethene based on a $BMCL_{10}$ of 1.59 ppm ($BMCL_{HEC}$ of 0.036 ppm) for nasal effects (necrosis of the olfactory epithelium) in rats exposed for 6 hours/day, 5 days/week for 14 weeks (NTP 2015). The $BMCL_{10}$ was adjusted to continuous duration exposure prior to conversion to a human equivalent concentration (HEC), and divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans after dosimetric adjustment and 10 for human variability).

ATSDR (2022c) adopted the intermediate-duration inhalation MRL of 0.001 ppm as the chronic-duration inhalation for 1,1-dichloroethene. The intermediate-duration inhalation MRL was adopted for the chronic-duration MRL because derivation of an MRL using chronic data would have resulted in an MRL which was higher than the intermediate-duration value.

ATSDR (2022c) did not derive an acute-duration oral MRL for 1,1-dichloroethene due to the limited oral gavage database and lack of acute dietary and drinking water exposure studies.

ATSDR (2022c) did not derive an intermediate-duration oral MRL for 1,1-dichloroethene due to the limited oral gavage database and lack of intermediate dietary and drinking water exposure studies.

ATSDR (2022c) derived a chronic-duration oral MRL of 0.05 mg/kg/day for 1,1-dichloroethene based on a $BMDL_{10}$ of 4.51 mg/kg/day in rats for hepatocellular changes in a 2-year exposure study (Humiston et al. 1978; Quast et al. 1983) and using an uncertainty factor of 100 (10 for animal to human extrapolations and 10 for human variability).

EPA (2002) derived a chronic RfC of 0.2 mg/m³ (0.05 ppm) for 1,1-dichloroethene based on benchmark concentration analysis of hepatic effects (fatty liver) in a chronic-duration study in rats exposed to 25 or 75 ppm for 6 hours/day, 5 days/week (Quast et al. 1986) and an uncertainty factor of 30 (3 for animal to human extrapolation using dosimetric adjustment and 10 for human variability).

EPA (2002) derived a chronic RfD of 0.05 mg/kg/day for 1,1-dichloroethene based on benchmark dose (BMD) analysis of hepatic effects (fatty liver) in a chronic-duration study in rats (Humiston et al. 1978; Quast et al. 1986) and an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability).

HHS's *Fifteenth Report on Carcinogens* (NTP 2021b) does not list 1,1-dichloroethene as a carcinogen.

EPA (2002) concluded that 1,1-dichloroethene exhibits *suggestive evidence* of carcinogenicity but not sufficient evidence to assess human carcinogenic potential following inhalation exposure in studies in rodents. Additionally, EPA (2002) noted "the data for 1,1-dichloroethene are *inadequate* for an assessment of human carcinogenic potential by the oral route." EPA (2002) has not performed quantitative assessments of carcinogenic potential for 1,1-dichloroethene for either the oral or inhalation route.

IARC (2019) classifies 1,1-dichloroethene, as vinylidene chloride, as *possibly carcinogenic to humans* (Group 2B) based on sufficient evidence in experimental animals.

B.5 Derivation of Target-Organ Toxicity Dose(s)

The endpoints of concern for 1,1-dichloroethene in this mixture are hepatic, renal, respiratory, and developmental effects. For endpoints that are not the basis of the MRL, TTDS are derived below, using the methods described by ATSDR (2018). The derivations are based primarily on data provided in ATSDR (2022c) and, in particular, the LSE tables.

Inhalation TTDS

The POD_{HEC} for an extra-respiratory effect is calculated by multiplying the POD by the ratio of the blood:gas partition coefficients in animals and humans $[(Hb/g)_A / (Hb/g)_H]$. Since information on the partition coefficients for 1,1-dichloroethene in humans was not available (EPA 2002), a default value of 1 is used for the ratio.

Hepatic Effects, Intermediate Inhalation. NTP (2015) identified NOAEL and LOAEL values of 6.25 and 12.5 ppm, respectively, based on centrilobular cytoplasmic alterations in the liver of male rats exposed to 1,1-dichloroethene for 6 hours/day, 5 days/week for 14 weeks. The NOAEL was duration-adjusted to 1.1 ppm for a continuous exposure scenario and converted to a $NOAEL_{HEC}$ of 1.1 ppm. Application of an uncertainty factor of 30 (3 for animal to human extrapolation using a dosimetric adjustment and 10 for human variability) yields a $TTD_{HEPATIC}$ of 0.04 ppm.

Renal Effects, Intermediate Inhalation. NTP (2015) identified a LOAEL of 6.25 ppm based on increased relative kidney weights in female mice exposed to 1,1-dichloroethene for 6 hours/day, 5 days/week for 14 weeks. The LOAEL was duration-adjusted to 1.1 ppm for a continuous exposure scenario and converted to a LOAEL_{HEC} of 1.1 ppm. Application of an uncertainty factor of 90 (3 for extrapolation from a minimal LOAEL to a NOAEL, 3 for animal to human extrapolation using a dosimetric adjustment, and 10 for human variability) yields a TTD_{RENAL} of 0.01 ppm.

Respiratory Effects, Intermediate Inhalation. The intermediate-duration inhalation MRL for 1,1-dichloroethene is 0.001 ppm is based on respiratory effects.

Neurological Effects, Intermediate Inhalation. No intermediate-duration studies evaluated the neurological effects of 1,1-dichloroethene. Acute-duration inhalation studies are limited to studies in rats and hamsters reporting clinical signs of neurotoxicity at concentrations ($\geq 2,000$ ppm) associated with lethality (Klimisch and Freisberg 1979; Zeller et al. 1979) and a study in rats reporting increased sympathetic activity leading to cardiac arrhythmia following a 10-minute exposure to 25,600 ppm (Siletnik and Carlson 1974). Available data on neurological effects are not a suitable basis for TTD derivation because they occurred only at or above exposure levels associated with significant mortality.

Developmental Effects, Intermediate Inhalation. No intermediate-duration inhalation studies evaluated the developmental toxicity of 1,1-dichloroethene. EPA (1977) reported incomplete ossification in the offspring of mice exposed to 15 ppm of 1,1-dichloroethene for 23 hours/day on GDs 6–16. Since developmental toxicity is dependent on exposure during sensitive timepoints and not duration of exposure, results of the EPA (1977) study were used to derive the intermediate inhalation TDD for developmental effects. The LOAEL of 15 ppm was duration-adjusted to 14 ppm for a continuous exposure scenario and converted to a LOAEL_{HEC} of 14 ppm. Application of an uncertainty factor of 300 (10 for use of a LOAEL, 3 for animal to human extrapolation using a dosimetric adjustment, and 10 for human variability) yields a TTD_{DEVEL} of 0.05 ppm.

Hepatic Effects, Chronic Inhalation. NTP (2015) identified a LOAEL of 25 ppm for chronic inflammation and diffuse fatty changes in the livers of rats exposed to 1,1-dichloroethene for 6 hours/day, 5 days/week, for 105 weeks. The LOAEL was duration-adjusted to 4.5 ppm for a continuous exposure scenario and converted to a LOAEL_{HEC} of 4.5 ppm. Application of an uncertainty factor of 300 (10 for use of a LOAEL, 3 for animal to human extrapolation using a dosimetric adjustment, and 10 for human variability) yields a TTD_{HEPATIC} of 0.02 ppm.

Renal Effects, Chronic Inhalation. NTP (2015) identified a LOAEL of 6.25 ppm based on an increased incidence of renal tubule hyperplasia in male mice exposed for 6 hours/day, 5 days/week for 105 weeks. The LOAEL was duration-adjusted to 1.1 ppm for a continuous exposure scenario and converted to a LOAEL_{HEC} of 1.1 ppm. Application of an uncertainty factor of 300 (10 for extrapolation from a LOAEL to a NOAEL, 3 for animal to human extrapolation using a dosimetric adjustment, and 10 for human variability) yields a TTD_{RENAL} of 0.004 ppm.

Respiratory Effects, Chronic Inhalation. The chronic-duration inhalation MRL for 1,1-dichloroethene is 0.001 ppm is based on respiratory effects.

Neurological Effects, Chronic Inhalation. No chronic-duration studies evaluated the neurological effects of 1,1-dichloroethene. Available acute-duration data on neurological effects (described above) are not a suitable basis for TTD derivation because they occurred only at or above exposure levels associated with significant mortality.

Developmental Effects, Chronic Inhalation. A TTD_{DEVEL} of 0.02 ppm is derived from the corresponding intermediate-duration value; see explanation in Chapter 3.

Oral TTDs

Hepatic Effects, Intermediate Oral. NTP (1982) identified a NOAEL for hepatic effects of 1,1-dichloroethene at 40 mg/kg/day, 5 days/week (adjusted to 29 mg/kg/day for continuous exposure) in 13-week studies in rats and mice. At the LOAELs of 100 mg/kg/day for both species, 1,1-dichloroethene produced hepatocytomegaly in male rats; fibrosis, bile duct hyperplasia, and pigmentation in female rats; and necrosis in male and female mice. Applying an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability) to the NOAEL_{ADJ} yields a TTD_{HEPATIC} of 0.3 mg/kg/day.

Renal Effects, Intermediate Oral. 1,1-Dichloroethene has not been adequately tested for non-hepatic effects in intermediate-duration oral studies, but chronic-duration oral studies did not report renal effects at dose levels that caused mild hepatic effects. Thus, there are no dose-response data suitable for derivation of a TTD. The chemical, however, caused renal effects in animals in acute-duration oral studies and in acute- and intermediate-to-chronic-duration inhalation studies. Thus, the WOE for renal effects suggests that 1,1-dichloroethene would cause renal damage at higher doses than tested in

intermediate- and chronic-duration oral studies. The intermediate-duration oral $TTD_{HEPATIC}$ of 0.3 mg/kg/day can be adopted as the TTD_{RENAL} for intermediate-duration exposure.

Developmental Effects, Intermediate Oral. No developmental effects were reported in the only oral developmental toxicity study of 1,1-dichloroethene available, which tested a single exposure level, 40 mg/kg/day, in rats on GDs 6–15 (Murray et al. 1979). A 3-generation reproductive study in rats (Nitschke et al. 1983) reported no dose-related changes at up to 30 mg/kg/day in the limited pup indices (number of pups/litter, postnatal survival and body weight) that were investigated. Mild liver effects (hepatocellular fatty change) were reported in the adults at 9–30 mg/kg/day. Although there are no data to indicate that this endpoint is affected by the oral route, the available studies are not fully adequate and only one species, the rat, was tested. Data from the inhalation route indicate that 1,1-dichloroethene was developmentally toxic at exposures that also were maternally toxic and that the mouse was the most sensitive species. Given the possibility that 1,1-dichloroethene may also be developmentally toxic by the oral route, the intermediate-duration oral $TTD_{HEPATIC}$ of 0.3 mg/kg/day can be adopted as the TTD_{DEVEL} for chronic-duration exposure.

Hepatic Effects, Chronic Oral. The chronic-duration oral MRL of 0.05 mg/kg/day is based on hepatic effects.

Renal Effects, Chronic Oral. Chronic-duration oral studies in animals did not report renal effects at dose levels of 1,1-dichloroethene that caused mild hepatic effects, and this chemical has not been adequately tested for non-hepatic effects in intermediate-duration oral studies. Thus, there are no dose-response data suitable for derivation of a TTD. The chemical, however, caused renal effects in animals in acute-duration oral studies and in acute- and intermediate-to-chronic inhalation studies. Thus, the WOE suggests that 1,1-dichloroethene may cause renal damage at higher doses than tested in intermediate- and chronic-duration oral studies. The chronic-duration oral MRL of 0.05 mg/kg/day can be adopted as the TTD_{RENAL} for chronic-duration exposure.

Developmental Effects, Chronic Oral. No developmental effects were reported in the only oral developmental toxicity study of 1,1-dichloroethene available, which tested a single exposure level, 40 mg/kg/day, in rats on GDs 6–15 (Murray et al. 1979). A 3-generation reproductive study in rats (Nitschke et al. 1983) reported no dose-related changes at up to 30 mg/kg/day in the limited pup indices (number of pups/litter, postnatal survival, and body weight) that were investigated. Mild liver effects (hepatocellular fatty change) were reported in the adults at 9–30 mg/kg/day. Although there are no data

to indicate that this endpoint is affected by the oral route, the available studies are not fully adequate and only one species, the rat, was tested. Data from the inhalation route indicate that 1,1-dichloroethene was developmentally toxic at exposures that also were maternally toxic and that the mouse was the most sensitive species. Given the possibility that 1,1-dichloroethene may also be developmentally toxic by the oral route, the chronic-duration oral MRL of 0.05 mg/kg/day can be adopted as the TTD_{DEVEL} for chronic-duration exposure.

Summary (TTDs for 1,1-Dichloroethene)

Intermediate-Duration Inhalation TTDs:

$$TTD_{HEPATIC} = 0.04 \text{ ppm}$$

$$TTD_{RENAL} = 0.01 \text{ ppm}$$

$$MRL_{RESPIRATORY} = 0.001 \text{ ppm}$$

$$TTD_{DEVEL} = 0.05 \text{ ppm}$$

Chronic-Duration Inhalation TTDs:

$$TTD_{HEPATIC} = 0.02 \text{ ppm}$$

$$TTD_{RENAL} = 0.004 \text{ ppm}$$

$$MRL_{RESPIRATORY} = 0.001 \text{ ppm}$$

$$TTD_{DEVEL} = 0.02 \text{ ppm}$$

Intermediate-Duration Oral TTDs:

$$TTD_{HEPATIC} = 0.3 \text{ mg/kg/day}$$

$$TTD_{RENAL} = 0.3 \text{ mg/kg/day}$$

$$TTD_{DEVEL} = 0.3 \text{ mg/kg/day}$$

Chronic-Duration Oral TTDs:

$$MRL_{HEPATIC} = 0.05 \text{ mg/kg/day}$$

$$TTD_{RENAL} = 0.05 \text{ mg/kg/day}$$

$$TTD_{DEVEL} = 0.05 \text{ mg/kg/day}$$

B.6 References

Andersen ME, Jones RA, Jenkins LJ. 1978. The acute toxicity of single, oral doses of 1,1-dichloroethylene in the fasted, male rat: effect of induction and inhibition of microsomal enzyme

- activities on mortality. *Toxicol Appl Pharmacol* 46(1):227-234. [https://doi.org/10.1016/0041-008x\(78\)90153-9](https://doi.org/10.1016/0041-008x(78)90153-9).
- Andersen ME, Thomas OE, Gargas ML, et al. 1980. The significance of multiple detoxification pathways for reactive metabolites in the toxicity of 1,1-dichloroethylene. *Toxicol Appl Pharmacol* 52(3):422-432. [https://doi.org/10.1016/0041-008x\(80\)90337-3](https://doi.org/10.1016/0041-008x(80)90337-3).
- ATSDR. 2018. Framework for assessing health impacts of multiple chemicals and other stressors (Update). Agency for Toxic Substances and Disease Registry. <https://www.atsdr.cdc.gov/interaction-profiles/media/pdfs/ipga-p.pdf>. January 26, 2025.
- ATSDR. 2022c. Toxicological profile for 1,1-dichloroethene. Agency for Toxic Substances and Disease Registry. <https://www.atsdr.cdc.gov/ToxProfiles/tp39.pdf>. December 16, 2024.
- Chieco P, Moslen MT, Reynolds ES. 1981. Effect of administrative vehicle on oral 1,1-dichloroethylene toxicity. *Toxicol Appl Pharmacol* 57(2):146-155. [https://doi.org/10.1016/0041-008x\(81\)90274-x](https://doi.org/10.1016/0041-008x(81)90274-x).
- Dallas CE, Weir FW, Feldman S, et al. 1983. The uptake and disposition of 1,1-dichloroethylene in rats during inhalation exposure. *Toxicol Appl Pharmacol* 68(1):140-151. [https://doi.org/10.1016/0041-008x\(83\)90363-0](https://doi.org/10.1016/0041-008x(83)90363-0).
- Dekant W, Vamvakas S, Anders MW. 1989. Bioactivation of nephrotoxic haloalkenes by glutathione conjugation: formation of toxic and mutagenic intermediates by cysteine conjugate beta-lyase. *Drug Metab Rev* 20(1):43-83. <https://doi.org/10.3109/03602538908994144>.
- D'Souza RW, Andersen ME. 1988. Physiologically based pharmacokinetic model for vinylidene chloride. *Toxicol Appl Pharmacol* 95(2):230-240. [https://doi.org/10.1016/0041-008x\(88\)90159-7](https://doi.org/10.1016/0041-008x(88)90159-7).
- EPA. 1977. Toxicity studies of selected chemicals: Task II. The development of vinylidene chloride inhaled by rats and mice during gestation. Washington, DC: U.S. Environmental Protection Agency. PB281713. EPA560677022. <https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/PB281713.xhtml>. January 28, 2025.
- EPA. 2002. 1,1-Dichloroethylene (1,1-DCE). Integrated Risk Information System (IRIS). Cincinnati, OH: U.S. Environmental Protection Agency. https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=39. August 13, 2002.
- Forkert PG, Stringer V, Troughton KM. 1986. Pulmonary toxicity of 1,1-dichloroethylene: correlation of early changes with covalent binding. *Can J Physiol Pharmacol* 64(2):112-121. <https://doi.org/10.1139/y86-017>.
- Gargas ML, Andersen ME, Clewell HJ. 1986. A physiologically based simulation approach for determining metabolic constants from gas uptake data. *Toxicol Appl Pharmacol* 86(3):341-352. [https://doi.org/10.1016/0041-008x\(86\)90361-3](https://doi.org/10.1016/0041-008x(86)90361-3).
- Humiston CG, Quast JF, Wade CE, et al. 1978. Results of a two-year toxicity and oncogenicity study with vinylidene chloride incorporated in the drinking water of rats. Manufacturing Chemists Association. Submitted to the U.S. Environmental Protection Agency under TSCA section FYI. OTS0000007-0. FYI-AX-0978-0007. <https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/OTS00000070.xhtml>. January 28, 2025.
- IARC. 2019. Some chemicals that cause tumours of the urinary tract in rodents. IARC Monographs on the evaluation of carcinogenic risks to humans. Vol. 119. Lyon, France: International Agency for Research on Cancer. <https://publications.iarc.fr/575>. January 28, 2025.
- Jaeger RJ, Shoner LG, Coffman L. 1977. 1,1-Dichloroethylene hepatotoxicity: proposed mechanism of action and distribution and binding of ¹⁴C radioactivity following inhalation exposure in rats. *Environ Health Perspect* 21:113-119. <https://doi.org/10.1289/ehp.7721113>.
- Jones BK, Hathway DE. 1978a. Differences in metabolism of vinylidene chloride between mice and rats. *Br J Cancer* 37(3):411-417. <https://doi.org/10.1038/bjc.1978.61>.
- Jones BK, Hathway DE. 1978b. Tissue-mediated mutagenicity of vinylidene chloride in *Salmonella typhimurium* TA1535. *Cancer Lett* 5(1):1-6. [https://doi.org/10.1016/S0304-3835\(78\)80002-0](https://doi.org/10.1016/S0304-3835(78)80002-0).
- Jones BK, Hathway DE. 1978c. The biological fate of vinylidene chloride in rats. *Chem Biol Interact* 20(1):27-41. [https://doi.org/10.1016/0009-2797\(78\)90078-9](https://doi.org/10.1016/0009-2797(78)90078-9).

