2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO TRICHLOROETHYLENE IN THE UNITED STATES

Trichloroethylene is a major nonflammable industrial solvent. In 2011, the estimated capacity of the commercial production of trichloroethylene in the United States was 270 million pounds. Historically, the most important use of trichloroethylene has been vapor degreasing of metal parts. This use has declined over the past decade due to increased environmental regulations governing trichloroethylene emissions. At the same time, trichloroethylene has found increasing use as a feedstock for the refrigerant, HFC-134a. Trichloroethylene is also widely used as a solvent for extraction, waterless drying and finishing, and as a general purpose solvent in adhesives, lubricants, paints, varnishes, paint strippers, pesticides, and cold metal cleaners. Trichloroethylene was used in the dry cleaning industry; although its general use in this industry was discontinued in the 1950s, it continued to be used in some spot removing products (Bakke et al. 2007; EPA 2017; IARC 2014). EPA (2017) has proposed banning uses of trichloroethylene in aerosol degreasers and spot cleaners.

Trichloroethylene is released to the environment during the course of its manufacture, formulation, and use. It is frequently detected in the atmosphere and in water. In 2017, environmental releases of trichloroethylene reported under the EPA Toxics Release Inventory (TRI) program were 1,886,809 pounds (855.8 metric tons) in air emissions, 34 pounds (0.02 metric tons) in surface water discharges, 115,793 pounds (52.5 metric tons) in releases to soil, and 3,723 pounds (1.7 metric tons) in releases via underground injection.

The most important routes of exposure to trichloroethylene for most members of the general population are inhalation of the compound in ambient air and ingestion of drinking water. Trichloroethylene may evaporate from contaminated groundwater and soil and migrate into air spaces beneath buildings to enter the indoor air, a process termed vapor intrusion. Mean trichloroethylene concentrations measured in air at locations across the United States are generally between 0.01 and 0.3 ppb, although mean levels as high as 3.4 ppb have been reported. Workers, particularly in the degreasing industry, are exposed by inhalation to the highest levels of trichloroethylene, ranging from approximately 1 to 100 ppm. Between 4.5 and 18% of the drinking water supply sources in the United States that are tested on a yearly basis by the EPA have measurable levels of trichloroethylene; these levels are typically <30 ppb. The general population can also be exposed to trichloroethylene by consumption of contaminated foods and by contact

with consumer products containing the compound. Trichloroethylene levels in the low ppb range have been measured in food; however, levels as high as 140 ppb were measured in a few samples.

Data from the National Health and Nutrition Examination Survey (NHANES) show that levels of trichloroethylene were generally below the detection limit of 0.012 ng/mL (ppb) in the blood of 17,419 members of the U.S. general population sampled between 2001 and 2014. Details of the results may be found in Section 6.5.

2.2 SUMMARY OF HEALTH EFFECTS

Available human and animal data indicate that the central nervous system is a target for trichloroethylene toxicity. Acute overexposure to trichloroethylene vapors results in effects that may include central nervous system depression, loss of consciousness, and even death. Available human and animal data identify the kidney, liver, immune system, male reproductive system, and developing fetus as other potential targets of trichloroethylene toxicity. Results from available animal studies suggest that the immune system and developing fetus may represent particularly sensitive targets of trichloroethylene toxicity. Trichloroethylene has been shown to cause dermal and ocular irritation and depressed body weight gain. Increased incidences of tumors in the kidney, liver, and lymphoid tissues have been reported in chronic bioassays of rats and mice exposed to very high levels of trichloroethylene via inhalation and oral exposure routes. Available human data provide strong support for trichloroethylene-induced kidney cancer and somewhat lesser support for trichloroethylene-induced liver cancer and malignant lymphoma in humans. The systemic effects elicited by trichloroethylene are not exposure-route-specific; similar effects can be elicited via oral and inhalation exposure routes. Physiologically-based pharmacokinetic (PBPK) models have been developed and used for route-to-route extrapolation (i.e., for a given effect elicited at a particular exposure level via one exposure route [inhalation or oral], PBPK modeling can predict the exposure level at which the same effect would be induced via the other exposure route). PBPK models have also been employed to predict exposure levels in humans that would result in effects similar to those observed in rodents.