- Klimisch HJ, Freisberg KO. 1979. [Report on the determination of acute toxicity (LC50) by inhalation of vinylidene chloride in Chinese striped hamsters (fed) during a 4-hour exposure period]. Ludwigshafen, Germany: BASF Corporation. HSE Translation No. 9M. (German)
- Lee CC, Bhandari JC, Winston JM, et al. 1977. Inhalation toxicity of vinyl chloride and vinylidene chloride. *Environ Health Perspect* 21:25-32. <https://doi.org/10.1289/ehp.772125>.
- Maltoni C, Lefemine G, Cotti G, et al. 1985. Experimental research on vinylidene chloride carcinogenesis. In: *Archives of research on industrial carcinogenesis*. Vol. III. Princeton: Princeton Scientific Publishers, Inc., 14-98.
- McKenna MJ, Watanabe PG, Gehring PJ. 1977. Pharmacokinetics of vinylidene chloride in the rat. *Environ Health Perspect* 21:99-105. <https://doi.org/10.1289/ehp.772199>.
- McKenna MJ, Zempel JA, Madrid EO, et al. 1978a. The pharmacokinetics of [¹⁴C]vinylidene chloride in rats following inhalation exposure. *Toxicol Appl Pharmacol* 45(2):599-610. [https://doi.org/10.1016/0041-008x\(78\)90121-7](https://doi.org/10.1016/0041-008x(78)90121-7).
- McKenna MJ, Zempel JA, Madrid EO, et al. 1978b. Metabolism and pharmacokinetic profile of vinylidene chloride in rats following oral administration. *Toxicol Appl Pharmacol* 45(3):821-835. [https://doi.org/10.1016/0041-008x\(78\)90173-4](https://doi.org/10.1016/0041-008x(78)90173-4).
- Murray FJ, Nitschke KD, Rampy LW, et al. 1979. Embryotoxicity and fetotoxicity of inhaled or ingested vinylidene chloride in rats and rabbits. *Toxicol Appl Pharmacol* 49(2):189-202. [https://doi.org/10.1016/0041-008x\(79\)90241-2](https://doi.org/10.1016/0041-008x(79)90241-2).
- Nitschke KD, Smith FA, Quast JF, et al. 1983. A three-generation rat reproductive toxicity study of vinylidene chloride in the drinking water. *Fundam Appl Toxicol* 3(2):75-79. [https://doi.org/10.1016/s0272-0590\(83\)80059-1](https://doi.org/10.1016/s0272-0590(83)80059-1).
- NJDH. 1992a. Population-based surveillance and etiological research of adverse reproductive outcomes and toxic wastes; Report on Phase IV-A: Public drinking water contamination and birthweight, fetal deaths, and birth defects; A cross-sectional study. Trenton, NJ: New Jersey Department of Health. <https://www.regulations.gov/document/EPA-HQ-OW-2002-0043-0697>. January 28, 2025.
- NJDH. 1992b. Population-based surveillance and etiological research of adverse reproductive outcomes and toxic wastes; Report on Phase IV-B: Public drinking water contamination and birthweight, fetal deaths, and birth defects; A cross-sectional study. Trenton, NJ: New Jersey Department of Health. https://www.nj.gov/health/ceohs/documents/eohap/haz_sites/regional_state/birth_infant/adv_repro_phase4b.pdf. January 28, 2025.
- NTP. 1982. NTP technical report on the carcinogenesis bioassay of vinylidene chloride (CAS No. 75-35-4) in F344 rats and B6C3F1 mice (gavage study). Research Triangle Park, NC: National Toxicology Program. NTP-80-82. NIH Publication No. 82-1784. https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr228.pdf. February 2, 2017.
- NTP. 2015. NTP technical report on the toxicology and carcinogenesis studies of vinylidene chloride (CAS No. 75-35-4) in F344/N rats and B6C3F1/N mice (inhalation studies). Research Triangle Park, NC: National Toxicology Program. https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr582_508.pdf. May 8, 2018.
- NTP. 2021b. Substances listed in the fifteenth report on carcinogens. 15th Report on carcinogens. National Toxicology Program. https://ntp.niehs.nih.gov/sites/default/files/ntp/roc/content/listed_substances_508.pdf. January 23, 2023.
- Ott MG, Fishbeck WA, Townsend JC, et al. 1976. A health study of employees exposed to vinylidene chloride. *J Occup Med* 18(11):735-738. <https://doi.org/10.1097/00043764-197611000-00009>.
- Ponomarev V, Tomatis L. 1980. Long-term testing of vinylidene chloride and chloroprene for carcinogenicity in rats. *Oncology* 37(3):136-141. <https://doi.org/10.1159/000225422>.
- Putcha L, Bruckner JV, D'Souza R, et al. 1986. Toxicokinetics and bioavailability of oral and intravenous 1,1-dichloroethylene. *Fundam Appl Toxicol* 6(2):240-250. <https://doi.org/10.1093/toxsci/6.2.240>.

- Quast JF, Humiston CG, Wade CE, et al. 1983. A chronic toxicity and oncogenicity study in rats and subchronic toxicity study in dogs on ingested vinylidene chloride. *Fundam Appl Toxicol* 3(1):55-62. [https://doi.org/10.1016/s0272-0590\(83\)80173-0](https://doi.org/10.1016/s0272-0590(83)80173-0).
- Quast JF, McKenna MJ, Rampy LW, et al. 1986. Chronic toxicity and oncogenicity study on inhaled vinylidene chloride in rats. *Fundam Appl Toxicol* 6(1):105-144. [https://doi.org/10.1016/0272-0590\(86\)90269-1](https://doi.org/10.1016/0272-0590(86)90269-1).
- Rampy LW, Quast JF, Humiston CG, et al. 1977. Interim results of two-year toxicological studies in rats of vinylidene chloride incorporated in the drinking water or administered by repeated inhalation. *Environ Health Perspect* 21:33-43. <https://doi.org/10.1289/ehp.772133>.
- Ramsey JC, Andersen ME. 1984. A physiologically based description of the inhalation pharmacokinetics of styrene in rats and humans. *Toxicol Appl Pharmacol* 73(1):159-175. [https://doi.org/10.1016/0041-008x\(84\)90064-4](https://doi.org/10.1016/0041-008x(84)90064-4).
- Reichert D, Werner HW, Metzler M, et al. 1979. Molecular mechanism of 1,1-dichloroethylene toxicity: excreted metabolites reveal different pathways of reactive intermediates. *Arch Toxicol* 42(3):159-169. <https://doi.org/10.1007/BF00353707>.
- Silechnik LM, Carlson GP. 1974. Cardiac sensitizing effects of 1,1-dichloroethylene: enhancement by phenobarbital pretreatment. *Arch Int Pharmacodyn Ther* 210(2):359-364.
- Vamvakas S, Anders MW. 1990. Formation of reactive intermediates by phase II enzymes: glutathione-dependent bioactivation reactions. In: Witmer CM, ed. *Advances in experimental medicine and biology*. New York, NY: Plenum Publishing Co, 13-24.
- Waxweiler RJ. 1981. Epidemiologic problems associated with exposure to several agents. *Environ Health Perspect* 42:51-56. <https://doi.org/10.1289/ehp.814251>.
- Zeller H, Klimisch HJ, Freisberg KO. 1979. [Report on the determination of acute toxicity (LC50) of vinylidene chloride in Sprague-Dawley rats (fed) during a 4-hour exposure]. Ludwigshafen, Germany: BASF Corporation. HSE Translation No. 9K. (German)

Appendix C. Background Information for Trichloroethylene

This appendix was written based primarily on the *Toxicological Profile for Trichloroethylene* (ATSDR 2019). For additional information beyond what is presented here, the reader is referred to the toxicological profile. Regarding the weight of evidence for, and human relevance of, fetal cardiac malformations observed in rats, the reader is referred to the updated conclusions reported in the *Targeted Systemic Evidence Map (SEM) and Rapid Systematic Review for Trichloroethylene and Developmental Cardiotoxicity* (ATSDR 2025). Primary references from these ATSDR publications are cited for the reader's convenience in identifying pertinent studies.

C.1 Toxicokinetics

Studies of humans and rats indicate that inhaled trichloroethylene is rapidly and efficiently absorbed (ATSDR 2019). Initial rates of uptake are high, but decrease as steady-state conditions are approached. Studies in humans indicated that 37–64% of inhaled trichloroethylene was absorbed. Ingested trichloroethylene is rapidly and completely absorbed by the gastrointestinal tract (ATSDR 2019). Fasted rats given gavage doses of 5–25 mg/kg trichloroethylene displayed peak blood concentrations within 6–10 minutes and absorbed >90% of the dose within 9 hours (D'Souza et al. 1985). Dermal absorption is rapid, as indicated by observations of peak blood and exhaled air concentrations occurring within 5 minutes after a human subject immersed one hand in a trichloroethylene solution (ATSDR 2019). Once absorbed, trichloroethylene is widely distributed to organs throughout the body (including the developing fetus) and, due to its lipophilic properties, can accumulate in fat to a limited degree (ATSDR 2019). For example, 17 hours after a 6-hour/day, 4-day exposure of rats to 200 ppm, trichloroethylene was detected in perirenal fat and blood, but was not detected in other tissues (Savolainen et al. 1977).

Studies of humans and rodents indicate that inhaled trichloroethylene is eliminated from the body predominantly in the urine as metabolites and, to a lesser degree, in exhaled breath as the parent chemical or other volatile metabolites such as trichloroethanol and carbon dioxide (ATSDR 2019). For example, following single or sequential daily exposures of human subjects to 50–380 ppm: 11 and 2% of the dose was eliminated as trichloroethylene and trichloroethanol, respectively, in exhaled breath; 58% was eliminated as urinary metabolites; and 30% was unaccounted for (Monster et al. 1976, 1979). Trichloroethylene was detected in exhaled breath of humans 18 hours after exposure ended due to the relatively long elimination half-life of trichloroethylene in fatty tissue (3.5–5 hours) compared with other tissues. Following inhalation exposure to radiolabeled trichloroethylene, mice excreted 75% of radioactivity in

the urine and 9% as carbon dioxide in exhaled breath (Stott et al. 1982). Similar patterns of elimination were observed in mice and rats following oral administration of trichloroethylene (Koizumi et al. 1986).

The principal urinary metabolites of trichloroethylene in humans and animals are trichloroethanol, trichloroethanol-glucuronide, and trichloroacetic acid (ATSDR 2019; Lash 2025; Lash et al. 2000). Trichloroethylene is principally metabolized in the liver, but metabolism can also occur in Clara cells of the lungs and in the kidney. The principal pathway in humans and animals involves initial oxidation catalyzed by cytochrome P450 isozymes (CYP2E1 and 2B1/2). It has been proposed that this reaction forms an epoxide intermediate (trichloroethylene oxide) that rapidly converts to chloral hydrate, but an alternative proposal indicates that chloral hydrate formation involves chlorine migration in an oxygenated trichloroethylene-CYP transition state (Lash et al. 2000). Chloral hydrate can be oxidized to trichloroacetic acid via chloral hydrate dehydrogenase or reduced to trichloroethanol via alcohol dehydrogenase. Trichloroacetic acid is a strong inducer of peroxisome proliferation and has been associated with hepatocarcinogenicity in rodents. Trichloroethanol can be conjugated with glucuronic acid via glucuronyl transferase to form trichloroethanol-glucuronide. Studies with human hepatic microsomes indicate that CYP2E1 is the predominant isozyme responsible for the initial steps in trichloroethylene metabolism, although there is evidence that cytochrome P450 isozymes induced by phenobarbital (i.e., CYP2B1/2) may also be involved. At high exposure levels, enzymes involved in the main oxidative metabolic pathway can be saturated, leading to conjugation with GSH to produce S-(1,2-dichlorovinyl) glutathione (DCVG). DCVG is acted on by GGT to remove glutamine, and the glycine is removed by the action of dipeptidases to yield S-(1,2-dichlorovinyl)-L-cysteine (DCVC). Cleavage of the cysteine by β -lyase in the kidney can lead to intermediates with reactive thiol groups that can react with cellular macromolecules leading to renal cytotoxicity and carcinogenicity. Sex-, strain-, and species-dependent differences in metabolism have been identified for trichloroethylene and need to be accounted for in the interpretation of animal data for human risk assessment (Lash 2025).

Minor metabolic pathways arising from the initial intermediate, trichloroethylene oxide, or the trichloroethylene-cytochrome P450 transition state include: (1) transformation to dichloroacetic acid through a dichloroacetyl chloride intermediate (this path appears to be more important in rodents than humans); (2) hydrolytic dechlorinations to form formic acid and carbon monoxide; and (3) hydrolytic dechlorinations to form carbon dioxide via, sequentially, glyoxylic acid chloride, glyoxylic acid, and oxalic acid (ATSDR 2019; Lash et al. 2000). Dichloroacetic acid can be conjugated with GSH followed by sequential removal of glutamine and glycine to form dichlorovinyl-cysteine. Dichlorovinyl-cysteine can be transported to the kidney, where cleavage by β -lyase produces an intermediate with a reactive thiol

group that can react with proteins and deoxyribonucleic acid (DNA), leading to kidney cytotoxicity and kidney tumor development. Another minor pathway that is possible via the cytochrome P450 isoenzyme metabolic path involves metabolism of trichloroethylene into trichloroacetaldehyde, which, instead of further oxidation to produce the choral hydrate, spontaneously reacts with the amino acid tryptamine to form trichloromethyl-1,2,3,4-tetrahydro-beta-carboline (TaClo) (Liu et al. 2025). While possible, there is limited evidence for formation of TaClo in humans following trichloroethylene exposure (Liu et al. 2025).

PBPK models have been developed for the disposition of trichloroethylene in mice, rats, and humans, including the prediction of target organ (e.g., liver, lung, brain, kidney) doses of biologically active metabolites (ATSDR 2019; Clewell et al. 2000; Fisher 2000; Lash 2025). The models are being used to aid assessment of noncancer and cancer human health risks based on rodent exposure-response data (Barton and Clewell 2000; Rhomberg 2000).

C.2 Health Effects

Hepatic Effects. Results of epidemiological studies indicate occupational populations exposed to trichloroethylene may develop hepatic effects including altered liver function indices and enlarged livers (ATSDR 2019); however, these findings are confounded by co-exposures to other chemicals, including solvents, and inadequate quantitative exposure assessments. Where quantitative exposure estimates were available, the trichloroethylene concentrations causing hepatotoxicity were generally greater than current-day occupational exposure limits. Evidence for trichloroethylene's hepatotoxicity in humans is stronger in case reports; patients exposed occupationally or non-occupationally presented with jaundice, hepatitis, hepatomegaly, hepatosplenomegaly, and/or liver failure (Ha et al. 2009; Huang et al. 2006; Jung et al. 2012; Kamijima et al. 2007; Xu et al. 2009).

In rodent studies, inhalation and oral trichloroethylene exposures produced dose-related increases in liver weight, increased plasma levels of liver-associated enzymes, inflammation and local immune response, and/or hepatocellular hypertrophy (ATSDR 2019; Lash 2025). A study with wild-type and CYP2E1 knockout mice indicated that CYP2E1-dependent metabolism of trichloroethylene was required to produce hepatotoxicity (Ramdhan et al. 2008). Relatively high exposure levels were necessary to induce hepatic effects in most animal studies.

Renal Effects. Limited epidemiological evidence points to the kidney as a target organ for trichloroethylene. Workers exposed to trichloroethylene and other chemicals in the workplace and renal

cancer patients with reported trichloroethylene exposures exhibited altered urinary protein levels (Bolt et al. 2004; Brüning et al. 1999; Carrieri et al. 2007; Selden et al. 1993). An increased risk for end-stage renal disease was identified for aircraft workers in a retrospective cohort study (Radican et al. 2006). No clear association between long-term exposure to trichloroethylene via drinking water and adverse renal effects has been reported (ATSDR 2019).

Results of acute inhalation toxicity studies in rats indicate trichloroethylene increases urinary proteins, glucosaminidase, γ -glutamyl transpeptidase, and glucose and serum urea nitrogen (ATSDR 2019). In longer-term inhalation studies, trichloroethylene increased kidney weights following intermediate- or chronic-duration exposures (Boverhof et al. 2013; Adams et al. 1951) and induced renal tubular megalonucleocytosis in male rats, but not female rats, following chronic-duration exposures (Maltoni et al. 1986, 1988). In intermediate-duration oral toxicity studies, trichloroethylene increased kidney weights, urinary protein and ketone levels, and incidences of renal tubular epithelial cell cytomegaly and karyomegaly (Berman et al. 1995; NTP 1990; Tucker et al. 1982). Oral dosing of rats and mice for chronic periods resulted in chronic nephropathy unlike that typically identified in aged animals (NCI 1976b; NTP 1988b, 1990).

Immunological Effects. Occupational exposure to trichloroethylene is associated with hypersensitivity-type reactions, scleroderma, decreased total lymphocyte counts and serum immunoglobulin G (IgG) and immunoglobulin M (IgM) levels, and modified serum cytokine levels (ATSDR 2019; Lash 2025). Inhalation exposures to trichloroethylene produced immunosuppression in animals including decreased splenic anti-sheep red blood cell (SRBC) IgM response and serum IgG levels in rats and mice, respectively (Boverhof et al. 2013; Kaneko et al. 2000). Results of oral studies in animals indicate that trichloroethylene enhances selected hypersensitivity or allergic reactions and may accelerate autoimmune responses (ATSDR 2019; Lash 2025). Keil et al. (2009) reported decreased thymus weights and increased numbers of activated T-cells in mice exposed via drinking water for 27–30 weeks.

Neurological Effects. As reviewed by ATSDR (2019), the nervous system has been identified as a toxicological target for trichloroethylene based on results of human and animal studies.

Trichloroethylene-induced neurological effects in humans include dizziness, headaches, sleepiness, nausea, and lethargy, and, at higher exposure levels, memory and reflex deficits, nerve damage, and unconsciousness. Experimental animal studies identified neurobehavioral effects following acute or repeated oral and inhalation exposures; these include impairment of visual, auditory, psychomotor, and cognitive function, neurochemical changes, neuropathy, and nerve cell morphological changes.