Neurological Effects. Reported neurological effects that have been associated with substantial exposure to trichloroethylene include euphoria, giddiness, lethargy, confusion, subjective symptoms of vestibular impairment (dizziness, headache, nausea), difficulty swallowing, facial effects that indicate possible trigeminal nerve damage (including sensation deficits, jaw weakness, increased blink reflex latency), dysfunction of cranial nerves other than the trigeminal nerve, memory deficits, impaired hearing,

impaired visual function, mood swings, muscle weakness, tremor, decreased psychomotor function, psychotic behavior, impaired cognitive function, and loss of consciousness.

Neurological effects similar to those associated with trichloroethylene exposure in humans have been reported in laboratory animals following acute or repeated inhalation or oral exposures. Short-term oral administration of trichloroethylene to rats resulted in morphological changes in the trigeminal nerve. Increased handling reactivity and increased sleep time (considered possible indicators of mood disturbances) were reported in rats repeatedly exposed to trichloroethylene. Other animal studies reported trichloroethylene-induced neuropathy, auditory impairment, visual impairment, impaired cognitive function, changes in some measures of psychomotor function, behavioral effects, cardiac arrhythmia, and neurochemical or molecular changes.

Cancer. The potential carcinogenicity of inhaled trichloroethylene has been evaluated in numerous epidemiological studies and experimental animal studies. HHS has classified trichloroethylene as "*known to be a human carcinogen*" based on sufficient evidence of carcinogenicity from humans. NTP specifically concluded that trichloroethylene causes kidney cancer in humans based on consistent results of epidemiological studies and has a causal association with non-Hodgkin's lymphoma based on results of several epidemiological studies; however, the epidemiological evidence for non-Hodgkin's lymphoma is less consistent than for kidney cancer. For other cancer types, NTP concluded that evidence from epidemiological studies is inadequate to evaluate associations. IARC has classified trichloroethylene as "carcinogenic to humans" based on sufficient evidence in humans (Group 1), concluding that the epidemiological evidence for kidney cancer is sufficient to establish a causal relationship, and "positive associations" have been observed for non-Hodgkin's lymphoma and liver cancer. EPA has characterized trichloroethylene as "carcinogenic in humans by all routes of exposure." EPA conclusions regarding epidemiological evidence for cancer are similar to the conclusions of NTP: convincing evidence for a causal relationship for trichloroethylene and kidney cancer; strong evidence for a causal relationship for non-Hodgkin's lymphoma, but less consistent that that for kidney cancer; limited evidence for liver cancer; and less evidence for other cancer types.

Hepatic Effects. There is some evidence for trichloroethylene-induced hepatic effects in occupationally-exposed humans; however, limitations generally include lack of quantifiable exposure data and concomitant exposure to other chemicals. Some studies reported changes in blood and urine indices of liver function and enlarged livers in persons occupationally exposed to trichloroethylene.

Where liver effects were observed, exposure levels were likely higher than present-day occupational exposure limits.

Case reports provide more convincing evidence of trichloroethylene-induced hepatic effects in humans. A 37-year-old male with occupational exposure to trichloroethylene and a reportedly unprotected high-level acute exposure to trichloroethylene vapors during the preparation of a solvent mixture presented to a hospital in a jaundiced condition and died several weeks later; acute massive liver necrosis was noted at autopsy. Acute hepatic necrosis was also seen in a degreaser who died after being exposed to trichloroethylene for at least 6 weeks and in another man who had accidentally ingested an unknown amount of trichloroethylene. Two case studies of people hospitalized after intentional acute inhalation of very high concentrations of trichloroethylene showed liver damage at autopsy in one and hepatocyte degeneration revealed by liver biopsy in the other. Liver effects such as jaundice, hepatomegaly, hepatosplenomegaly, hepatitis, and liver failure have been reported in patients with occupational or nonoccupational exposure to trichloroethylene.

Dose-related increases in liver weight and hepatocellular hypertrophy have been consistently reported in trichloroethylene-exposed animals. Increasing severity of liver necrosis with dose was also seen in other studies. Indicators of trichloroethylene-induced peroxisomal proliferation have been reported in both rats and mice; mice appear to be somewhat more sensitive than rats. Relatively high exposure levels were necessary to induce hepatic effects in most animal studies.

Renal Effects. Renal toxicity, as indicated by changes in urinary proteins and N-acetyl-β-d-glucos-aminidase (NAG), was noted in workers exposed to trichloroethylene and other chemicals in the workplace. Changes in urinary proteins were also observed in renal cancer patients with reported exposure to trichloroethylene. A retrospective cohort study of end-stage renal disease in aircraft workers exposed to trichloroethylene and other hydrocarbons reported increased risk for trichloroethylene-related end-stage renal disease. No clear evidence of kidney effects has been reported in studies examining the association of long-term exposure to trichloroethylene in drinking water and adverse health effects.

Acute inhalation exposure of rats to high concentrations of trichloroethylene resulted in increases in urinary glucose, proteins, glucosaminidase, gamma glutamyl transpeptidase, and serum urea nitrogen. Following intermediate-duration (>14 days, but <1 year) inhalation exposure of animals to trichloroethylene, increased kidney weights were observed. Chronic-duration (lifetime) inhalation exposure of rats to trichloroethylene resulted in renal tubular megalonucleocytosis in males but not

females. Mild to moderate cytomegaly and karyomegaly in the renal tubular epithelial cells were observed in an intermediate-duration oral study in mice. Following intermediate-duration oral exposure, effects noted included increased kidney weights, elevated urinary protein and ketones, minimal to mild cytomegaly, and karyomegaly of the renal tubular epithelial cells. Treatment-related nephropathy was observed in rats and mice following chronic oral exposure to trichloroethylene. Rats appeared to be more sensitive than mice. The observed nephropathy was described as cytomegaly, megalonucleocytosis, and degenerative/regenerative tubular alterations dissimilar to lesions characteristic of chronic nephropathy commonly noted in aged animals.

Immunological and Lymphoreticular Effects. Dermal effects in persons occupationally exposed to trichloroethylene may be sensitivity reactions (termed Stevens-Johnson syndrome) in many cases and may include effects on mucous membranes. Other immunological effects observed in occupational settings include decreased numbers of total lymphocytes and selected lymphocyte subsets in blood samples from workers exposed to trichloroethylene that was used for cleaning a variety of materials and products, altered serum inflammatory cytokine levels, and decreases in serum IgG and IgM.

People who drank trichloroethylene-contaminated water in Woburn, Massachusetts, had immunological abnormalities, but these people were also exposed to other volatile chlorinated hydrocarbons in the water. Symptoms of systemic lupus erythematosus were increased in residents of Tucson, Arizona, exposed to trichloroethylene and other chemicals in drinking water. Diffuse fasciitis with eosinophilia (clinically and histologically distinct from scleroderma) was reported in a woman who used well water contaminated with trichloroethylene. The trichloroethylene level was measured at 14 ppm (2,800 times higher than the maximum permissible contaminant level of 0.005 ppm). The woman's condition improved after she started using bottled drinking water.

There is some evidence for an association between occupational exposure to trichloroethylene and the occurrence of scleroderma (systemic sclerosis, a chronic autoimmune disease primarily of the skin). A meta-analysis of these studies indicated increased risk of scleroderma for any exposure to trichloroethylene in men and women. It should be noted that the incidence of scleroderma in women is, on average, 3 times higher than in men, thus making detection of small increases in rate difficult in women.