Several studies suggest that exposure to trichloroethylene is associated with Parkinson's disease in humans and the induction of Parkinson's disease-like symptoms in experimental animals, as reviewed by Lash (2025) and Liu et al. (2025). For example, inhalation exposures to trichloroethylene were shown to induce nigrostriatal dopaminergic neurodegeneration and motor and gait impairments, effects observed in Parkinson's disease patients, in rats exposed to 50 ppm for 8 weeks and mice exposed 100 ppm for 12 weeks (Adamson et al. 2023). Trichloroethylene-exposed rats are a proposed model of Parkinson's disease to test drug interventions using a battery of motor tests and biochemical assays to evaluate oxidative stress (Srivastava et al. 2024).

Developmental Effects. Epidemiological studies provide limited evidence for developmental effects, including spontaneous abortions, congenital heart disease, and low birth weight, following gestational trichloroethylene exposure; critical limitations of these studies include small sample sizes and/or co-exposures to other chemicals (ATSDR 2019). ATSDR (2025) concluded that there is inadequate evidence for developmental cardiotoxicity in humans following oral exposure and a low level of evidence following inhalation exposure in humans due to confounding via co-exposure to other chemicals, including other chlorinated solvents.

Trichloroethylene exposures to pregnant laboratory animals may induce adverse developmental effects, namely decreased fetal weights, perinatal survival, and litter size and incomplete skeletal ossification, these typically occur at maternally toxic exposure levels (ATSDR 2019). Developmental effects induced at non-maternally toxic doses across several studies include fetal heart malformations and alterations to the hippocampal brain region following dam exposures via drinking water. It should be noted that ATSDR (2025) concluded "developmental cardiotoxicity is not classifiable as a health effect in humans following inhalation or oral exposure to trichloroethylene." This conclusion is based on inadequate and low levels of evidence in animal studies following inhalation and oral exposure, respectively. Specifically, the oral exposure animal studies that reported development cardiotoxicity with trichloroethylene exposure (Dawson et al. 1993; Johnson et al. 2003) have critical design flaws, including the use of non-concurrent controls and exposure groups (Hardin et al. 2004; Johnson et al. 2004). Further, ATSDR (2025) reviewed evidence that mechanistic data do not provide sufficient support for an association between congenital heart defects and trichloroethylene exposure based on a systematic review conducted by Urban et al. (2020); ATSDR determined that mechanistic studies published since the systematic review were unlikely to alter its conclusions.

In a developmental immunotoxicity test, Peden-Adams et al. (2006) identified decreased plaque-forming cell (PFC) response to SRBCs in mouse pups born to dams exposed to trichloroethylene via drinking water during gestation and lactation. A review by Lash (2025) identified several studies that indicate that trichloroethylene elicits developmental immunotoxicity and that the placenta is a target organ.

Cancer. IARC (2014) concluded that there is sufficient evidence in humans and experimental animals for the carcinogenicity of trichloroethylene. Specifically, the weight of evidence is sufficient to conclude that trichloroethylene produces kidney tumors in humans; additionally, positive associations have been established between trichloroethylene exposure and increased incidences of liver cancer and non-Hodgkin lymphoma. Chronic-duration animal studies have shown that cancer can be caused by inhalation or oral exposure to trichloroethylene, but do not point to a single target organ for increased tumor incidence. Carcinogenic responses have been observed in the liver, kidney, testes, lymphatic system, and lung, but the observed responses are not consistent across studies of different species and strains of animals (ATSDR 2019).

In general, carcinogenic responses to trichloroethylene are thought to involve trichloroethylene metabolites (Bull 2000; Green 2000; Lash et al. 2000). This hypothesis is supported by observations that mice appear to be uniquely susceptible to trichloroethylene-induced liver and lung tumors and display higher rates of trichloroethylene metabolism than rats. In contrast, rats appear to be uniquely susceptible to trichloroethylene-induced kidney damage and tumors. Based on its review of available data, ATSDR (2019) concluded that there is adequate evidence to indicate that trichloroethylene is carcinogenic in mice, that the evidence for trichloroethylene carcinogenicity in rats is equivocal, and that further study is required to determine whether or not the processes that induce liver cancer in mice also operate in the human liver.

C.3 Mechanisms of Action

Like other solvents, nervous system effects from trichloroethylene are likely to involve disruption of neural membranes by the parent chemical, but trichloroethanol is also involved. In support of this hypothesis, Mikisková and Mikiska (1966) reported that i.p. administration of trichloroethanol was 5–6 times more potent than trichloroethylene in altering the electrical excitability of the motor cerebral cortex, threshold current intensity of electrical skin stimulation, and electroencephalogram and electrocardiograph results associated with CNS depression in guinea pigs. Blain et al. (1992) found that effects on visual evoked potentials in rabbits exposed to trichloroethylene by inhalation correlated better

with blood levels of trichloroethanol than trichloroethylene. A similar relationship was identified for electroretinographic measurements in rabbits exposed to trichloroethylene by inhalation (Blain et al. 1994).

Parkinson-like effects observed in animals exposed to trichloroethylene are attributed to degeneration of dopaminergic neurons in the substantia nigra (Lash 2025; Liu et al. 2025). Proposed underlying mechanisms include induction of leucine-rich repeat kinase 2 (LRRK2) activity, mitochondrial dysfunction, and oxidative stress (Lash 2025; Liu et al. 2025; Srivastava et al. 2024). Effects are likely due to a metabolite of trichloroethylene. One candidate is TaClo due to similarity in structure to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a compound linked to Parkinson's disease (Liu et al. 2025). However, while animal studies have confirmed an association between TaClo exposure and development of Parkinson-like effects, direct evidence of TaClo formation in humans is limited (Liu et al. 2025).

As proposed for neurological effects, renal effects associated with trichloroethylene exposure have also been attributed to mitochondrial dysfunction and oxidative stress (Lash et al. 2025).

Metabolism of trichloroethylene is expected to produce cytotoxic and carcinogenic metabolites, including trichloroacetic acid, dichloroacetic acid, chloral hydrate, and 2-chloroacetaldehyde (ATSDR 2019).

Drinking water administration of trichloroacetic acid to rodents has produced carcinogenic changes in the liver that are associated with the proliferation of peroxisomes. Reactive oxygen species produced by peroxisomes are thought to be involved in a sequence of DNA damage, cytotoxicity, regenerative cell growth, and tumor development. Phenobarbital pretreatment and induction of hepatic cytochrome P450 isozymes appear to be associated with enhancement of acute trichloroethylene hepatotoxicity in rodents (Allemand et al. 1978; Moslen et al. 1977; Nakajima et al. 1990), providing further support for the idea that metabolites are responsible for the hepatotoxicity of trichloroethylene. Trichloroethylene-induced liver cancer and peroxisomal proliferation have been associated with rapid metabolism of trichloroethylene to trichloroacetic acid in mice, but this metabolic pathway appears to be limited in rats and humans. Dichloroacetic acid has also been shown to produce liver cancer in mice, but its hepatocarcinogenicity has been hypothesized to involve some other, as yet unspecified, mechanism of action. The mouse liver displays much higher rates of metabolism of trichloroethylene, and is more susceptible to the hepatotoxicity and hepatocarcinogenicity of trichloroethylene, than are the livers of rats and humans. With chronic-duration oral exposure to high doses of trichloroethylene by gavage, increased incidence of toxic nephrosis and renal tumors occurred in male rats, but in female rats, the nephrosis was not

accompanied by an increase in kidney tumors. Trichloroethylene-induced kidney damage has been proposed to involve conjugation products of trichloroethylene with GSH. The conjugated products (e.g., dichlorovinyl-cysteine) can be hydrolyzed by β -lyase in the kidney, forming a reactive thiol group that can react with cellular macromolecules and lead to cell damage. In support of this mechanistic hypothesis, chemical agents that inhibit β -lyase protected against dichlorovinyl-cysteine nephrotoxicity in rats (ATSDR 2019).

Trichloroethylene-induced cardiac arrhythmias are thought to involve parent-chemical sensitization of the heart to epinephrine-induced arrhythmias (ATSDR 2019). In animals, chemicals that inhibited the metabolism of trichloroethylene increased the potency of trichloroethylene to induce cardiac arrhythmias, whereas chemicals enhancing trichloroethylene metabolism decreased its potency.

C.4 Health Guidelines

ATSDR (2019) did not establish an acute-duration inhalation MRL for trichloroethylene.

ATSDR (2019) established intermediate- and chronic-duration inhalation MRLs of 0.0004 ppm for trichloroethylene based on EPA's inhalation RfC (see below for details) (EPA 2011).

ATSDR (2019) did not establish an acute-duration oral MRL for trichloroethylene.

ATSDR (2019) established intermediate- and chronic-duration oral MRLs of 0.0005 mg/kg/day for trichloroethylene based on EPA's oral RfD (see below for details) (EPA 2011).

EPA (2011) derived a chronic RfD of 0.0005 mg/kg/day for trichloroethylene based on the midpoint and rounding of three candidate critical study RfD values: increased incidence of fetal heart malformations in rats (Johnson et al. 2003), decreased thymus weights in female mice (Keil et al. 2009), and immunotoxicity (increased delayed-type hypersensitivity and decreased PFC response) in mice (Peden-Adams et al. 2006). EPA performed BMD modeling on the fetal heart malformation incidence in rats (Johnson et al. 2003) resulting in a BMDL₀₁ (1% extra risk) of 0.0207 mg/kg/day, which was used to calculate a PBPK model-based human equivalent dose (HED₉₉) of 0.0051 mg/kg/day. Dividing the HED₉₉ by a total uncertainty factor of 10 (accounting for extrapolation from animals to humans and human variability) resulted in a candidate RfD_{heart malformations} of 0.00051 mg/kg/day. For the thymus weight effects (Keil et al. 2009), EPA used the LOAEL of 0.35 mg/kg/day to derive a PBPK-model-based

HED₉₉ of 0.048 mg/kg/day. Dividing the HED₉₉ by a total uncertainty factor of 100 (accounting for extrapolation from a LOAEL to NOAEL and animals to humans and human variability) resulted in a candidate RfD_{thymus weight} of 0.00048 mg/kg/day. For immunotoxicity (Peden-Adams et al. 2006), EPA divided the LOAEL of 0.37 mg/kg/day by a total uncertainty factor of 1,000 (accounting for extrapolation from a LOAEL to a NOAEL and animals to humans, and human variability), producing a candidate chronic RfD_{immunotoxicity} of 0.00037 mg/kg/day. EPA selected 0.0005 mg/kg/day as the chronic RfD since it was the midpoint of the candidate RfDs following rounding to one significant figure. It should be noted that inclusion of developmental cardiotoxicity as a co-critical effect for the derivation of the RfD is considered controversial, and the quality of the Johnson et al. (2003) study has been challenged (ATSDR 2025). As discussed in ATSDR (2025), several evaluations determined that the database is insufficient to support an association between developmental cardiotoxicity and trichloroethylene exposure in humans (Bukowski 2014; EPA 2014; Wikoff et al. 2018), while others concluded that the weight of evidence indicates that trichloroethylene exposure may cause congenital heart defects (EPA 2020). Specifically, the rapid systematic review by ATSDR (2025) assigned the Johnson et al. (2003) study a low study confidence based on significant design flaws, including the lack of a concurrent control group.

EPA (2011) derived a chronic RfC of 0.0004 ppm for trichloroethylene based on the midpoint (rounded up) of candidate RfDs for two endpoints considered for the chronic RfD (see above): increased incidence of heart malformations in rats (Johnson et al. 2003) and decreased thymus weights in female mice (Keil et al. 2009). For heart malformations (Johnson et al. 2003), EPA performed BMD modeling and route-to-route extrapolation via a PBPK model to produce an HEC₉₉ of 0.0037 ppm. The HEC₉₉ was divided by a total uncertainty factor of 10 (accounting for extrapolation from animals to humans and human variability using a PBPK model), resulting in a candidate chronic RfC_{heart malformations} of 0.00037 ppm. For thymus weights (Keil et al. 2009), EPA performed route-to-route extrapolation via a PBPK model of the mouse LOAEL of 0.35 mg/kg/day to produce a HEC_{99LOAEL} of 0.033 ppm. Dividing the HEC_{99LOAEL} by a total uncertainty factor of 100 (accounting for extrapolation from a LOAEL to a NOAEL and animals to humans, and human variability using a PBPK model) produced a candidate RfC_{thymus weight} of 0.00033 ppm. EPA selected the midpoint of 0.0004 ppm (rounded up from 0.00035 ppm) as the chronic RfC for trichloroethylene. As noted above, both the critical study (Johnson et al. 2003) and the endpoint (developmental cardiotoxicity) have been heavily scrutinized for inclusion in the derivation of EPA RfDs.

NTP (2021c) listed trichloroethylene as *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans. EPA (2011) concluded that trichloroethylene is *carcinogenic to humans* via a mutagenic mode of action according to the 2005 cancer guidelines (EPA 2005) based on

sufficient epidemiological evidence, and derived an oral slope factor of 4.6×10^{-2} per mg/kg-day and an inhalation unit risk of 4.1×10^{-6} per $\mu\text{g}/\text{m}^3$ for trichloroethylene. IARC (2014) assigned trichloroethylene to Cancer Group 1, *carcinogenic to humans*, based on sufficient evidence in humans and sufficient evidence in experimental animals.

C.5 Derivation of Target-Organ Toxicity Dose(s)

The noncancer endpoints of concern for trichloroethylene in this mixture are hepatic, renal, immunological, neurological, and developmental. TTDs are derived below for endpoints that are not the basis of the MRL, using the methods described by ATSDR (2018). The derivations are based primarily on data provided in ATSDR (2019) and, in particular, the LSE tables.

Inhalation TTDs

The POD_{HEC} for an extra-respiratory effect is calculated by multiplying the duration-adjusted animal POD by the ratio of the blood:gas partition coefficients in animals and humans $[(\text{Hb}/\text{g})\text{A} / (\text{Hb}/\text{g})\text{H}]$. Since the partition coefficients for trichloroethylene in rodents are greater than in humans, a default value of 1 is used for the ratio.

Hepatic Effects, Intermediate Inhalation. Kjellstrand et al. (1983) identified a NOAEL of 37 ppm and a LOAEL of 75 ppm for increased enzyme activity and liver weight in male mice exposed to trichloroethylene 24 hours/day for 30 days. The NOAEL was converted to a $\text{NOAEL}_{\text{HEC}}$ of 37 ppm as described previously under the heading, Inhalation TTDs. An uncertainty factor of 30 (3 for animal to human extrapolation using a dosimetric adjustment and 10 for human variability) was applied to the $\text{NOAEL}_{\text{HEC}}$ to derive the $\text{TTD}_{\text{HEPATIC}}$ of 1 ppm.

Renal Effects, Intermediate Inhalation. Kjellstrand et al. (1983) reported NOAEL and LOAEL values of 37 and 75 ppm, respectively, for increased kidney weights in male mice exposed to trichloroethylene for 24 hours/day for 30 days. The NOAEL was converted to a $\text{NOAEL}_{\text{HEC}}$ of 37 ppm as described previously under the heading, Inhalation TTDs. An uncertainty factor of 30 (3 for animal to human extrapolation using a dosimetric adjustment and 10 for human variability) was applied to the $\text{NOAEL}_{\text{HEC}}$ to derive the $\text{TTD}_{\text{RENAL}}$ of 1 ppm.

Immunological Effects, Intermediate Inhalation. EPA (2011) derived a chronic RfC for trichloroethylene based, in part, on decreased thymus weights in mice exposed to trichloroethylene in the drinking water at ≥ 1.4 ppm for 30 weeks (Keil et al. 2009) and route-to-route extrapolation. Since the intermediate-duration MRL for trichloroethylene is based on the EPA chronic RfC (ATSDR 2019), the intermediate-duration MRL of 0.0004 ppm can be adopted as the TTD_{IMMUNO} .

Neurological Effects, Intermediate Inhalation. Arito et al. (1994) reported a LOAEL of 50 ppm based on reduced wakefulness during exposure and postexposure sleeping heart rate in male mice exposed to trichloroethylene for 8 hours/day, 5 days/week for 6 weeks. The LOAEL was duration-adjusted to 11.9 ppm for a continuous exposure scenario and converted to a $LOAEL_{HEC}$ of 11.9 ppm as described previously under the heading, Inhalation TTDs. An uncertainty factor of 300 (10 for use of a LOAEL, 3 for animal to human extrapolation using a dosimetric adjustment, and 10 for human variability) was applied to the $LOAEL_{HEC}$ to derive the TTD_{NEURO} of 0.04 ppm.

Developmental Effects, Intermediate Inhalation. While no single study has identified both a NOAEL and a LOAEL for developmental effects following inhalation of trichloroethylene, NIOSH (1980) and Hardin et al. (1981) identified a NOAEL of 500 ppm, while Dorfmueller et al. (1979) identified a LOAEL of 1,800 ppm for decreased fetal weight and incomplete skeletal ossification. ATSDR based its chronic-duration inhalation MRL on EPA's chronic RfC for trichloroethylene (EPA 2011). The chronic RfC is estimated as the midpoint (rounded up) of two candidate RfCs for different endpoints, one of which is developmental cardiotoxicity in rats following maternal exposure to trichloroethylene in drinking water (extrapolated to an inhaled concentration) on GDs 1–22 (Johnson et al. 2003). The chronic-duration inhalation MRL was adopted for an intermediate-duration inhalation MRL of 0.0004 ppm. Because the chronic-duration MRL is based on the EPA chronic RfC (ATSDR 2019), the chronic-duration MRL of 0.0004 ppm can be adopted as the TTD_{DEVEL} .

Hepatic Effects, Chronic Inhalation. A $TTD_{HEPATIC}$ of 0.3 ppm is derived from the intermediate-duration $TTD_{HEPATIC}$; see explanation in Chapter 3.

Renal Effects, Chronic Inhalation. Maltoni et al. (1988) reported a NOAEL of 100 ppm and a LOAEL of 300 ppm for renal tubule megalonucleocytosis in male rats exposed 7 hours/day, 5 days/week for 104 weeks. The NOAEL was duration-adjusted to 20.8 ppm for a continuous exposure scenario and converted to a $NOAEL_{HEC}$ of 20.8 ppm as described previously under the heading, Inhalation TTDs. An

uncertainty factor of 30 (3 for animal to human extrapolation using a dosimetric adjustment, 10 for human variability) was applied to the $\text{NOAEL}_{\text{HEC}}$ to derive the $\text{TTD}_{\text{RENAL}}$ of 0.7 ppm.