Results of several animal studies indicate that selected allergic or hypersensitivity reactions are enhanced following oral exposure to trichloroethylene. Exposure of rats and mice to trichloroethylene in the

drinking water resulted in an enhancement of antigen-stimulated reactions. Increased hypersensitivity responses were observed in male mouse pups that had been sensitized by subcutaneous injection of sheep red blood cells (SRBCs) and exposed to trichloroethylene via their mothers during gestation and lactation and postnatally from the drinking water.

Trichloroethylene-induced acceleration of autoimmune disease has been demonstrated in autoimmune-prone strains of mice; reported effects include changes in cytokine levels, autoimmune hepatitis, inflammatory skin lesions, and alopecia. B6C3F1 mice (not particularly susceptible to autoimmune disease) exhibited increased anti-double-stranded deoxyribonucleic acid (DNA) antibodies when exposed to trichloroethylene as adults and decreased thymus weight and decreased plaque-forming cell response when exposed prenatally or neonatally. A decrease in plaque-forming cell response was observed in Sprague-Dawley rats repeatedly exposed to trichloroethylene vapors for 4 weeks at 1,000 ppm.

Animal studies provide some evidence of trichloroethylene-induced immunosuppression. Effects associated with inhalation exposure to trichloroethylene include reduced splenic anti-SRBC IgM response in female rats, decreased serum IgM levels, liver inflammation, splenomegaly, and hyperplasia of lymphatic follicles in an autoimmune-prone strain of male mice, and depressed resistance to *Streptococcus zooepidemicus*. Another animal study, in which mice were exposed to trichloroethylene in the drinking water, showed treatment-related decreases in both cellular- and antibody-mediated immunity; however, the effects did not occur consistently or in a dose-dependent manner.

Reproductive Effects. Possible associations between exposure to organic solvents (including trichloroethylene) and measures of fertility and fecundity have been assessed to some extent in occupationally-exposed men and women. Suggestive evidence of an association between exposure to trichloroethylene and adverse female reproductive outcomes includes reports of reduced fecundability and menstrual cycle disturbances (including amenorrhea). Evidence of trichloroethylene-induced effects in occupationally-exposed men includes reports of decreased potency, altered sex drive or function, decreased sperm quality, and decreased serum levels of reproductive hormones.

Studies in animals demonstrate the toxicity of trichloroethylene to the male reproductive system. Repeated exposures of male rats or mice to high doses of trichloroethylene resulted in effects such as degeneration of epididymal epithelium, decreased sperm quality, testicular atrophy, histopathologic lesions of the testes or epididymides, decreased sperm count and motility, epididymal epithelial damage, decreased serum hormone levels, impaired libido/copulatory behavior, and decreased numbers of sperm

capable of attaching to eggs *in vitro*. Reproductive performance was not tested in most of the animal studies.

Developmental Effects. The potential for trichloroethylene-induced developmental effects in humans has been assessed to some extent. Epidemiological data are typically limited by concomitant exposure to other potentially hazardous substances, and case-control studies are limited by small numbers of cases. Evidence for trichloroethylene-induced developmental effects in humans derives from studies that evaluated exposures to trichloroethylene in workplace or residential environments or from the drinking water.