Immunological Effects, Chronic Inhalation. EPA (2011) derived a chronic RfC for trichloroethylene based in part on decreased thymus weights in rats exposed to trichloroethylene in the drinking water at ≥ 1.4 ppm for 30 weeks (Keil et al. 2009) and route-to-route extrapolation. Since the chronic-duration MRL for trichloroethylene is based on the EPA chronic RfC (ATSDR 2019), the chronic-duration MRL of 0.0004 ppm can be adopted as the $\text{TTD}_{\text{IMMUNO}}$.

Neurological, Chronic Inhalation. A $\text{TTD}_{\text{NEURO}}$ of 0.01 ppm is derived from the intermediate-duration $\text{TTD}_{\text{NEURO}}$; see explanation in Chapter 3.

Developmental Effects, Chronic Inhalation. EPA (2011) derived a chronic RfC for trichloroethylene based on the midpoint (rounded up) of candidate RfCs for two endpoints, including developmental cardiotoxicity in rats following maternal exposure to trichloroethylene via drinking water at ≥ 0.25 ppm on GDs 1–22 (Johnson et al. 2003) and route-to-route extrapolation. Because the chronic-duration inhalation MRL for trichloroethylene is based on the EPA chronic RfC (ATSDR 2019), the chronic-duration MRL of 0.0004 ppm can be adopted as the $\text{TTD}_{\text{DEVEL}}$.

Oral TTDs

Hepatic Effects, Intermediate Oral. The lowest intermediate-duration hepatic LOAEL of 400 mg/kg/day was reported by Buben and O’Flaherty (1985) based on enlarged hepatocytes in mice administered gavage doses of trichloroethylene 5 days/week for 6 weeks. The NOAEL for this study was 100 mg/kg/day; the duration-adjusted NOAEL is 71 mg/kg/day. Application of an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability) applied to the $\text{NOAEL}_{\text{ADJ}}$ results in a TTD of 0.7 mg/kg/day for hepatic effects.

Renal Effects, Intermediate Oral. Tucker et al. (1982) reported a NOAEL of 217 mg/kg/day and a LOAEL of 393 mg/kg/day in male mice for elevated urinary protein and ketone levels from 6 months of exposure to trichloroethylene in the drinking water. Application of an uncertainty factor of 100 (10 for animal to human extrapolations and 10 for human variability) results in a $\text{TTD}_{\text{RENAL}}$ of 2 mg/kg/day.

Immunological Effects, Intermediate Oral. EPA (2011) derived a chronic RfD for trichloroethylene based in part on decreased thymus weights in mice exposed to trichloroethylene via drinking water at ≥ 1.4 ppm for 30 weeks (Keil et al. 2009) and decreased PFC response and increased delayed-type sensitivity in pups exposed *in utero* via drinking water at ≥ 1.4 ppm (Peden-Adams et al. 2006). Since the intermediate-duration oral MRL for trichloroethylene is based on the EPA chronic RfD (ATSDR 2019), the intermediate-duration MRL of 0.0005 mg/kg/day can be adopted as the TTD_{IMMUNO}.

Neurological Effects, Intermediate Oral. The lowest intermediate-duration neurological LOAEL of 1,000 mg/kg/day was identified by Gash et al. (2008) for decreased dopaminergic neurons in the substantia nigra brain region of male rats administered gavage doses of trichloroethylene 5 days/week for 6 weeks. A NOAEL was not identified for this study. Due to the nature of the critical effect, the dose of 1,000 mg/kg/day is designated as a serious LOAEL, which is not suitable for derivation of TTDs per ATSDR guidance. As the other neurological LOAELs identified for trichloroethylene are greater than the serious LOAEL of 1,000 mg/kg/day, they also are not suitable for TTD derivation. Since developmental toxicity and immunotoxicity, the effects for which the oral MRL is based, were detected at lower doses than those that cause neurotoxicity, the intermediate-duration MRL of 0.0005 mg/kg/day can be adopted as the TTD_{NEURO}.

Developmental Effects, Intermediate Oral. EPA (2011) derived a chronic RfD for trichloroethylene based on the midpoint (rounded) of candidate RfDs for developmental cardiotoxicity in rats following maternal exposure to trichloroethylene at ≥ 0.25 ppm in drinking water on GDs 1–22 (Johnson et al. 2003) and decreased PFC response and increased delayed-type sensitivity in pups exposed *in utero* via drinking water at ≥ 1.4 ppm (Peden-Adams et al. 2006). Since the intermediate-duration oral MRL for trichloroethylene is based on the EPA chronic RfD (ATSDR 2019), the intermediate-duration MRL of 0.0005 mg/kg/day can be adopted as the TTD_{DEVEL}.

Hepatic Effects, Chronic Oral. Chronic-duration studies of trichloroethylene toxicity have failed to report noncancer hepatic effects, even at doses as high as 1,000 mg/kg/day. The lowest intermediate-duration hepatic LOAEL of 400 mg/kg/day was reported by Buben and O’Flaherty (1985) based on enlarged hepatocytes in mice administered gavage doses of trichloroethylene 5 days/week for 6 weeks. The NOAEL value for this study was 100 mg/kg/day; the duration-adjusted NOAEL is 71 mg/kg/day. Application of an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability) applied to the NOAEL_{ADJ} results in a TTD of 0.7 mg/kg/day for hepatic effects.

Renal Effects, Chronic Oral. Chronic-duration studies of trichloroethylene have reported kidney effects in rats and mice (Maltoni et al. 1986; NCI 1976b; NTP 1988b, 1990). The lowest LOAEL was 250 mg/kg/day based on an increased incidence of renal tubular nucleocytosis in male rats dosed 5 days/week for 52 weeks (Maltoni et al. 1986); the NOAEL was 50 mg/kg/day. Using the duration-adjusted NOAEL of 36 mg/kg/day and applying an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability) results in a TTD_{RENAL} of 0.4 mg/kg/day.

Immunological Effects, Chronic Oral. EPA (2011) derived a chronic RfD for trichloroethylene based, in part, on decreased thymus weights in mice exposed to trichloroethylene via drinking water at ≥ 1.4 ppm for 30 weeks (Keil et al. 2009) and decreased PFC response and increased delayed-type sensitivity in pups exposed *in utero* via drinking water at ≥ 1.4 ppm (Peden-Adams et al. 2006). Since the chronic-duration MRL for trichloroethylene is based on the EPA chronic RfD (ATSDR 2019), the chronic-duration MRL of 0.0005 mg/kg/day can be adopted as the TTD_{IMMUNO}.

Neurological, Chronic Oral. No chronic-duration oral studies evaluated neurological endpoints. The lowest intermediate-duration LOAEL of 1,000 mg/kg/day was identified by Gash et al. (2008) for decreased dopaminergic neurons in the substantia nigra brain region of male rats administered gavage doses of trichloroethylene 5 days/week for 6 weeks. A NOAEL was not identified for this study. Due to the nature of the critical effect, the dose of 1,000 mg/kg/day is designated as a serious LOAEL, which is not suitable for derivation of TTDs per ATSDR guidance. As the other intermediate-duration neurological LOAELs identified for trichloroethylene are greater than the serious LOAEL of 1,000 mg/kg/day, they also are not suitable for TTD derivation. Since developmental toxicity and immunotoxicity, the effects for which the chronic oral MRL is based, were detected at lower doses than those that cause neurotoxicity, the chronic-duration MRL of 0.0005 mg/kg/day can be adopted as the TTD_{NEURO}.

Developmental Effects, Chronic Oral. EPA (2011) derived a chronic RfD for trichloroethylene based in part on increased incidence of fetal cardiac malformations in rats following maternal exposure to trichloroethylene at ≥ 0.25 ppm in drinking water on GDs 1–22 (Johnson et al. 2003) and decreased PFC response and increased delayed-type sensitivity in pups exposed *in utero* via drinking water at ≥ 1.4 ppm (Peden-Adams et al. 2006). Since the chronic-duration oral MRL for trichloroethylene is based on the EPA chronic RfD (ATSDR 2019), the chronic-duration MRL of 0.0005 mg/kg/day can be adopted as the TTD_{DEVEL}.

Summary (TTDs for Trichloroethylene)

Intermediate-Duration Inhalation TTDs:

$$\text{TTD}_{\text{HEPATIC}} = 1 \text{ ppm}$$

$$\text{TTD}_{\text{RENAL}} = 1 \text{ ppm}$$

$$\text{MRL}_{\text{IMMUNO}} = 0.0004 \text{ ppm}$$

$$\text{TTD}_{\text{NEURO}} = 0.04 \text{ ppm}$$

$$\text{MRL}_{\text{DEVEL}} = 0.0004 \text{ ppm}$$

Chronic-Duration Inhalation TTDs:

$$\text{TTD}_{\text{HEPATIC}} = 0.3 \text{ ppm}$$

$$\text{TTD}_{\text{RENAL}} = 0.7 \text{ ppm}$$

$$\text{MRL}_{\text{IMMUNO}} = 0.0004 \text{ ppm}$$

$$\text{TTD}_{\text{NEURO}} = 0.01 \text{ ppm}$$

$$\text{MRL}_{\text{DEVEL}} = 0.0004 \text{ ppm}$$

Intermediate-Duration Oral TTDs:

$$\text{TTD}_{\text{HEPATIC}} = 0.7 \text{ mg/kg/day}$$

$$\text{TTD}_{\text{RENAL}} = 2 \text{ mg/kg/day}$$

$$\text{MRL}_{\text{IMMUNO}} = 0.0005 \text{ mg/kg/day}$$

$$\text{TTD}_{\text{NEURO}} = 0.0005 \text{ mg/kg/day}$$

$$\text{MRL}_{\text{DEVEL}} = 0.0005 \text{ mg/kg/day}$$

Chronic-Duration Oral TTDs:

$$\text{TTD}_{\text{HEPATIC}} = 0.7 \text{ mg/kg/day}$$

$$\text{TTD}_{\text{RENAL}} = 0.4 \text{ mg/kg/day}$$

$$\text{MRL}_{\text{IMMUNO}} = 0.0005 \text{ mg/kg/day}$$

$$\text{TTD}_{\text{NEURO}} = 0.0005 \text{ mg/kg/day}$$

$$\text{MRL}_{\text{DEVEL}} = 0.0005 \text{ mg/kg/day}$$

C.6 References

Adams EM, Spencer HC, Rowe VK, et al. 1951. Vapor toxicity of trichloroethylene determined by experiments on laboratory animals. *AMA Arch Ind Hyg Occup Med* 4:469-481.

- Adamson A, Ilieva N, Stone WJ, et al. 2023. Low-dose inhalation exposure to trichloroethylene induces dopaminergic neurodegeneration in rodents. *Toxicol Sci* 196(2):218-228. <https://doi.org/10.1093/toxsci/kfad090>.
- Allemand H, Pessayre D, Descatoire V, et al. 1978. Metabolic activation of trichloroethylene into a chemically reactive metabolite toxic to the liver. *J Pharmacol Exp Ther* 204(3):714-723.
- Arito H, Takahashi M, Ishikawa T. 1994. Effect of subchronic inhalation exposure to low-level trichloroethylene on heart rate and wakefulness-sleep in freely moving rats. *Jpn J Ind Health* 36:1-8.
- ATSDR. 2018. Framework for assessing health impacts of multiple chemicals and other stressors (Update). Agency for Toxic Substances and Disease Registry. <https://www.atsdr.cdc.gov/interaction-profiles/media/pdfs/ipga-p.pdf>. January 26, 2025.
- ATSDR. 2019. Toxicological profile for trichloroethylene. Agency for Toxic Substances and Disease Registry. <https://www.atsdr.cdc.gov/ToxProfiles/tp19.pdf>. December 16, 2024.
- ATSDR. 2025. Targeted systematic evidence map (SEM) and rapid systematic review for trichloroethylene and developmental cardiotoxicity. Agency for Toxic Substances and Disease Registry. <https://www.atsdr.cdc.gov/ToxProfiles/SEM-for-Trichloroethylene-508.pdf>. January 22, 2026.
- Barton HA, Clewell HJ. 2000. Evaluating noncancer effects of trichloroethylene: dosimetry, mode of action, and risk assessment. *Environ Health Perspect* 108(Suppl 2):323-334. <https://doi.org/10.1289/ehp.00108s2323>.
- Berman E, Schlicht M, Moser VC, et al. 1995. A multidisciplinary approach to toxicological screening: I. Systemic toxicity. *J Toxicol Environ Health* 45:127-143. <https://doi.org/10.1080/15287399509531986>.
- Blain L, Lachapelle P, Molotchnikoff S. 1992. Evoked potentials are modified by long term exposure to trichloroethylene. *Neurotoxicology* 13(1):203-206.
- Blain L, Lachapelle P, Molotchnikoff S. 1994. Electroretinal responses are modified by chronic exposure to trichloroethylene. *Neurotoxicology* 15(3):627-631.
- Bolt HM, Lammert M, Selinski S, et al. 2004. Urinary alpha1-microglobulin excretion as biomarker of renal toxicity in trichloroethylene-exposed persons. *Int Arch Occup Environ Health* 77(Apr):186-190. <https://doi.org/10.1007/s00420-003-0500-3>.
- Boverhof DR, Krieger SM, Hotchkiss JA, et al. 2013. Assessment of the immunotoxic potential of trichloroethylene and perchloroethylene in rats following inhalation exposure. *J Immunotoxicol* 10(3):311-320. <https://doi.org/10.3109/1547691x.2012.735275>.
- Bürning T, Sundberg AG, Birner G, et al. 1999. Glutathione transferase alpha as a marker for tubular damage after trichloroethylene exposure. *Arch Toxicol* 73(Jun-Jul):246-254. <https://doi.org/10.1007/s002040050613>.
- Buben JA, O'Flaherty EJ. 1985. Delineation of the role of metabolism in the hepatotoxicity of trichloroethylene and perchloroethylene: A dose-effect study. *Toxicol Appl Pharmacol* 78:105-122. [https://doi.org/10.1016/0041-008X\(85\)90310-2](https://doi.org/10.1016/0041-008X(85)90310-2).
- Bukowski J. 2014. Critical review of the epidemiologic literature regarding the association between congenital heart defects and exposure to trichloroethylene. *Crit Rev Toxicol* 44(7):581-589. <https://doi.org/10.3109/10408444.2014.910755>.
- Bull RJ. 2000. Mode of action of liver tumor induction by trichloroethylene and its metabolites, trichloroacetate and dichloroacetate. *Environ Health Perspect* 108 Suppl 2(May):241-259. <https://doi.org/10.1289/ehp.00108s2241>.
- Carrieri M, Magosso D, Piccoli P, et al. 2007. Acute, nonfatal intoxication with trichloroethylene. *Arch Toxicol* 81(Jul):529-532. <https://doi.org/10.1007/s00204-007-0180-y>.
- Clewell HJ, Gentry PR, Covington TR, et al. 2000. Development of a physiologically based pharmacokinetic model of trichloroethylene and its metabolites for use in risk assessment. *Environ Health Perspect* 108 Suppl 2(Suppl 2):283-305. <https://doi.org/10.1289/ehp.00108s2283>.

- Dawson BV, Johnson PD, Goldberg SJ, et al. 1993. Cardiac teratogenesis of halogenated hydrocarbon-contaminated drinking water. *J Am Coll Cardiol* 21(6):1466-1472. [https://doi.org/10.1016/0735-1097\(93\)90325-u](https://doi.org/10.1016/0735-1097(93)90325-u).
- Dorfmueller MA, Henne SP, York RG, et al. 1979. Evaluation of teratogenicity and behavioral toxicity with inhalation exposure of maternal rats to trichloroethylene. *Toxicology* 14:153-166. [https://doi.org/10.1016/0300-483X\(79\)90061-1](https://doi.org/10.1016/0300-483X(79)90061-1).
- D'Souza RW, Bruckner JV, Feldman S. 1985. Oral and intravenous trichloroethylene pharmacokinetics in the rat. *J Toxicol Environ Health* 15:587-601. <https://doi.org/10.1080/15287398509530688>.
- EPA. 2005. Guidelines for carcinogen risk assessment. U.S. Environmental Protection Agency. EPA630P03001F. https://www.epa.gov/sites/default/files/2013-09/documents/cancer_guidelines_final_3-25-05.pdf. June 29, 2021.
- EPA. 2011. Trichloroethylene. Integrated Risk Information System (IRIS). Cincinnati, OH: U.S. Environmental Protection Agency. https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=199. September 28, 2011.
- EPA. 2014. Attachment: TCE developmental cardiac toxicity assessment update. Washington, DC: U.S. Environmental Protection Agency. EPA-HQ-OPPT-2019-0500-0139. <http://www.noticeandcomment.com/TCE-Developmental-Cardiac-Toxicity-Assessment-Update-fn-148249.aspx>. October 27, 2015.
- EPA. 2020. TCE Supplemental information file data table for congenital heart defects weight of evidence analysis. U.S. Environmental Protection Agency. EPA-HQ-OPPT-2019-0500-0139. <https://downloads.regulations.gov/EPA-HQ-OPPT-2019-0500-0139/content.xlsx>. January 22, 2026.
- Fisher JW. 2000. Physiologically based pharmacokinetic models for trichloroethylene and its oxidative metabolites. *Environ Health Perspect* 108(May):265-273. <https://doi.org/10.1289/ehp.00108s2265>.
- Gash DM, Rutland K, Hudson NL, et al. 2008. Trichloroethylene: Parkinsonism and complex 1 mitochondrial neurotoxicity. *Ann Neurol* 63(Feb):184-192. <https://doi.org/10.1002/ana.21288>.
- Green T. 2000. Pulmonary toxicity and carcinogenicity of trichloroethylene: species differences and modes of action. *Environ Health Perspect* 108 Suppl 2(May):261-264. <https://doi.org/10.1289/ehp.00108s2261>.
- Ha JH, Lee CG, Yoon SH, et al. 2009. A case of hypersensitive exfoliative dermatitis with hepatitis after a occupational exposure to trichloroethylene. *Korean J Asmtha Allergy Clin Immunol* 29(2):132-137.
- Hardin B, Bond G, Sikov M, et al. 1981. Testing of selected workplace chemicals for teratogenic potential. *Scand J Work Environ Health* 7(Suppl 4):66-75.
- Hardin BD, Kelman BJ, Brent RL. 2004. Correspondence: Re: Paper published in *Environmental Health Perspectives* [including response from original authors Johnson et al.] (Comment on: *Environ Health Perspect* 111(3):289-292). *Environ Health Perspect* 112(11):A607-A608. <https://doi.org/10.1289/ehp.5125>.
- Huang H, Kamijima M, Wang H, et al. 2006. Human herpesvirus 6 reactivation in trichloroethylene-exposed workers suffering from generalized skin disorders accompanied by hepatic dysfunction. *J Occup Health* 48(Nov):417-423. <https://doi.org/10.1539/joh.48.417>.
- IARC. 2014. Trichloroethylene, tetrachloroethylene, and some chlorinated agents. IARC Monographs on the evaluation of carcinogenic risks to humans. Vol. 106. Lyon, France: International Agency for Research on Cancer. <https://publications.iarc.fr/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/Trichloroethylene-Tetrachloroethylene-And-Some-Other-Chlorinated-Agents-2014>. July 8, 2014.
- Johnson PD, Goldberg SJ, Mays MZ, et al. 2003. Threshold of trichloroethylene contamination in maternal drinking waters affecting fetal heart development in the rat. (Comment in: *Environ Health Perspect* 112(11):A607-A609; Erratum in: *Environ Health Perspect* 113(1):A18). *Environ Health Perspect* 111(Mar):289-292. <https://doi.org/10.1289/ehp.5125>.

- Johnson PD, Dawson BV, Goldberg SJ, et al. 2004. Trichloroethylene: Johnson et al.'s response. *Environ Health Perspect* 112(11):A608-A609.
- Jung HG, Kim HH, Song BG, et al. 2012. Trichloroethylene hypersensitivity syndrome: A disease of fatal outcome. *Yonsei Med J* 53(1):231-235. <https://doi.org/10.3349/ymj.2012.53.1.231>.
- Kamijima M, Hisanaga N, Wang H, et al. 2007. Occupational trichloroethylene exposure as a cause of idiosyncratic generalized skin disorders and accompanying hepatitis similar to drug hypersensitivities. *Int Arch Occup Environ Health* 80(Apr):357-370. <https://doi.org/10.1007/s00420-006-0147-y>.
- Kaneko T, Saegusa M, Tasaka K, et al. 2000. Immunotoxicity of trichloroethylene: A study with MRL-lpr/lpr mice. *J Appl Toxicol* 20(Nov-Dec):471-475. [https://doi.org/10.1002/1099-1263\(200011/12\)20:6<471::AID-JAT716>3.0.CO;2-E](https://doi.org/10.1002/1099-1263(200011/12)20:6<471::AID-JAT716>3.0.CO;2-E).
- Keil DE, Peden-Adams MM, Wallace S, et al. 2009. Assessment of trichloroethylene (TCE) exposure in murine strains genetically-prone and non-prone to develop autoimmune disease. *J Environ Sci Health A Tox Hazard Subst Environ Eng* 44(Apr):443-453. <https://doi.org/10.1080/10934520902719738>.
- Kjellstrand P, Holmquist B, Alm P, et al. 1983. Trichloroethylene: further studies of the effects on body and organ weights and plasma butyrylcholinesterase activity in the mice. *Acta Pharmacol Toxicol* 53:375-384. <https://doi.org/10.1111/j.1600-0773.1983.tb03438.x>.
- Koizumi A, Kastl PE, Reitz RH, et al. 1986. Fate of ¹⁴C-trichloroethylene administered to rats in drinking water. Draft. Dow Chemical.
- Lash LH, Fisher JW, Lipscomb JC, et al. 2000. Metabolism of trichloroethylene. *Environ Health Perspect* 108(May):177-200. <https://doi.org/10.1289/ehp.00108s2177>.
- Lash LH. 2025. Trichloroethylene: An update on an environmental contaminant with multiple health effects. *Annu Rev Pharmacol Toxicol* 65(1):507-527. <https://doi.org/10.1146/annurev-pharmtox-022724-120525>.
- Liu R, Zhang F, Lou J, et al. 2025. Trichloroethylene exposure and Parkinson's disease: Environmental risk, metabolic pathways, and mechanistic insights. *Mol Neurobiol* 62(12):15336-15348. <https://doi.org/10.1007/s12035-025-05172-1>.
- Maltoni C, Lefemine G, Cotti G. 1986. Trichloroethylene. In: *Experimental research on trichloroethylene carcinogenesis*. Princeton, NJ: Princeton Scientific Publishing Co., Inc, 45-81, 93, 99-100, 112, 116, 130, 136-153, 157-186, 240-393.
- Maltoni C, Lefemine G, Cotti G, et al. 1988. Long-term carcinogenicity bioassays on trichloroethylene administered by inhalation to Sprague-Dawley rats and Swiss and B6C3F1 mice. *Ann N Y Acad Sci* 534:316-342. <https://doi.org/10.1111/j.1749-6632.1988.tb30120.x>
- Mikisková H, Mikiska A. 1966. Trichloroethanol in trichloroethylene poisoning. *Br J Ind Med* 23(2):116-125. <https://doi.org/10.1136/oem.23.2.116>.
- Monster AC, Boersma G, Duba WC. 1976. Pharmacokinetics of trichloroethylene in volunteers: Influence of workland and exposure concentration. *Int Arch Occup Environ Health* 38:87-102. <https://doi.org/10.1007/BF00378619>.
- Monster AC, Boersma G, Duba WC. 1979. Kinetics of trichloroethylene in repeated exposure of volunteers. *Int Arch Occup Environ Health* 42(Jan 15):283-292. <https://doi.org/10.1007/BF00377782>.
- Moslen MT, Reynolds ES, Szabo S. 1977. Enhancement of the metabolism and hepatotoxicity of trichloroethylene and perchloroethylene. *Biochem Pharmacol* 26:369-375. [https://doi.org/10.1016/0006-2952\(77\)90193-9](https://doi.org/10.1016/0006-2952(77)90193-9).
- Nakajima T, Wang RS, Murayama N, et al. 1990. Three forms of trichloroethylene-metabolizing enzymes in rat liver induced by ethanol, phenobarbital, and 3-methylcholanthrene. *Toxicol Appl Pharmacol* 102:546-552. [https://doi.org/10.1016/0041-008X\(90\)90049-Z](https://doi.org/10.1016/0041-008X(90)90049-Z).
- NCI. 1976b. Carcinogenesis bioassay of trichloroethylene. CAS No. 79-01-6. National Cancer Institute. NCI-CG-TR-2. DHEW Publication No. (NIH) 76-802. https://ntp.niehs.nih.gov/sites/default/files/ntp/htdocs/lt_rpts/tr002.pdf. January 28, 2025.

- NIOSH. 1980. Teratogenic-mutagenic risk of workplace contaminants: Trichloroethylene, perchloroethylene, and carbon disulfide. Cincinnati, OH: National Institute for Occupational Safety and Health. PB82185075.
<https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/PB82185075.xhtml>. January 28, 2025.
- NTP. 1988b. Toxicology and carcinogenesis studies of trichloroethylene (CAS No. 79-01-6) in four strains of rats (ACI, August, Marshall, Osborne-Mendel) (gavage studies). Research Triangle Park, NC: National Toxicology Program. NTP TR 273.
<https://ntp.niehs.nih.gov/publications/reports/tr/tr273>. January 28, 2025.
- NTP. 1990. Carcinogenesis studies of trichloroethylene (without epichlorohydrin) (CAS No. 79-01-6) in Fischer-344/N rats and B6C3F1 mice (gavage studies). Research Triangle Park, NC: National Toxicology Program. <https://ntp.niehs.nih.gov/publications/reports/tr/tr243>. January 28, 2025.
- NTP. 2021c. Trichloroethylene. 15th Report on carcinogens. National Toxicology Program. <https://ntp.niehs.nih.gov/sites/default/files/ntp/roc/content/profiles/trichloroethylene.pdf>. January 23, 2023.
- Peden-Adams MM, Eudaly JG, Heesemann LM, et al. 2006. Developmental immunotoxicity of trichloroethylene (TCE): Studies in B6C3F1 mice. *J Environ Sci Health A Tox Hazard Subst Environ Eng* 41(3):249-271. <https://doi.org/10.1080/10934520500455289>.
- Radican L, Wartenberg D, Rhoads GG, et al. 2006. A retrospective occupational cohort study of end-stage renal disease in aircraft workers exposed to trichloroethylene and other hydrocarbons. *J Occup Environ Med* 48(Jan):1-12.
- Ramdhan DH, Kamijima M, Yamada N, et al. 2008. Molecular mechanism of trichloroethylene-induced hepatotoxicity mediated by CYP2E1. *Toxicol Appl Pharmacol* 231(Sep 15):300-307.
<https://doi.org/10.1016/j.taap.2008.04.020>.
- Rhomberg LR. 2000. Dose-response analyses of the carcinogenic effects of trichloroethylene in experimental animals. *Environ Health Perspect* 108 Suppl 2(May):343-358.
<https://doi.org/10.1289/ehp.00108s2343>.
- Savolainen H, Pfaffli P, Tengen M, et al. 1977. Trichloroethylene and 1,1,1-trichloroethane: Effects on brain and liver after five days intermittent inhalation. *Arch Toxicol* 38:229-237.
<https://doi.org/10.1007/BF00293657>.
- Selden A, Hultberg B, Ulander A, et al. 1993. Trichloroethylene exposure in vapour degreasing and the urinary excretion of N-acetyl-b-D-glucosaminidase. *Arch Toxicol* 67:224-226.
<https://doi.org/10.1007/BF01973312>.
- Srivastava R, Chauhan K, Sharma R. 2024. Evaluating motor dysfunction and oxidative stress induced by trichloroethylene in Wistar rats. *Methods Mol Biol* 2761:499-510. https://doi.org/10.1007/978-1-0716-3662-6_34.
- Stott WT, Quast JF, Watanabe PG. 1982. Pharmacokinetics and macromolecular interaction of trichloroethylene in mice and rats. *Toxicol Appl Pharmacol* 62:137-151.
[https://doi.org/10.1016/0041-008X\(82\)90110-7](https://doi.org/10.1016/0041-008X(82)90110-7).
- Tucker AN, Sanders VM, Barnes DW, et al. 1982. Toxicology of trichloroethylene in the mouse. *Toxicol Appl Pharmacol* 62:351-357. [https://doi.org/10.1016/0041-008X\(82\)90137-5](https://doi.org/10.1016/0041-008X(82)90137-5).
- Urban JD, Wikoff DS, Chappell GA, et al. 2020. Systematic evaluation of mechanistic data in assessing in utero exposures to trichloroethylene and development of congenital heart defects. *Toxicology* 436:152427. <https://doi.org/10.1016/j.tox.2020.152427>.
- Wikoff D, Urban JD, Harvey S, et al. 2018. Role of risk of bias in systematic review for chemical risk assessment: a case study in understanding the relationship between congenital heart defects and exposures to trichloroethylene. *Int J Toxicol* 37(2):125-143.
<https://doi.org/10.1177/1091581818754330>.
- Xu X, Yang R, Wu N, et al. 2009. Severe hypersensitivity dermatitis and liver dysfunction induced by occupational exposure to trichloroethylene. *Industrial Health* 47(Apr):107-112.
<https://doi.org/10.2486/indhealth.47.107>.

Appendix D. Background Information for Vinyl Chloride

This appendix was written based primarily on the *Toxicological Profile for Vinyl Chloride* (ATSDR 2024b). Primary references are cited for the reader's convenience in identifying pertinent studies. For additional information beyond what is presented here, the reader is referred to the toxicological profile.

D.1 Toxicokinetics

Both human and animal studies have indicated a rapid absorption of vinyl chloride following inhalation exposure. For example, young adult male volunteers exposed to vinyl chloride concentrations of 2.9, 5.1, 11.7, or 23.5 ppm by gas mask for 6 hours (Krajewski et al. 1980) retained approximately 42% of the inhaled dose, regardless of concentration. Similar results have been reported in animal studies and have been incorporated into PBPK models for vinyl chloride (described below). While no studies of the absorption of vinyl chloride in humans are available, vinyl chloride is rapidly and completely absorbed following oral exposure in animals (Feron et al. 1981; Watanabe et al. 1976a; Withey 1976), with peak blood levels being reached 10–20 minutes after a single gavage dose (Withey 1976).

Studies of the disposition of vinyl chloride in humans are not available for any route of exposure. In animals, vinyl chloride is rapidly distributed following inhalation exposure, with highest levels in the kidney and brain (Bolt et al. 1976; Buchter et al. 1977). Unless metabolism is inhibited, vinyl chloride does not appear to deposit or accumulate for long periods within the body (Buchter et al. 1977). A similar pattern is seen following oral exposure (Watanabe et al. 1976a). Vinyl chloride can cross the placenta following absorption (Ungvary et al. 1978).

The major metabolic pathway of vinyl chloride involves oxidation by mixed-function oxidases, specifically CYP2E1, to form a highly reactive epoxide intermediate, 2-chloroethylene oxide, which spontaneously rearranges to form 2-chloroacetaldehyde (Guengerich et al. 1979, 1981; Gwinner et al. 1983; Laib 1982). These intermediates are detoxified mainly through conjugation with GSH catalyzed by GST enzymes. The conjugated products are excreted in urine as substituted cysteine derivatives and include thiodiglycolic acid, S-formyl-methylcysteine, and N-acetyl-S-(2-hydroxyethyl) cysteine (Bolt et al. 1980; Hefner et al. 1975). Metabolism is very rapid and is saturable (Bolt et al. 1977; Buchter et al. 1980; Filser and Bolt 1979; Watanabe et al. 1976a) at high exposure levels (~250 ppm by inhalation, and between 1 and 100 mg/kg by oral exposure).

Regardless of route of exposure, vinyl chloride is rapidly eliminated in the urine, primarily as metabolites. However, at very high concentrations when metabolism becomes saturated, elimination in the expired air may become a relevant pathway (Watanabe and Gehring 1976; Watanabe et al. 1976b).

Numerous PBPK models for vinyl chloride exposure have been published, for both inhalation and oral exposures; modeled species include rats, mice, hamsters, and humans. Several different modifications of these models have been used to estimate human cancer risk following vinyl chloride inhalation (Clewell et al. 1995, 2001; Reitz et al. 1996). The PBPK model described in Clewell et al. (2001) and in EPA (2000) was used to derive the chronic-duration oral MRL, based on exposures from the Til et al. (1983, 1991) dietary study. For additional details on PBPK models, see ATSDR (2024b).

D.2 Health Effects

Hepatic Effects. Following both inhalation and oral exposure, the most sensitive effects of vinyl chloride are on the liver. Numerous studies of workers exposed to atmospheres containing vinyl chloride have reported hepatic changes, including hepatic proliferation, hepatomegaly, fibrosis, and hepatocellular degeneration (ATSDR 2024b). While exposure characterization in these studies has been limited, effects have been reported at exposure levels ranging from 1 to 2,300 ppm (Ho et al. 1991; Suciú et al. 1975). The incidence and severity of the effects generally correlate well with the duration of exposure (Gedigke et al. 1975; Lilis et al. 1975; NIOSH 1977). Studies of humans following oral exposure to vinyl chloride are not available. Animal studies have identified noncancer hepatic effects beginning at inhaled concentrations of 10 ppm (Thornton et al. 2002) or oral doses of 1.7 mg/kg/day (Til et al. 1983, 1991). Chronic-duration exposure to vinyl chloride by inhalation has also been demonstrated to result in hepatic cancer, specifically angiosarcoma (ATSDR 2024b).

Immunological Effects. Workers exposed to vinyl chloride have shown a number of immunological effects, including “vinyl chloride disease” characterized by a syndrome consisting of Raynaud's phenomenon, acroosteolysis, joint and muscle pain, enhanced collagen deposition, stiffness of the hands, and scleroderma-like skin changes; these changes are thought to be immunologic in nature. 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 extent of the immunologic abnormality (Grainger et al. 1980; Langauer-Lewowicka et al. 1976; Ward 1976), although these symptoms have been reported without immunological findings (Black et al. 1986; Ostlere et al. 1992). In workers with severe clinical

signs, there have also been reports of an increased incidence of B-cell proliferation, hyperimmunoglobulinemia (Ward 1976), cryoglobulinemia (Grainger et al. 1980; Saad et al. 2017), and complement activation (Grainger et al. 1980; Saad et al. 2017; Ward 1976). Vinyl chloride workers who developed steatohepatitis (liver inflammation with fat accumulation) exhibited increased levels of proinflammatory cytokines (tumor necrosis factor- α , interleukins -1 β , -6, and -8) (Cave et al. 2010). Exposed workers were also found to have significantly increased percentages of lymphocytes compared to controls (Fučić et al. 1995, 1997). Evidence of a structurally altered IgG has been obtained, and it has been proposed that vinyl chloride or a metabolite binds to IgG (Grainger et al. 1980). Results of animal studies indicate that vinyl chloride inhalation exposure increases spleen weights (Bi et al. 1985; Sokal et al. 1980) and thymus weights (Sharma et al. 1980), induces spontaneous lymphocyte proliferation and, in mice, increases mitogen-stimulated responses (Sharma and Gehring 1979; Sharma et al. 1980) and increases the number of pulmonary interstitial macrophages (Zelko et al. 2022). No studies of immunological effects of oral exposure to vinyl chloride in humans or animals were located.

Neurological Effects. The most commonly reported CNS effects of vinyl chloride inhalation in humans are ataxia or dizziness, drowsiness or fatigue, loss of consciousness, and/or headache (ATSDR 2024b). Other CNS effects that have been reported by vinyl chloride workers include euphoria and irritability (Suciu et al. 1963, 1975), visual and/or hearing disturbances (Marsteller et al. 1975), nausea (Marsteller et al. 1975; Spirtas et al. 1975), memory loss (Langauer-Lewowicka et al. 1983; Suciu et al. 1963, 1975), and nervousness and sleep disturbances (Langauer-Lewowicka et al. 1983; Suciu et al. 1963). CNS tests revealed pyramidal signs and cerebellar disturbances in some exposed subjects (Langauer-Lewowicka et al. 1983). Reliable estimates of exposure levels producing these effects were not available, but they generally occur only at fairly high (>4,000 ppm) acute exposure levels (Lester et al. 1963; Patty et al. 1930). Chronic-duration inhalation exposure to lower levels of vinyl chloride may result in the development of a peripheral neuropathy characterized by tingling (paresthesia) in the extremities (Lilis et al. 1975; Sakabe 1975; Spirtas et al. 1975; Suciu et al. 1963, 1975; Veltman et al. 1975; Walker 1976), numbness in the fingers (Lilis et al. 1975; Sakabe 1975), weakness (Langauer-Lewowicka et al. 1983; Suciu et al. 1963, 1975), depressed reflexes (NIOSH 1977), warmth in the extremities (Suciu et al. 1963, 1975), and pain in the fingers (Sakabe 1975). However, it is unclear whether some of these symptoms are associated with tissue anoxia due to vascular insufficiency or whether they represent the direct toxic effects of vinyl chloride on peripheral nerves. Animal studies of inhaled vinyl chloride have also reported changes to nervous tissues, but generally only at very high (>5,000 ppm) exposure levels. No studies of neurological effects following oral exposure in humans or animals were located.