In one retrospective case-control study, a 3-fold increased rate of spontaneous abortion was reported among women who had been occupationally or nonoccupationally exposed to trichloroethylene (and other solvents) compared to a group of women without trichloroethylene exposure. Other case-control studies found no evidence of increased risk of spontaneous abortion with occupational or nonoccupational exposure of the women or their husbands to trichloroethylene. However, these studies are limited by small numbers of spontaneous abortion. ATSDR found no support for an association between living in an area around Endicott, New York, where residents may have been exposed to volatile organic compounds (including trichloroethylene) via soil vapor intrusion into homes, and rates of spontaneous fetal death. In another study of the same area around Endicott, New York, elevated risk was reported for low birth weight, small for gestational age, term low birth weight, cardiac defects, and conotruncal defects. A 3-fold increased risk of congenital heart defects was reported for women living within 1.32 miles of at least one trichloroethylene-emitting site in the area of Milwaukee, Wisconsin, compared to those living outside the 1.32 mile radius; however, the risk was increased only among those women who were ≥38 years old at delivery. Proximity to trichloroethylene-emitting sites was not of itself a significant factor for risk of congenital heart defects in this study. In a birth outcome analysis conducted in the area of Endicott, New York, where residents may have been exposed to volatile organic compounds (including trichloroethylene) via soil vapor intrusion into homes, total cardiac defects were twice as prevalent as expected. This finding was not linked to trichloroethylene exposure *per se*, and the results did not support an association between living in the study area and increased risk of fetal death. One study reported a 2.5-fold increase in rate of congenital heart disease in children whose parents were exposed to trichloroethylene in the drinking water during the month before conception and the first trimester of pregnancy. Moreover, the rate of congenital heart disease decreased after the trichloroethylene-contaminated wells were shut down. There was suggestive evidence of an association between trichloroethylene exposure and cardiac defects in a survey conducted within an area of New Jersey that

was serviced with trichloroethylene-contaminated public drinking water. Other studies found no association between exposure to trichloroethylene from the drinking water and heart defects.

A small effect on birth weight was noted in a report on adverse birth outcomes for a population living at Camp Lejeune, North Carolina. The study authors reported strong associations between long-term maternal exposure to trichloroethylene in the range of 1 ppm and decreased mean body weight and small for gestational age in male (but not female) infants. The result is limited by small sample size (only 31 total births in the trichloroethylene-exposed group). There was no conclusive effect on birth weight in other studies of individuals exposed to trichloroethylene in the drinking water.

Other developmental effects that have been associated with trichloroethylene in the drinking water include ocular and auditory defects and other central nervous system abnormalities, oral cleft, choanal atresia (a rare respiratory disorder) and hypospadias/congenital chordee, and developmental immunosuppression (reduction in Th1 IL-2 producing T-cells). However, most of these studies are limited in statistical power due to small numbers of cases.

Decreased fetal weight was noted in offspring of rats exposed to 1,800 ppm trichloroethylene vapors 6 hours/day on gestation days (GDs) 0–20. Effects such as decreases in litter size and perinatal survival have been reported in rats at maternally toxic oral doses. Increased incidences of cardiac malformations were observed in fetuses of rat dams exposed to trichloroethylene in the drinking water during premating and gestation or gestation alone at non-maternally toxic concentrations (estimated doses of 0.218, 0.25, and 129 mg/kg/day), but not in fetuses of rat dams administered gavage doses of trichloroethylene during GDs 6–15 at 500 mg/kg/day. The basis for conflicting results regarding trichloroethylene-induced cardiac malformations in the animal studies is not clear; however, it may be due, in part, to differences in procedures used to evaluate fetal cardiac morphology and/or the relative ability to detect cardiac malformations.

Functional alterations were observed in the immune system of young mice exposed to trichloroethylene via their mothers during gestation and postnatal periods via lactation or direct exposure in the drinking water.

Trichloroethylene-induced neurodevelopmental toxicity has been assessed in young animals that were exposed either during *in utero* development via their mothers, or by direct oral exposure during postnatal development. Reduced rearing was reported in young male mice receiving trichloroethylene orally at

doses of 50 and 290 mg/kg/day during postnatal days 10–16. Dose-related altered open-field activity was noted in young rats whose mothers had received dietary trichloroethylene at 75–300 mg/kg/day during gestation and lactation. Other studies have reported decreases in numbers of myelinated fibers, decreased glucose uptake in the brain, and increased activity in the offspring of rats receiving trichloroethylene at an estimated oral dose level of 37 mg/kg/day during premating, mating, gestation, and lactation.