Developmental Effects. Although evidence has been presented indicating that members of communities with nearby vinyl chloride polymerization facilities have significantly greater incidences of some forms of developmental toxicity, these studies failed to demonstrate a statistically significant correlation between the developmental toxicity and either parental occupation or proximity to the facility (Edmonds et al. 1978; Infante et al. 1976; Rosenman et al. 1989; Theriault et al. 1983). Additionally, case-control studies have not identified associations between vinyl chloride exposure and developmental toxicity outcomes (Ruckart et al. 2013; Swartz et al. 2015a; Talbott et al. 2015). A number of inhalation studies have examined the effects of vinyl chloride exposure on pregnancy outcome in animals; results of these studies generally indicate that vinyl chloride produces adverse developmental effects (ATSDR 2024b). For example, John et al. (1977, 1981) reported a NOAEL of 50 ppm and a LOAEL of 500 ppm for maternal toxicity and delayed ossification in fetuses of mice and rabbits exposed during organogenesis, while Ungvary et al. (1978) reported that rats exposed to 1,500 ppm showed changes in maternal relative liver weights as well as increased litter resorption. Thornton et al. (2002) reported no adverse effects in rats following inhalation exposures to vinyl chloride at up to 1,100 ppm. No studies of developmental effects following oral exposure in humans or animals were located.

Cancer. The most compelling evidence for the carcinogenic potential of vinyl chloride in humans comes from the cluster of reports of greater than expected incidences of angiosarcoma of the liver in workers occupationally exposed to vinyl chloride (ATSDR 2024b). Angiosarcoma of the liver is considered to be a very rare type of cancer (25–30 cases/year in the United States) (Heath et al. 1975). However, 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 this type of tumor. Other liver tumors, including hepatocellular carcinoma and cholangiocellular carcinoma, have also been associated with occupational exposure to vinyl chloride (ATSDR 2024b). Based on this information, vinyl chloride is considered to be a human carcinogen by IARC (2012), HHS (NTP 2021d), and EPA (EPA 2000). It has been suggested that inhalation exposure to vinyl chloride in humans may also result in increased incidences of cancers of the brain, CNS, respiratory tract, connective and other soft tissues, and lymphatic/hematopoietic systems (for additional details, see ATSDR 2024b); however, the evidence for these tumors is considerably less convincing than the evidence for hepatic tumors. No data on the carcinogenicity of vinyl chloride following oral exposure in humans were located. Studies in animals by both the inhalation and oral routes have confirmed the carcinogenic properties of vinyl chloride (ATSDR 2024b).

D.3 Mechanisms of Action

The majority of the proposed mechanisms of vinyl chloride toxicity involve the metabolism of the compound by CYP2E1 to a reactive intermediate, such as 2-chloroethylene oxide or 2-chloroacetaldehyde (Rusyn et al. 2021). The intermediary metabolites bind to macromolecules in the body. 2-Chloroethylene oxide is believed to bind primarily to DNA and ribonucleic acid (RNA), whereas 2-chloroacetaldehyde binds primarily to proteins (ATSDR 2024b). Modification of proteins may result in toxicity, as is believed to occur in vinyl chloride-induced liver lesions, or may alter their antigenicity, possibly resulting in the autoimmune responses associated with vinyl chloride exposure. The mechanisms resulting in the neurological effects of vinyl chloride are not well characterized.

Many studies have characterized the mutation profile associated with DNA adducts formed by the reactive metabolites of vinyl chloride (ATSDR 2024b). Four primary cyclic DNA etheno-adducts are formed by the reactive metabolites of vinyl chloride (1,N⁶-ethenoadenine, 3,N⁴-ethenocytosine, N^{2,3}-ethenoguanine, and 1,N²-ethenoguanine). These adducts can produce base-pair (i.e., purine-to-purine or pyrimidine-to-pyrimidine exchange) transitions during transcription (Cullinan et al. 1997; Pandya and Moriya 1996; Singer 1996; Singer et al. 1987). The role of etheno-adducts in the carcinogenesis of vinyl chloride has been recently reviewed (Guengerich and Ghodke 2021; Rioux and Delaney 2020). DNA crosslinks can also be formed because chloroacetaldehyde is bifunctional (Singer 1996). The mechanisms for clastogenic effects of vinyl chloride exposure were examined by Fučić et al. (1990); 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 the chromosome. Additionally, vinyl chloride induces cancer formation via epigenetic mechanisms including cell cycle disruption (Pan et al. 2021) and altering DNA methylation (Chappell et al. 2016).

D.4 Health Guidelines

ATSDR (2024b) derived an acute-duration inhalation MRL for vinyl chloride of 0.5 ppm based on a NOAEL of 50 ppm for developmental effects in mice exposed 7 hours/day on GDs 6–15 (John et al. 1977, 1981). The next higher exposure level, 500 ppm, produced mortality in the dams. The NOAEL of 50 ppm for intermittent exposure (7 hours/day) was converted to a continuous exposure (50 ppm x 7/24 = 15 ppm) and then converted to a HEC. Since the blood:gas partition coefficient for vinyl chloride in mice is greater than that in humans, a default value of 1 was used for the ratio resulting in a NOAEL_{HEC}

of 15 ppm. A total uncertainty factor of 30 (3 for extrapolation from mice to humans using a dosimetric adjustment and 10 for human variability) was applied to the $\text{NOAEL}_{\text{HEC}}$ to derive the MRL of 0.5 ppm.

ATSDR (2024b) derived an intermediate-duration inhalation MRL of 0.02 ppm for vinyl chloride based on a BMCL_{10} value of 2.05 ppm (BMCL_{HEC} of 0.5 ppm following adjustment to continuous duration and multiplication of the human to animal partition coefficient ratio default value of 1) for hepatic centrilobular hypertrophy in rats (Thornton et al. 2002) and a total uncertainty factor of 30 (3 for extrapolation from mice to humans using a dosimetric adjustment and 10 for human variability).

ATSDR (2024b) did not derive a chronic-duration inhalation MRL for vinyl chloride because of the absence of a suitable LOAEL or NOAEL for derivation.

ATSDR (2024b) did not derive acute- or intermediate-duration oral MRLs for vinyl chloride because of an absence of data on the effects of oral exposure to vinyl chloride for these duration categories.

ATSDR (2024b) derived a chronic-duration oral MRL of 0.003 mg/kg/day based on a NOAEL of 0.17 mg/kg/day for noncancerous liver effects (i.e., liver cell polymorphism) in rats (Til et al. 1983, 1991) and application of a PBPK model (Clewell et al. 2001; EPA 2000). The human model was run iteratively, until the model converged with the internal dose estimate for the rat (3.16 mg/L liver). The human dose was assumed to be uniformly distributed over a 24-hour period, with the resulting human equivalent dose (HED) of 0.09 mg/kg/day. Therefore, the $\text{NOAEL}_{\text{HED}}$ 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 chronic-duration oral MRL for vinyl chloride. A total uncertainty factor of 30 (3 for extrapolating from animals to humans using a dose metric conversion and 10 for human variability) was applied to the $\text{NOAEL}_{\text{HED}}$.

EPA (2000) derived a chronic RfD of 0.003 mg/kg/day for vinyl chloride using the same principal study, critical effect (hepatic changes), NOAEL, and PBPK model as described above for the chronic-duration oral MRL for vinyl chloride. A total uncertainty factor of 30 (3 for extrapolating from animals to humans using a dose metric conversion and 10 for human variability) was applied.

EPA (2000) derived a chronic RfC of 0.1 mg/m³ for vinyl chloride based on hepatic effects using a route-to-route extrapolation of the oral data from Til et al. (1983, 1991) using the Clewell et al. (2001) PBPK model. A total uncertainty factor of 30 (3 for extrapolating from animals to humans using a dose metric conversion and 10 for human variability) was applied.

HHS's *Fifteenth Report on Carcinogens* (NTP 2021d) reports that vinyl chloride is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity in humans.

EPA has concluded that sufficient evidence of carcinogenicity exists in humans and animals and has classified vinyl chloride according to its 1986 classification scheme as a Group A or *known human carcinogen* (EPA 2000). EPA's current WOE characterization for vinyl chloride concludes that vinyl chloride is a *known human carcinogen* by the inhalation route of exposure, based on human epidemiological data. 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, vinyl chloride is also considered highly *likely to be carcinogenic* by the dermal route because it acts systemically (EPA 2000). Because the epidemiological evidence does not provide sufficient exposure and incidence data to quantify risk based solely on human data, EPA cancer potency factors for inhalation and oral exposure have been calculated based on animal studies. An inhalation unit risk of 8.8×10^{-6} per $\mu\text{g}/\text{m}^3$ for continuous lifetime exposure from birth was estimated by EPA (2000) based on the incidence of liver tumors observed in rats in the inhalation study by Maltoni et al. (1981). An inhalation unit risk of 4.4×10^{-6} per $\mu\text{g}/\text{m}^3$ for continuous lifetime exposure during adulthood was also estimated by EPA (2000). EPA (2000) derived the oral slope factor for continuous lifetime exposure as 1.5 per mg/kg/day based on the incidence of liver tumors in rats in the study by Feron et al. (1981). An oral slope factor of 7.5×10^{-1} per mg/kg/day for continuous lifetime exposure during adulthood was also estimated (EPA 2000).

IARC (2012) lists vinyl chloride in Group 1 (*carcinogenic to humans*) based on sufficient evidence of carcinogenicity in humans and animals.

D.5 Derivation of Target-Organ Toxicity Dose(s)

The noncancer endpoints of concern for vinyl chloride in this mixture are hepatic, immunological, neurological, and developmental. TTDs are derived below for endpoints that are not the basis of the MRL, using the methods described by ATSDR (2018). The derivations are based primarily on data provided in ATSDR (2024b) and, in particular, the LSE tables.

Inhalation TTDs

The POD_{HEC} for an extra-respiratory effect is calculated by multiplying the duration-adjusted animal POD by the ratio of the blood:gas partition coefficients in animals and humans $[(Hb/g)_A / Hb/g)_H]$. Since the partition coefficients for vinyl chloride in rodents are greater than in humans (see ATSDR 2024b), a default value of 1 is used for the ratio.

Hepatic Effects, Intermediate Inhalation. The intermediate-duration MRL for vinyl chloride is 0.02 ppm, based on hepatic effects.

Immunological Effects, Intermediate Inhalation. Zelko et al. (2022) reported a LOAEL of 0.8 ppm for increased pulmonary interstitial macrophages in mice exposed to vinyl chloride for 6 hours/day, 5 days/week for 12 weeks. The LOAEL was duration-adjusted to 0.14 ppm for a continuous exposure scenario and a $LOAEL_{HEC}$ of 0.14 ppm was calculated as described previously under the heading, Inhalation TTDs. Application of an uncertainty factor of 300 (10 for use of a LOAEL, 3 for animal to human extrapolation using a dosimetric adjustment, and 10 for human variability) would yield a TTD_{IMMUNO} of 0.0005 ppm. However, this would fall below the MRL; thus, the MRL of 0.02 ppm will be adopted as the TTD_{IMMUNO} for vinyl chloride.

Neurological Effects, Intermediate Inhalation. No appropriate data were available for intermediate-duration inhalation exposure. The intermediate-duration inhalation MRL of 0.02 ppm based on liver effects is adopted as the TTD_{NEURO} as a conservative value for intermediate-duration exposure.

Developmental Effects, Intermediate Inhalation. The acute-duration MRL of 0.5 ppm is based on developmental effects in mice exposed to 50 ppm of vinyl chloride for 7 hours/day (15 ppm $NOAEL_{HEC}$) on GDs 6–15, and is adopted as the TTD_{DEVEL} for intermediate-duration exposure.

Hepatic Effects, Chronic Inhalation. A $TTD_{HEPATIC}$ of 0.007 ppm was derived from the intermediate-duration MRL; see explanation in Chapter 3.

Immunological Effects, Chronic Inhalation. As for the intermediate-duration TTD_{IMMUNO} , the MRL of 0.02 ppm will be adopted as the chronic-duration TTD_{IMMUNO} for vinyl chloride.

Neurological Effects, Chronic Inhalation. No appropriate data were available for chronic-duration inhalation exposure. The intermediate-duration inhalation MRL of 0.02 ppm, based on liver effects, is adopted as the TTD_{NEURO} as a conservative value for chronic-duration exposure.

Developmental Effects, Chronic Inhalation. A TTD_{DEVEL} of 0.2 ppm was derived from the intermediate-duration value, using the approach explained in Chapter 3.

Oral TTDs

Hepatic Effects, Intermediate and Chronic Oral. No appropriate data were available for intermediate-duration oral exposure. The chronic-duration oral MRL of 0.003 mg/kg/day based on liver effects is adopted as a conservative value for intermediate-duration exposure.

Immunological Effects, Intermediate and Chronic Oral. No studies of immunological effects following oral exposure to vinyl chloride were located.

Neurological Effects, Intermediate and Chronic Oral. No appropriate data were available for intermediate-duration oral exposure. Feron et al. (1981) reported neurological NOAEL and LOAEL values of 5 and 14.1 mg/kg/day, respectively, based on lethargy, humpback position, and emaciation in rats administered gavage doses of vinyl chloride 5 days/week for 84 weeks to 2.7 years. The NOAEL was duration-adjusted to 3.6 mg/kg/day for continuous exposure. Application of an uncertainty factor of 100 (10 for animal to human extrapolations and 10 for human variability) yields a TTD_{NEURO} of 0.04 mg/kg/day.

Developmental Effects, Intermediate and Chronic Oral. No studies of developmental effects following oral exposure to vinyl chloride were located.

Summary (TTDs for Vinyl Chloride)

Intermediate-Duration Inhalation TTDs:

$MRL_{HEPATIC} = 0.02$ ppm

$TTD_{IMMUNO} = 0.02$ ppm

$TTD_{NEURO} = 0.02$ ppm

$TTD_{DEVEL} = 0.5$ ppm

Chronic-Duration Inhalation TTDs:

TTD_{HEPATIC} = 0.007 ppm

TTD_{IMMUNO} = 0.02 ppm

TTD_{NEURO} = 0.02 ppm

TTD_{DEVEL} = 0.2 ppm

Intermediate- and Chronic-Duration Oral TTDs:

MRL_{HEPATIC} = 0.003 mg/kg/day (chronic), adopted as TTD_{HEPATIC} for intermediate

TTD_{IMMUNO} = not derived, no data

TTD_{NEURO} = 0.04 mg/kg/day

TTD_{DEVEL} = not derived, no data

D.6 References

- ATSDR. 2024b. Toxicological profile for vinyl chloride. Agency for Toxic Substances and Disease Registry. <https://www.atsdr.cdc.gov/ToxProfiles/tp20.pdf>. December 16, 2024.
- Bi WF, Wang YS, Huang MY, et al. 1985. Effect of vinyl chloride on testis in rats. *Ecotoxicol Environ Saf* 10(3):281-289. [https://doi.org/10.1016/0147-6513\(85\)90074-0](https://doi.org/10.1016/0147-6513(85)90074-0).
- Black C, Pereira S, McWhirter A, et al. 1986. Genetic susceptibility to scleroderma-like syndrome in symptomatic and asymptomatic workers exposed to vinyl chloride. *J Rheumatol* 13(6):1059-1062.
- Bolt HM, Kappus H, Buchter A, et al. 1976. Disposition of (1,2-¹⁴C) vinyl chloride in the rat. *Arch Toxicol* 35(3):153-162. <https://doi.org/10.1007/BF00293562>.
- Bolt HM, Laib RJ, Kappus H, et al. 1977. Pharmacokinetics of vinyl chloride in the rat. *Toxicology* 7(2):179-188. [https://doi.org/10.1016/0300-483x\(77\)90063-4](https://doi.org/10.1016/0300-483x(77)90063-4).
- Bolt HM, Filser JG, Laib RJ, et al. 1980. Binding kinetics of vinyl chloride and vinyl bromide at very low doses. *Arch Toxicol Suppl* 3:129-142. https://doi.org/10.1007/978-3-642-67389-4_10.
- Buchter A, Bolt HM, Kappus H, et al. 1977. [Tissue distribution of 1,2-¹⁴C-vinyl chloride in the rat]. *Int Arch Occup Environ Health* 39:27-32. (German)
- Buchter A, Filser JG, Peter H, et al. 1980. Pharmacokinetics of vinyl chloride in the Rhesus monkey. *Toxicol Lett* 6(1):33-36. [https://doi.org/10.1016/0378-4274\(80\)90099-5](https://doi.org/10.1016/0378-4274(80)90099-5).
- Cave M, Falkner KC, Ray M, et al. 2010. Toxicant-associated steatohepatitis in vinyl chloride workers. *Hepatology* 51(2):474-481. <https://doi.org/10.1002/hep.23321>.
- Chappell G, Pogribny IP, Guyton KZ, et al. 2016. Epigenetic alterations induced by genotoxic occupational and environmental human chemical carcinogens: A systematic literature review. *Mutat Res* 768:27-45. <https://doi.org/10.1016/j.mrrev.2016.03.004>.
- Clewell HJ, Gentry PR, Gearhart JM, et al. 1995. Considering pharmacokinetic and mechanistic information in cancer risk assessments for environmental contaminants: examples with vinyl chloride and trichloroethylene. *Chemosphere* 31(1):2561-2578. [https://doi.org/10.1016/0045-6535\(95\)00124-q](https://doi.org/10.1016/0045-6535(95)00124-q).
- Clewell HJ, Gentry PR, Gearhart JM, et al. 2001. Comparison of cancer risk estimates for vinyl chloride using animal and human data with a PBPK model. *Sci Total Environ* 274:37-66. [https://doi.org/10.1016/S0048-9697\(01\)00730-6](https://doi.org/10.1016/S0048-9697(01)00730-6).