Cardiovascular Effects. Chronic cardiovascular disease has not been reported in workers occupationally exposed to low levels of trichloroethylene, although deaths following acute high-level inhalation exposures to trichloroethylene have been attributed to cardiac arrhythmias. Case studies have described cardiac arrhythmias that in some instances led to death after occupational exposure, or anesthesia. Accidental oral exposure to trichloroethylene has resulted in cardiac arrythmias. Cardiac arrhythmias reported in a small number of people who drank from contaminated wells could not be attributed to trichloroethylene alone. Increased congenital heart defects were noted in another population exposed to trichloroethylene in their drinking water, but a cause-and-effect relationship could not be established. When compared with a national sample, excess of stroke was consistently reported in ATSDR Trichloroethylene Subregistry baseline and follow-up reports of persons environmentally exposed to trichloroethylene. However, inherent limitations in study design preclude establishment of a cause-and-effect relationship.

Studies in laboratory animals have indicated that trichloroethylene-induced cardiac sensitization to catecholamines may explain the arrhythmias that have been documented in humans exposed to high vapor concentrations of this agent. Cardiac arrhythmias were reported in rats exposed to trichloroethylene. Exposure to trichloroethylene has been correlated with cardiac abnormalities in developing chick embryos as well as rat fetuses. Histopathological changes in the heart have not been observed in animals exposed to trichloroethylene following intermediate-duration exposure periods. Changes in serum polyunsaturated fatty acid ratios, which are implicated in cardiovascular disease, have been observed in rats exposed to 300 ppm trichloroethylene vapor for 12 weeks.

2.3 MINIMAL RISK LEVELS (MRLs)

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made for trichloroethylene. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of

effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute-duration exposure (≤14 days), intermediate-duration exposure (15–364 days), and chronic duration exposure (≥365 days) for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

ATSDR reviewed and concurred with the approach presented by EPA for their reference dose (RfD) and reference concentration (RfC) (EPA 2011e). The RfD and RfC are based on the results of oral exposure studies that reported impaired immune function in mice (RfD only) (Peden-Adams et al. 2006), decreased thymus weight in female mice (Keil et al. 2009), and fetal heart malformations in rats (Johnson et al. 2003). EPA used PBPK modeling to calculate internal dose points of departure (idPODs) and to perform route-to-route extrapolation (RfC only) (EPA 2011e). Potential points of departure (PODs) for candidate chronic RfC and RfD values for numerous studies were determined by utilizing the lowest-observed-adverse-effect level (LOAEL)/no-observed-adverse-effect level (NOAEL) approach, benchmark dose (BMD) analysis, and/or physiologically based pharmacokinetic (PBPK) modeling of human and animal data considered suitable for dose-response assessment (EPA 2011e; IRIS 2011). Candidate critical effects included trichloroethylene-induced neurological effects in humans and animals (Albee et al. 2006; Arito et al. 1994a; Barret et al. 1992; Blain et al. 1994; Crofton and Zhao 1997; Gash et al. 2008; Isaacson et al. 1990; Kjellstrand et al. 1987; Kulig 1987; Mhiri et al. 2004; Moser et al. 1995; Nunes et al. 2001; Rebert et al. 1991; Ruijten et al. 1991; Waseem et al. 2001); effects on kidney, liver, and body weight in animals (Boverhof et al. 2013; Buben and O'Flaherty 1985; Kjellstrand et al. 1983b; Maltoni et al. 1986; NCI 1976; NTP 1988, 1990); immunological effects in animals (Boverhof et al. 2013; Cai et al. 2008; Griffin et al. 2000a, 2000b; Kaneko et al. 2000; Keil et al. 2009; Sanders et al. 1982); reproductive effects in humans and animals (Chia et al. 1996; DuTeaux et al. 2004; Forkert et al. 2002; Kan et al. 2007; Kumar et al. 2000a, 2001b; Land et al. 1981; Manson et al. 1984; Narotsky et al. 1995; NTP 1985, 1986; Schwetz et al. 1975; Xu et al. 2004; Zenick et al. 1984); and developmental effects in animals

(Fredriksson et al. 1993; Healy et al. 1982; Isaacson and Taylor 1989; Johnson et al. 2003; Manson et al. 1984; NTP 1985, 1986; Narotsky et al. 1995; Peden-Adams et al. 2006; Taylor et al. 1985).

A PBPK model was employed to calculate an idPOD for plausible internal dose-metrics based on present understanding of the role that different trichloroethylene metabolites play in trichloroethylene toxicity and the mode of action for toxicity. The PBPK model was used to estimate interspecies and intraspecies pharmacokinetic variability and resulted in 99th percentile estimates of human equivalent dose (HED_{99}) or human equivalent concentration (HEC_{99}) for candidate critical effects (EPA 2011e). The PBPK modeling exercise simulated 100 weeks of exposure for humans and was considered representative of continuous lifetime exposure for humans because longer simulations did not add substantially to the average (e.g., doubling the simulated exposure time resulted in less than a few percent change in the resulting HED). The PBPK model was not used for one study that included a complex exposure scenario in which mouse dams were administered trichloroethylene in the drinking water during gestation and lactation and pups were subsequently exposed via their drinking water (Peden-Adams et al. 2006) because no adequate model parameters were available for this exposure scenario.

Oral MRLs. The available database for trichloroethylene was considered adequate for derivation of chronic- and intermediate-duration oral MRLs, which are briefly presented below; see Appendix A for additional information on these values. The database was not considered adequate for derivation of an acute-duration oral MRL.

Chronic-Duration Oral MRL. The chronic-duration oral MRL is based on the results of three critical oral exposure studies that reported immunotoxicity (decreased plaque-forming cell response and increased delayed-type hypersensitivity) in mice (Peden-Adams et al. 2006), decreased thymus weight in female mice (Keil et al. 2009), and fetal heart malformations in rats (Johnson et al. 2003). In the EPA assessment for trichloroethylene (EPA 2011e), independent candidate chronic RfD values were calculated for each of these effects. The Peden-Adams et al. (2006) immunotoxicity LOAEL of 0.37 mg/kg/day was divided by a total uncertainty factor of 1,000 (to account for use of a LOAEL, interspecies extrapolation, and human variability), resulting in a candidate chronic RfD of 0.00037 mg/kg/day. The Keil et al. (2009) thymus weight LOAEL of 0.35 mg/kg/day was used to derive a PBPK model-based human equivalent dose (HED_{99}) of 0.048 mg/kg/day, which was divided by a total uncertainty factor of 100 (to account for use of a LOAEL, interspecies extrapolation, and human variability using a PBPK model), resulting in a candidate chronic RfD of 0.00048 mg/kg/day. The Johnson et al. (2003) fetal heart malformation data were subjected to benchmark dose analysis. The resulting $BMDL_{01}$ (1% extra risk) of

0.0207 mg/kg/day was used to calculate a PBPK model-based HED_{99} of 0.0051 mg/kg/day, which was divided by a total uncertainty factor of 10 (to account for interspecies extrapolation and human variability using a PBPK model). The resulting candidate chronic RfD was 0.00051 mg/kg/day. EPA (2011e) elected to use a chronic RfD value of 0.0005 mg/kg/day and noted that this value was supported by results for multiple effects. ATSDR agreed that this was a reasonable approach. Therefore, the chronic-duration oral MRL is 0.0005 mg/kg/day.

Intermediate-Duration Oral MRL. ATSDR has adopted the chronic-duration oral MRL of 0.0005 mg/kg/day as the intermediate-duration oral MRL for trichloroethylene. The PBPK model used to calculate the idPOD for the chronic value utilized a 100-week simulation to represent continuous lifetime exposure for humans. Sample simulations for a 52-week exposure (within the range of an ATSDR-defined intermediate-duration exposure [15–364 days]) resulted in the same idPOD as the idPOD from the simulation using the 100-week exposure. It should be noted that the co-critical studies (Johnson et al. 2003; Keil et al. 2009; Peden-Adams et al. 2006), which served as basis for the chronic-duration oral MRL for trichloroethylene, each employed intermediate-duration oral exposure.