- Cullinan D, Johnson F, Grollman AP, et al. 1997. Solution structure of a DNA duplex containing the exocyclic lesion 3,N4-etheno-2'-deoxycytidine opposite 2'-deoxyguanosine. *Biochemistry* 36(39):11933-11943. <https://doi.org/10.1021/bi9705725>.
- Edmonds LD, Anderson CE, Flynt JW, et al. 1978. Congenital central nervous system malformations and vinyl chloride monomer exposure: a community study. *Teratology* 17(2):137-142. <https://doi.org/10.1002/tera.1420170205>.
- EPA. 2000. Vinyl chloride. Integrated Risk Information System (IRIS). Cincinnati, OH: U.S. Environmental Protection Agency. https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=1001. August 7, 2000.
- Feron VJ, Hendriksen CF, Speek AJ, et al. 1981. Lifespan oral toxicity study of vinyl chloride in rats. *Food Cosmet Toxicol* 19(3):317-333. [https://doi.org/10.1016/0015-6264\(81\)90391-6](https://doi.org/10.1016/0015-6264(81)90391-6).
- Filser JG, Bolt HM. 1979. Pharmacokinetics of halogenated ethylenes in rats. *Arch Toxicol* 42(2):123-136. <https://doi.org/10.1007/BF00316492>.
- Fučić A, Horvat D, Dimitrovic B. 1990. Localization of breaks induced by vinyl chloride in the human chromosomes of lymphocytes. *Mutat Res* 243(2):95-99. [https://doi.org/10.1016/0165-7992\(90\)90029-j](https://doi.org/10.1016/0165-7992(90)90029-j).
- Fučić A, Hitrec V, Garaj-Vrhovac V, et al. 1995. Relationship between locations of chromosome breaks induced by vinyl chloride monomer and lymphocytosis. *Am J Ind Med* 27(4):565-571. <https://doi.org/10.1002/ajim.4700270409>.
- Fučić A, Hitrec V, Garaj-Vrhovac V, et al. 1997. Clinical cytogenetics and toxogenetics with the common aim-risk assessment of chemical mutagens. *Cytogenet Cell Genet* 77(1-2):69. <https://doi.org/10.1159/000317460>.
- Gedigke P, Muller R, Bechtelsheimer H. 1975. Morphology of liver damage among polyvinyl chloride production workers. A report on 51 cases. *Ann N Y Acad Sci* 246:278-285. <https://doi.org/10.1111/j.1749-6632.1975.tb51103.x>.
- Grainger RG, Walker AE, Ward AM. 1980. Vinyl chloride monomer-induced disease: Clinical, radiological and immunological aspects. In: Preger L, ed. *Induced disease, drug, irradiation, occupation*. New York, NY: Grune and Stratton, 191-214.
- Guengerich FP, Ghodke PP. 2021. Etheno adducts: from tRNA modifications to DNA adducts and back to miscoding ribonucleotides. *Genes Environ* 43(1):24. <https://doi.org/10.1186/s41021-021-00199-x>.
- Guengerich FP, Crawford WM, Watanabe PG. 1979. Activation of vinyl chloride to covalently bound metabolites: roles of 2-chloroethylene oxide and 2-chloroacetaldehyde. *Biochemistry* 18(23):5177-5182. <https://doi.org/10.1021/bi00590a023>.
- Guengerich FP, Mason PS, Stott WJ, et al. 1981. Roles of 2-haloethylene oxide and 2-haloacetaldehydes derived from vinyl bromide and vinyl chloride in irreversible binding to protein and DNA. *Cancer Res* 41:4391-4398.
- Gwinner LM, Laib RJ, Filser JG, et al. 1983. Evidence of chloroethylene oxide being the reactive metabolite of vinyl chloride towards DNA: Comparative studies with 2,2'-dichlorodiethyl ether. *Carcinogenesis* 4(11):1483-1486. <https://doi.org/10.1093/carcin/4.11.1483>.
- Heath CW, Fable H, Creech JL. 1975. Characteristics of cases of angiosarcoma of the liver among vinyl chloride workers in the United States. *Ann N Y Acad Sci* 246:231-236. <https://doi.org/10.1111/j.1749-6632.1975.tb51097.x>
- Hefner RE, Watanabe PG, Gehring PJ. 1975. Preliminary studies on the fate of inhaled vinyl chloride monomer (VCM) in rats. *Environ Health Perspect* 11:85-95. <https://doi.org/10.1289/ehp.751185>.
- Ho SF, Phoon WH, Gan SL, et al. 1991. Persistent liver dysfunction among workers at a vinyl chloride monomer polymerization plant. *J Soc Occup Med* 41(1):10-16. <https://doi.org/10.1093/ocmed/41.1.10>.
- IARC. 2012. Chemical agents and related occupations. IARC Monographs on the evaluation of carcinogenic risks to humans. Vol. 100F. Lyon, France: International Agency for Research on Cancer. <https://publications.iarc.fr/123>. February 4, 2021.

- Infante PF, Wagoner JK, Waxweiler RJ. 1976. Carcinogenic, mutagenic and teratogenic risks associated with vinyl chloride. *Mutat Res* 41:131-141. [https://doi.org/10.1016/0027-5107\(76\)90083-x](https://doi.org/10.1016/0027-5107(76)90083-x).
- Jenkins LJ, Andersen ME. 1978. 1,1-Dichloroethylene nephrotoxicity in the rat. *Toxicol Appl Pharmacol* 46(1):131-141. [https://doi.org/10.1016/0041-008x\(78\)90144-8](https://doi.org/10.1016/0041-008x(78)90144-8).
- John JA, Smith FA, Leong BK, et al. 1977. The effects of maternally inhaled vinyl chloride on embryonal and fetal development in mice, rats, and rabbits. *Toxicol Appl Pharmacol* 39(3):497-513. [https://doi.org/10.1016/0041-008x\(77\)90141-7](https://doi.org/10.1016/0041-008x(77)90141-7).
- John JA, Smith FA, Schwetz BA. 1981. Vinyl chloride: inhalation teratology study in mice, rats and rabbits. *Environ Health Perspect* 41:171-177. <https://doi.org/10.1289/ehp.8141171>.
- Krajewski J, Dobecki M, Gromiec J. 1980. Retention of vinyl chloride in the human lung. *Br J Ind Med* 37(4):373-374. <https://doi.org/10.1136/oem.37.4.373>.
- Laib RJ. 1982. Specific covalent binding and toxicity of aliphatic halogenated xenobiotics. *Q Rev Drug Metab Drug Interact* 4(1):1-48. <https://doi.org/10.1515/dmdi.1982.4.1.1>.
- Langauer-Lewowicka H, Dudziak Z, Byczkowska Z, et al. 1976. Cryoglobulinemia in Raynaud's phenomenon due to vinyl chloride. *Int Arch Occup Environ Health* 35:197-207. <https://doi.org/10.1007/BF00378274>.
- Langauer-Lewowicka H, Kurzbauer H, Byczkowska Z, et al. 1983. Vinyl chloride disease-neurological disturbances. *Int Arch Occup Environ Health* 52(2):151-157. <https://doi.org/10.1007/BF00405418>.
- Lester D, Greenberg LA, Adams WR. 1963. Effects of single and repeated exposures of humans and rats to vinyl chloride. *Am Ind Hyg Assoc J* 24:265-275. <https://doi.org/10.1080/00028896309342963>.
- Lilis R, Anderson H, Nicholson WJ, et al. 1975. Prevalence of disease among vinyl chloride and polyvinyl chloride workers. *Ann NY Acad Sci* 246:22-41. <https://doi.org/10.1111/j.1749-6632.1975.tb51078.x>.
- Maltoni C, Lefemine G, Ciliberti A, et al. 1981. Carcinogenicity bioassays of vinyl chloride monomer: a model of risk assessment on an experimental basis. *Environ Health Perspect* 41:3-29. <https://doi.org/10.1289/ehp.81413>.
- Marsteller HJ, Lebach WK, Muller R, et al. 1975. Unusual splenomegalic liver disease as evidenced by peritoneoscopy and guided liver biopsy among polyvinyl chloride production workers. *Ann NY Acad Sci* 246:95-134. <https://doi.org/10.1111/j.1749-6632.1975.tb51085.x>.
- NIOSH. 1977. A cross-sectional epidemiologic survey of vinyl chloride workers. Cincinnati, OH: National Institute for Occupational Safety and Health. PB274193. <https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/PB274193.xhtml>. August 29, 2021.
- NTP. 2021d. Vinyl halides. 15th Report on carcinogens. National Toxicology Program. <https://ntp.niehs.nih.gov/sites/default/files/ntp/roc/content/profiles/vinylhalides.pdf>. January 23, 2023.
- Ostlere LS, Harris D, Buckley C, et al. 1992. Atypical systemic sclerosis following exposure to vinyl chloride monomer. A case report and review of the cutaneous aspects of vinyl chloride disease. *Clin Exp Dermatol* 17(3):208-210. <https://doi.org/10.1111/j.1365-2230.1992.tb00210.x>.
- Pan W, Yu S, Jia J, et al. 2021. Deregulation of the cell cycle and related microRNA expression induced by vinyl chloride monomer in the hepatocytes of rats. *Toxicol Ind Health* 37(6):365-376. <https://doi.org/10.1177/07482337211015591>.
- Pandya GA, Moriya M. 1996. 1,N6-ethenodeoxyadenosine, a DNA adduct highly mutagenic in mammalian cells. *Biochemistry* 35(35):11487-11492. <https://doi.org/10.1021/bi960170h>.
- Patty FA, Yapt WP, Waite CP. 1930. Acute response of guinea pigs to vapors of some new commercial organic compounds. V. Vinyl chloride. *Public Health Rep* 45:1963-1971. <https://doi.org/10.2307/4581959>.
- Reitz RH, Gargas ML, Andersen ME, et al. 1996. Predicting cancer risk from vinyl chloride exposure with a physiologically based pharmacokinetic model. *Toxicol Appl Pharmacol* 137(2):253-267. <https://doi.org/10.1006/taap.1996.0079>.
- Rioux KL, Delaney S. 2020. 1,N(6)-Ethenoadenine: From molecular to biological consequences. *Chem Res Toxicol* 33(11):2688-2698. <https://doi.org/10.1021/acs.chemrestox.0c00326>.

- Rosenman KD, Rizzo JE, Conomos MG, et al. 1989. Central nervous system malformations in relation to two polyvinyl chloride production facilities. *Arch Environ Health* 44(5):279-282. <https://doi.org/10.1080/00039896.1989.9935894>.
- Ruckart PZ, Bove FJ, Maslia M. 2013. Evaluation of exposure to contaminated drinking water and specific birth defects and childhood cancers at Marine Corps Base Camp Lejeune, North Carolina: a case-control study. *Environ Health* 12:104. <https://doi.org/10.1186/1476-069x-12-104>.
- Rusyn I, Arzuaga X, Cattley RC, et al. 2021. Key characteristics of human hepatotoxicants as a basis for identification and characterization of the causes of liver toxicity. *Hepatology* 74(6):3486-3496. <https://doi.org/10.1002/hep.31999>.
- Saad AAA, Mohsen MA, Kandil SM, et al. 2017. Predictive values of some atherogenic risk factors in young workers occupationally exposed to vinyl chloride and heavy metals. *Arabian J Chem* 10(1):100-108. <https://doi.org/10.1016/j.arabjc.2014.01.003>.
- Sakabe H. 1975. Bone lesions among polyvinyl chloride production workers in Japan. *Ann NY Acad Sci* 246:78-79. <https://doi.org/10.1111/j.1749-6632.1975.tb51082.x>
- Sharma RP, Gehring PJ. 1979. Immunologic effects of vinyl chloride in mice. *Ann N Y Acad Sci* 320:551-563. <https://doi.org/10.1111/j.1749-6632.1979.tb56633.x>.
- Sharma RP, Yakel HO, Gehring PJ. 1980. Immunotoxicologic studies with vinyl chloride in rabbits and mice. *Int J Immunopharmacol* 2(4):295-299. [https://doi.org/10.1016/0192-0561\(80\)90029-6](https://doi.org/10.1016/0192-0561(80)90029-6).
- Singer B. 1996. DNA damage: chemistry, repair, and mutagenic potential. *Regul Toxicol Pharmacol* 23:2-13. <https://doi.org/10.1006/rtph.1996.0002>.
- Singer B, Spengler SJ, Chavez F, et al. 1987. The vinyl chloride-derived nucleoside, N2,3-ethenoguanosine, is a highly efficient mutagen in transcription. *Carcinogenesis* 8(5):745-747. <https://doi.org/10.1093/carcin/8.5.745>.
- Sokal JA, Baranski B, Majka J, et al. 1980. Experimental studies on the chronic toxic effects of vinyl chloride in rats. *J Hyg Epidemiol Microbiol Immunol* 24(3):285-294.
- Spirtas R, McMichael AJ, Gamble J, et al. 1975. The association of vinyl chloride exposures with morbidity symptoms. *Am Ind Hyg Assoc J* 36(10):779-789. <https://doi.org/10.1080/0002889758507339>.
- Suciu I, Drejman I, Valeskai M. 1963. [Investigation of the diseases caused by vinyl chloride]. *Med Interna* 15:967-977. (Spanish)
- Suciu I, Prodan L, Ilea E, et al. 1975. Clinical manifestations in vinyl chloride poisoning. *Ann N Y Acad Sci* 246:53-69. <https://doi.org/10.1111/j.1749-6632.1975.tb51080.x>.
- Talbott EO, Marshall LP, Rager JR, et al. 2015. Air toxics and the risk of autism spectrum disorder: the results of a population based case-control study in southwestern Pennsylvania. *Environ Health* 14:80. <https://doi.org/10.1186/s12940-015-0064-1>.
- Theriault G, Iturra H, Gingras S. 1983. Evaluation of the association between birth defects and exposure to ambient vinyl chloride. *Teratology* 27:359-370. <https://doi.org/10.1002/tera.1420270310>.
- Thornton SR, Schroeder RE, Robison RL, et al. 2002. Embryo-fetal developmental and reproductive toxicology of vinyl chloride in rats. *Toxicol Sci* 68(1):207-219. <https://doi.org/10.1093/toxsci/68.1.207>.
- 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(10):713-718. [https://doi.org/10.1016/0278-6915\(91\)90130-y](https://doi.org/10.1016/0278-6915(91)90130-y).
- Ungvary G, Hudak A, Tatrai E, et al. 1978. Effects of vinyl chloride exposure alone and in combination with trypan blue-applied systematically during all thirds of pregnancy on the fetuses of CFY rats. *Toxicology* 11:45-54. [https://doi.org/10.1016/S0300-483X\(78\)90389-X](https://doi.org/10.1016/S0300-483X(78)90389-X).
- Veltman G, Lange CE, Juhe S, et al. 1975. Clinical manifestations and course of vinyl chloride disease. *Ann N Y Acad Sci* 246:6-17. <https://doi.org/10.1111/j.1749-6632.1975.tb51076.x>.
- Walker AE. 1976. Clinical aspects of vinyl chloride disease: skin. *Proc R Soc Med* 69(4):286-289. <https://doi.org/10.1177/003591577606900420>.

- Ward AM. 1976. Clinical aspects of vinyl chloride disease: Evidence of an immune complex disorder in vinyl chloride workers. *Proc R Soc Med* 69:289-290. <https://doi.org/10.1177/003591577606900421>.
- Watanabe PG, Gehring PJ. 1976. Dose-dependent fate of vinyl chloride and its possible relationship to oncogenicity in rats. *Environ Health Perspect* 17:145-152. <https://doi.org/10.1289/ehp.7617145>.
- Watanabe PG, McGowan GR, Gehring PJ. 1976a. Fate of [¹⁴C]vinyl chloride after single oral administration in rats. *Toxicol Appl Pharmacol* 36(2):339-352. [https://doi.org/10.1016/0041-008x\(76\)90013-2](https://doi.org/10.1016/0041-008x(76)90013-2).
- Watanabe PG, McGowan GR, Madrid EO, et al. 1976b. Fate of [¹⁴C]vinyl chloride following inhalation exposure in rats. *Toxicol Appl Pharmacol* 37(1):49-59. [https://doi.org/10.1016/s0041-008x\(76\)80007-5](https://doi.org/10.1016/s0041-008x(76)80007-5).
- Withey JR. 1976. Pharmacodynamics and uptake of vinyl chloride monomer administered by various routes to rats. *J Toxicol Environ Health* 1:381-394. <https://doi.org/10.1080/15287397609529338>.
- Zelko IN, Taylor BS, Das TP, et al. 2022. Effect of vinyl chloride exposure on cardiometabolic toxicity. *Environ Toxicol* 37(2):245-255. <https://doi.org/10.1002/tox.23394>.

Appendix E. Database Query Strings for Combinations of Chloroform, 1,1-Dichloroethene, Trichloroethylene, and Vinyl Chloride

Information to prepare this profile was obtained via searches of the literature. The search objective was to identify noncancer and cancer toxicity, toxicokinetic, and interaction data from studies of humans and laboratory animals, as well as mechanistic studies using tissue, cell, or *in vitro* systems.

Initial searches of PubMed and Embase were conducted in September 2024 to identify references with records mentioning two or more of the four compounds of interest (chloroform, 1,1-dichloroethylene, trichloroethylene, and vinyl chloride) using Chemical Abstracts Service Registry Numbers (CASRN) and synonyms. Agency review documents were also collected for each of the compounds when available from IARC, EPA Integrated Risk Information System (IRIS) summaries and reviews, and National Toxicology Program (NTP). Table E-1 presents the CASRN and names of the compounds, as well as synonyms used in the search. The ATSDR Toxicological Profiles for chloroform, 1,1-dichloroethylene, trichloroethylene, and vinyl chloride were consulted to identify CASRN. Synonyms were generated by searching EPA's CompTox Chemicals Dashboard and Substance Registry Services and Chemical Abstracts Service (CAS) Common Chemistry database.

Table E-1. Substances Searched for Joint Toxic Action Studies in PubMed and Embase

Component	CAS Registry Number	Synonyms searched
Chloroform	67-66-3	1,1,1-trichloromethane; carbon trichloride; chloroform; chloroforme; chloroformium pro narcosi; cloroformio; cloroformo; formyl trichloride; freon 20; methane trichloride; methenyl chloride; methenyl trichloride; methyl trichloride; methylidyne trichloride; trichloormethaan; trichlormethan; trichloro-methane; trichloroform; trichloromethane; trichloromethyl radical; tricolorometano; (f 20 or f20) and freon; (r 20 or r20) and refrigerant
1,1-Dichloroethene	75-35-4	1,1-dce; 1,1-dichloraethen; 1,1-dichlorethylen; 1,1-dichlorethylene; 1,1-dichloroethene; 1,1-dichloroethylene; 1,1-dicloroetileno; as-dichloroethylene; asym-dichloroethylene; chlorure de vinylidene; diofan a 565s; f 1130a; hcc 1130a; hco 1130a; iso-dichloroethylene; r 1130a; vinylidene chloride; vinylidene dichloride; vinylidine chloride

Table E-1. Substances Searched for Joint Toxic Action Studies in PubMed and Embase

Component	CAS Registry Number	Synonyms searched
Trichloroethylene	79-01-6	1,1,2-trichloroethene; 1,1,2-trichloroethylene; 1,1-dichloro-2-chloroethylene; 1,2,2-trichloroethylene; 1-chloro-2,2-dichloroethylene; acetylene trichloride; algylen; anamenth; benzinol; blacosolv; blancosolv; cecolene; chlorilen; chlorylea; chlorylen; chorylen; circosolv; crawhaspol; densinfluat; dow-tri; dukeron; ethinyl trichloride; ethylene trichloride; f 1120; fleck-flip; flock flip; fluate; germalgene; hco 1120; lanadin; lethurin; lps hdx heavy duty degreaser; narcogen; narkosoid; per-a-clor; perm-a-chlor; petzinol; r 1120; tce (chlorohydrocarbon); threthylen; threthylene; trethylene; tri-clene; tri-plus; triasol; trichloorethen; trichloorethylene; trichloraethen; trichloraethylen; trichloraethylenum; trichloran; trichloren; trichlorethylen; trichlorethylene; trichlorethylenum; trichloroethene; trichloroethylene; trichloroethylenum; triciene; triclene; tricloretene; tricloroetilene; tricloroetileno; trielene; trielin; trielina; trieline; triklone n; trilen; trilene; trilene te-141; trimar; vestrol; vitran; westrosol
Vinyl chloride	75-01-4	1-chloroethene; 1-chloroethylene; chlorethene; chlorethylen; chlorethylene; chloroethene; chloroethylene; chlorure de vinyle; cloroetileno; cloruro de vinilo; cloruro di vinile; ethylene monochloride; f 1140; hco 1140; monochloroethene; monochloroethylene; monovinyl chloride; vinyl c monomer; vinyl chloride; vinylchloride

The query strings used for the literature searches are presented in Table E-2.

Table E-2. Database Query Strings

Database search date	Query string
PubMed 09/2024	((("Trichloroethylene"[mh] OR 79-01-6[rn] OR "1,1,2-Trichloroethene"[tw] OR "1,1,2-Trichloroethylene"[tw] OR "1,1-Dichloro-2-chloroethylene"[tw] OR "1,2,2-Trichloroethylene"[tw] OR "1-Chloro-2,2-dichloroethylene"[tw] OR "Acetylene trichloride"[tw] OR "Algylen"[tw] OR "Anamenth"[tw] OR "Benzinol"[tw] OR "Blacosolv"[tw] OR "Blancosolv"[tw] OR "Cecolene"[tw] OR "Chlorilen"[tw] OR "Chlorylea"[tw] OR "Chlorylen"[tw] OR "Chorylen"[tw] OR "CirCosolv"[tw] OR "Crawhaspol"[tw] OR "Densinfluat"[tw] OR "Dow-Tri"[tw] OR "Dukeron"[tw] OR "Ethinyl trichloride"[tw] OR "Ethylene trichloride"[tw] OR "F 1120"[tw] OR "Fleck-flip"[tw] OR "Flock FLIP"[tw] OR "Fluate"[tw] OR "Germalgene"[tw] OR "HCO 1120"[tw] OR "Lanadin"[tw] OR "Lethurin"[tw] OR "LPS HDX Heavy Duty Degreaser"[tw] OR "Narcogen"[tw] OR "Narkosoid"[tw] OR "Per-A-Clor"[tw] OR "Perm-A-chlor"[tw] OR

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	<p>"Petzinol"[tw] OR "R 1120"[tw] OR "TCE (chlorohydrocarbon)"[tw] OR "Threthylen"[tw] OR "Threthylene"[tw] OR "Trethylene"[tw] OR "Tri-clene"[tw] OR "Tri-plus"[tw] OR "Triasol"[tw] OR "Trichlooretheen"[tw] OR "Trichloorethyleen"[tw] OR "Trichloraethen"[tw] OR "TRICHLORAETHYLEN"[tw] OR "Trichloraethylenum"[tw] OR "Trichloran"[tw] OR "Trichloren"[tw] OR "Trichlorethylen"[tw] OR "Trichlorethylene"[tw] OR "Trichlorethylenum"[tw] OR "TRICHLOROETHENE"[tw] OR "Trichloroethylene"[tw] OR "trichloroethylenum"[tw] OR "triciene"[tw] OR "Triclene"[tw] OR "Tricloretene"[tw] OR "Tricloroetilene"[tw] OR "tricloroetileno"[tw] OR "Trielene"[tw] OR "Trielin"[tw] OR "Trielina"[tw] OR "Trieline"[tw] OR "Triklone N"[tw] OR "Trilen"[tw] OR "Trilene"[tw] OR "Trilene TE-141"[tw] OR "Trimar"[tw] OR "Vestrol"[tw] OR "Vitran"[tw] OR "Westrosol"[tw]) AND ((75-35-4[rn] OR "vinylidene chloride"[nm] OR "1,1-DCE"[tw] OR "1,1-DICHLORAETHEN"[tw] OR "1,1-Dichlorethylen"[tw] OR "1,1-Dichlorethylene"[tw] OR "1,1-dichloroethene"[tw] OR "1,1-Dichloroethylene"[tw] OR "1,1-dicloroetileno"[tw] OR "as-Dichloroethylene"[tw] OR "asym-Dichloroethylene"[tw] OR "Chlorure de vinylidene"[tw] OR "Diofan A 565S"[tw] OR "F 1130a"[tw] OR "HCC 1130a"[tw] OR "HCO 1130a"[tw] OR "Iso-dichloroethylene"[tw] OR "R 1130a"[tw] OR "Vinylidene chloride"[tw] OR "Vinylidene dichloride"[tw] OR "Vinylidine chloride"[tw]) OR ("Vinyl Chloride"[mh] OR 75-01-4[rn] OR "1-Chloroethene"[tw] OR "1-Chloroethylene"[tw] OR "Chlorethene"[tw] OR "Chlorethylen"[tw] OR "Chlorethylene"[tw] OR "Chloroethene"[tw] OR "Chloroethylene"[tw] OR "chlorure de vinyle"[tw] OR "cloroetileno"[tw] OR "Cloruro de Vinilo"[tw] OR "Cloruro di vinile"[tw] OR "ethylene monochloride"[tw] OR "F 1140"[tw] OR "HCO 1140"[tw] OR "monochloroethene"[tw] OR "Monochloroethylene"[tw] OR "monovinyl chloride"[tw] OR "Vinyl c monomer"[tw] OR "Vinyl chloride"[tw] OR "Vinylchloride"[tw]) OR ("Chloroform"[mh] OR 67-66-3[rn] OR "1,1,1-Trichloromethane"[tw] OR "CARBON TRICHLORIDE"[tw] OR "Chloroform"[tw] OR "Chloroforme"[tw] OR "chloroformium pro narcosi"[tw] OR "Chloroformwith amylen"[tw] OR "Chloroformwith ethanol"[tw] OR "Cloroformio"[tw] OR "cloroformo"[tw] OR "Formyl trichloride"[tw] OR "Freon 20"[tw] OR "Methane trichloride"[tw] OR "Methenyl chloride"[tw] OR "Methenyl trichloride"[tw] OR "Methyl trichloride"[tw] OR "Methylidyne trichloride"[tw] OR "Trichloormethaan"[tw] OR "Trichlormethan"[tw] OR "Trichloro-Methane"[tw] OR "Trichloroform"[tw] OR "Trichloromethane"[tw] OR "Trichloromethyl radical"[tw] OR "Triclorometano"[tw] OR ((("F 20"[tw] OR "F20"[tw]) AND "freon**"[tw]) OR ((("R 20"[tw] OR "R20"[tw]) AND "refrigerant**"[tw]))) OR ((75-35-4[rn] OR "vinylidene chloride"[nm] OR "1,1-DCE"[tw] OR "1,1-DICHLORAETHEN"[tw] OR "1,1-Dichlorethylen"[tw] OR "1,1-Dichlorethylene"[tw] OR "1,1-dichloroethene"[tw] OR "1,1-Dichloroethylene"[tw] OR "1,1-dicloroetileno"[tw] OR "as-Dichloroethylene"[tw] OR "asym-Dichloroethylene"[tw] OR "Chlorure de vinylidene"[tw] OR "Diofan A 565S"[tw] OR "F 1130a"[tw] OR "HCC 1130a"[tw] OR "HCO 1130a"[tw] OR "Iso-dichloroethylene"[tw] OR "R 1130a"[tw] OR "Vinylidene chloride"[tw] OR "Vinylidene dichloride"[tw] OR "Vinylidine chloride"[tw]) AND ((("Vinyl Chloride"[mh] OR 75-01-4[rn] OR "1-Chloroethene"[tw] OR "1-Chloroethylene"[tw] OR "Chlorethene"[tw] OR "Chlorethylen"[tw] OR "Chlorethylene"[tw] OR "Chloroethene"[tw] OR "Chloroethylene"[tw] OR "chlorure de vinyle"[tw] OR "cloroetileno"[tw] OR "Cloruro de Vinilo"[tw] OR "Cloruro di vinile"[tw] OR "ethylene monochloride"[tw] OR "F 1140"[tw] OR "HCO 1140"[tw] OR "monochloroethene"[tw] OR "Monochloroethylene"[tw] OR "monovinyl chloride"[tw] OR "Vinyl c monomer"[tw] OR "Vinyl chloride"[tw] OR "Vinylchloride"[tw]) OR ("Chloroform"[mh] OR 67-66-3[rn] OR "1,1,1-Trichloromethane"[tw] OR "CARBON TRICHLORIDE"[tw] OR "Chloroform"[tw] OR "Chloroforme"[tw] OR "chloroformium pro narcosi"[tw] OR "Chloroformwith amylen"[tw] OR "Chloroformwith ethanol"[tw] OR "Cloroformio"[tw] OR "cloroformo"[tw])</p>

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Database search date	Query string
	<p>OR "Formyl trichloride"[tw] OR "Freon 20"[tw] OR "Methane trichloride"[tw] OR "Methenyl chloride"[tw] OR "Methenyl trichloride"[tw] OR "Methyl trichloride"[tw] OR "Methylidyne trichloride"[tw] OR "Trichloormethaan"[tw] OR "Trichlormethan"[tw] OR "Trichloro-Methane"[tw] OR "Trichloroform"[tw] OR "Trichloromethane"[tw] OR "Trichloromethyl radical"[tw] OR "Triclorometano"[tw] OR (("F 20"[tw] OR "F20"[tw]) AND "freon**"[tw]) OR (("R 20"[tw] OR "R20"[tw]) AND "refrigerant**"[tw])) OR (("Vinyl Chloride"[mh] OR 75-01-4[rn] OR "1-Chloroethene"[tw] OR "1-Chloroethylene"[tw] OR "Chlorethene"[tw] OR "Chlorethylen"[tw] OR "Chlorethylene"[tw] OR "Chloroethene"[tw] OR "Chloroethylene"[tw] OR "chlorure de vinyle"[tw] OR "cloroetileno"[tw] OR "Cloruro de Vinilo"[tw] OR "Cloruro di vinile"[tw] OR "ethylene monochloride"[tw] OR "F 1140"[tw] OR "HCO 1140"[tw] OR "monochloroethene"[tw] OR "Monochloroethylene"[tw] OR "monovinyl chloride"[tw] OR "Vinyl c monomer"[tw] OR "Vinyl chloride"[tw] OR "Vinylchloride"[tw]) AND ("Chloroform"[mh] OR 67-66-3[rn] OR "1,1,1-Trichloromethane"[tw] OR "CARBON TRICHLORIDE"[tw] OR "Chloroform"[tw] OR "Chloroforme"[tw] OR "chloroformium pro narcosi"[tw] OR "Chloroformwith amylene"[tw] OR "Chloroformwith ethanol"[tw] OR "Cloroformio"[tw] OR "cloroformo"[tw] OR "Formyl trichloride"[tw] OR "Freon 20"[tw] OR "Methane trichloride"[tw] OR "Methenyl chloride"[tw] OR "Methenyl trichloride"[tw] OR "Methyl trichloride"[tw] OR "Methylidyne trichloride"[tw] OR "Trichloormethaan"[tw] OR "Trichlormethan"[tw] OR "Trichloro-Methane"[tw] OR "Trichloroform"[tw] OR "Trichloromethane"[tw] OR "Trichloromethyl radical"[tw] OR "Triclorometano"[tw] OR (("F 20"[tw] OR "F20"[tw]) AND "freon**"[tw]) OR (("R 20"[tw] OR "R20"[tw]) AND "refrigerant**"[tw])) AND (2004:3000[edat] OR 2004:3000[crdt] OR 2004:3000[mhda] OR 2004:3000[dp])</p>
Embase 09/2024	<p>Limit to (embase and yr="2004 -Current") ((Trichloroethylene/ or 79-01-6.rn. or (1,1,2-Trichloroethene or 1,1,2-Trichloroethylene or 1,1-Dichloro-2-chloroethylene or 1,2,2-Trichloroethylene or 1-Chloro-2,2-dichloroethylene or Acetylene trichloride or Algylen or Anamenth or Benzinol or Blacosolv or Blancosolv or Cecolene or Chlorilen or Chlorylea or Chlorylen or Chorylen or CirCosolv or Crawhaspol or Densinfluat or Dow-Tri or Dukeron or Ethinyl trichloride or Ethylene trichloride or F 1120 or Fleck-flip or Flock FLIP or Fluate or Germalgene or HCO 1120 or Lanadin or Lethurin or LPS HDX Heavy Duty Degreaser or Narcogen or Narkosoid or Per-A-Clor or Perm-A-chlor or Petzinol or R 1120 or TCE chlorohydrocarbon or Threthylen or Threthylene or Trethylene or Tri-clene or Tri-plus or Triazol or Trichlooretheen or Trichloorethylene or Trichloraethen or TRICHLORAETHYLEN or Trichloraethylenum or Trichloran or Trichloren or Trichlorethylen or Trichlorethylene or Trichlorethylenum or TRICHLOROETHENE or Trichloroethylene or trichloroethylenum or triciene or Triclene or Tricloretene or Trichloroetilene or trichloroetileno or Trielene or Trielin or Trielina or Trieline or Triklone N or Trilen or Trilene or Trilene TE-141 or Trimar or Vestrol or Vitran or Westrosol).ti,ab,kf.) and ((75-35-4.rn. or vinylidene chloride/ or (1,1-DCE or 1,1-DICHLORAETHEN or 1,1-Dichlorethylen or 1,1-Dichlorethylene or 1,1-dichloroethene or 1,1-Dichloroethylene or 1,1-dicloroetileno or asym-Dichloroethylene or Chlorure de vinylidene or "Diofan A 565S" or F 1130a or HCC 1130a or HCO 1130a or Iso-dichloroethylene or R 1130a or Vinylidene chloride or Vinylidene dichloride or Vinylidine chloride).ti,ab,kf.) or (Vinyl Chloride/ or 75-01-4.rn. or (1-Chloroethene or 1-Chloroethylene or Chlorethene or Chlorethylen or Chlorethylene or Chloroethene or Chloroethylene or chlorure de vinyle or cloroetileno or Cloruro de Vinilo or Cloruro di vinile or ethylene monochloride or HCO 1140 or monochloroethene or Monochloroethylene or monovinyl chloride or Vinyl c monomer or Vinyl chloride or</p>

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Database search date	Query string
	<p>Vinylchloride).ti,ab,kf.) or (Chloroform/ or 67-66-3.rn. or (1,1,1-Trichloromethane or CARBON TRICHLORIDE or Chloroform or Chloroforme or chloroformium pro narcosi or Chloroformwith amyleno or Chloroformwith ethanol or Cloroformio or cloroformo or Formyl trichloride or Freon 20 or Methane trichloride or Methenyl chloride or Methenyl trichloride or Methyl trichloride or Methylidyne trichloride or Trichloormethaan or Trichlormethan or Trichloro-Methane or Trichloroform or Trichloromethane or Trichloromethyl radical or Triclorometano or ((F 20 or F20) AND freon*) or ((R 20 or R20) AND refrigerant*).ti,ab,kf.)) or ((75-35-4.rn. or vinylidene chloride/ or (1,1-DCE or 1,1-DICHLORAETHEN or 1,1-Dichloroethylen or 1,1-Dichloroethylene or 1,1-dichloroethene or 1,1-Dichloroethylene or 1,1-dicloroetileno or asym-Dichloroethylene or Chlorure de vinylidene or "Diofan A 565S" or F 1130a or HCC 1130a or HCO 1130a or Iso-dichloroethylene or R 1130a or Vinylidene chloride or Vinylidene dichloride or Vinylidine chloride).ti,ab,kf.) and ((Vinyl Chloride/ or 75-01-4.rn. or (1-Chloroethene or 1-Chloroethylene or Chlorethene or Chlorethylen or Chlorethylene or Chloroethene or Chloroethylene or chlorure de vinyle or cloroetileno or Cloruro de Vinilo or Cloruro di vinile or ethylene monochloride or HCO 1140 or monochloroethene or Monochloroethylene or monovinyl chloride or Vinyl c monomer or Vinyl chloride or Vinylchloride).ti,ab,kf.) or (Chloroform/ or 67-66-3.rn. or (1,1,1-Trichloromethane or CARBON TRICHLORIDE or Chloroform or Chloroforme or chloroformium pro narcosi or Chloroformwith amyleno or Chloroformwith ethanol or Cloroformio or cloroformo or Formyl trichloride or Freon 20 or Methane trichloride or Methenyl chloride or Methenyl trichloride or Methyl trichloride or Methylidyne trichloride or Trichloormethaan or Trichlormethan or Trichloro-Methane or Trichloroform or Trichloromethane or Trichloromethyl radical or Triclorometano or ((F 20 or F20) AND freon*) or ((R 20 or R20) AND refrigerant*).ti,ab,kf.)) or ((Vinyl Chloride/ or 75-01-4.rn. or (1-Chloroethene or 1-Chloroethylene or Chlorethene or Chlorethylen or Chlorethylene or Chloroethene or Chloroethylene or chlorure de vinyle or cloroetileno or Cloruro de Vinilo or Cloruro di vinile or ethylene monochloride or HCO 1140 or monochloroethene or Monochloroethylene or monovinyl chloride or Vinyl c monomer or Vinyl chloride or Vinylchloride).ti,ab,kf.) and (Chloroform/ or 67-66-3.rn. or (1,1,1-Trichloromethane or CARBON TRICHLORIDE or Chloroform or Chloroforme or chloroformium pro narcosi or Chloroformwith amyleno or Chloroformwith ethanol or Cloroformio or cloroformo or Formyl trichloride or Freon 20 or Methane trichloride or Methenyl chloride or Methenyl trichloride or Methyl trichloride or Methylidyne trichloride or Trichloormethaan or Trichlormethan or Trichloro-Methane or Trichloroform or Trichloromethane or Trichloromethyl radical or Triclorometano or ((F 20 or F20) AND freon*) or ((R 20 or R20) AND refrigerant*).ti,ab,kf.))</p>