Acute-Duration Oral MRL. An acute-duration oral MRL was not derived for trichloroethylene due to the lack of adequate human or animal data for exposures ≤14 days in duration. Intermediate-duration oral gestational or early postnatal exposure studies have reported sensitive developmental effects (e.g., cardiac malformations, developmental immunotoxicity). These effects could potentially be elicited by trichloroethylene exposure for <15 days if exposure were to occur during critical periods of development; acute-duration studies have not investigated these potential outcomes. Derivation of an acute-duration oral MRL based on a less sensitive effect might underestimate the health concern. Therefore, using a conservative approach, the intermediate-duration oral MRL for trichloroethylene based on developmental effects is considered protective for acute-duration oral exposure as well.

Inhalation MRLs. The available database for trichloroethylene was considered adequate for derivation of chronic- and intermediate-duration inhalation MRLs, which are briefly presented below; see Appendix A for additional information on these values. The database was not considered adequate for derivation of an acute-duration inhalation MRL.

Chronic-Duration Inhalation MRL. The chronic-duration inhalation MRL is based on the results of two critical oral exposure studies that reported decreased thymus weight in female mice (Keil et al. 2009) and fetal heart malformations in rats (Johnson et al. 2003). In the EPA assessment for trichloroethylene (EPA

2011e), EPA developed a PBPK model, which was used to calculate the idPOD and perform route-to-route extrapolation to human equivalency concentrations (HECs) for these studies. The resulting HEC_{99} values were 0.033 ppm based on thymus weight and 0.0037 ppm based on fetal heart malformations. The HEC_{99} of 0.033 ppm for thymus weight was divided by a total uncertainty factor of 100 (to account for use of a LOAEL and to account for species extrapolation and human variability using a PBPK model); the resulting candidate chronic RfC was 0.00033 ppm. The HEC_{99} of 0.0037 ppm for fetal heart malformations was divided by a total uncertainty factor of 10 (to account for species extrapolation and human variability using a PBPK model); the resulting candidate chronic RfC was 0.00037 ppm. EPA (2011e) selected the midpoint value of the studies (0.0004 ppm, rounded up from 0.00035 ppm) as the chronic RfC for trichloroethylene. ATSDR agreed that this was a reasonable approach. The resulting chronic-duration inhalation MRL is 0.0004 ppm.

Intermediate-Duration Inhalation MRL. ATSDR has adopted the chronic-duration inhalation MRL of 0.0004 ppm as the intermediate-duration inhalation MRL for trichloroethylene. The PBPK model used to calculate the idPOD for the chronic value utilized a 100-week simulation to represent continuous lifetime exposure for humans. Sample simulations for a 52-week exposure (within the range of an ATSDR-defined intermediate-duration exposure [15–364 days]) resulted in the same idPOD as the idPOD from the simulation using the 100-week exposure. It should be noted that the co-critical studies (Johnson et al. 2003; Keil et al. 2009), which served as basis for the MRL, employed intermediate-duration oral exposure.

Acute-Duration Inhalation MRL. An acute-duration inhalation MRL was not derived for trichloroethylene due to the lack of adequate human or animal data for exposures via inhalation (or PBPK model-extrapolated results from oral studies) of ≤14 days in duration. Intermediate-duration oral gestational or early postnatal exposure studies have reported sensitive developmental effects (e.g., cardiac malformations, developmental immunotoxicity). These effects could potentially be elicited by trichloroethylene exposure for <15 days if exposure were to occur during critical periods of development; acute-duration inhalation studies have not investigated these potential outcomes. Derivation of an acute-duration inhalation MRL based on a less sensitive effect might underestimate the health concern.