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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 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 2011, environmental releases of trichloroethylene reported under the EPA Toxics Release Inventory (TRI) program were >2.6 million pounds (1,190 metric tons) in air emissions, 452 pounds (0.21 metric tons) in surface water discharges, 18,364 pounds (8.33 metric tons) in releases to soil, and 9,578 pounds (4.34 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.

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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 3,178 members of the U.S. general population sampled between 2001 and 2006. 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.

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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. Available epidemiological data provide convincing evidence for a causal association between exposure to trichloroethylene and kidney cancer in humans. Although statistically significantly increased risk of kidney cancer was reported in only a few occupational cohort studies and case-control studies, other studies provide suggestive evidence for increased risk. For overall exposure to trichloroethylene, meta-analysis performed using 15 of the most reliable occupational cohort studies and case-control studies resulted in a summary relative risk (RR) estimate of 1.27 (95% confidence interval [CI] 1.13–1.43) for kidney cancer. In a case-control study of 1,097 kidney cancer cases and 1,476 controls in Central Europe, a significant association was reported between occupational exposure to trichloroethylene and risk of kidney cancer; the association was also significant among trichloroethylene-exposed subjects with at least one intact GSTT1, but not among subjects with two deleted alleles. The GSTT1 enzyme is known to conjugate small, halogenated compounds such as trichloroethylene.

There is some evidence for an association between exposure to trichloroethylene and non-Hodgkin's lymphoma. Significantly increased risk for lymphoma with trichloroethylene exposure was reported in three occupational cohort studies, one case-control study, and one population-based case-control study. For overall exposure to trichloroethylene, meta-analysis using results from these studies and 14 other studies considered to meet standards of epidemiologic design and analysis and with a high likelihood of trichloroethylene exposure in individual subjects resulted in a summary RR of 1.23 (95% CI 1.07–1.42) for lymphoma. In other meta-analyses of occupational cohort and case-control studies that explored occupational trichloroethylene exposure in relation to five different lymphatic and hematopoietic cancers, a significant association was reported between trichloroethylene exposure and risk of non-Hodgkin's lymphoma. A study reported a significant association between exposure to trichloroethylene and risk of non-Hodgkin's lymphoma in a cohort of workers at a gaseous diffusion plant.

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Evidence for trichloroethylene-induced liver cancer in humans is less convincing. Reliable information is limited to a few occupational cohort studies, most of which reported RR estimates for liver and gallbladder cancer between 0.5 and 2.0 for overall trichloroethylene exposure; these estimates were generally based on low incidences of liver and gallbladder cancer. However, within a cohort of female workers employed for at least 3 months at trichloroethylene-using companies (118,270 person-years), 7 cases of liver cancer were observed compared to 2.5 expected (standardized incidence ratio [SIR] 2.8; 95% CI 1.13–5.80) and 9 cases of cancer of the biliary tract were observed compared to 3.2 expected (SIR 2.8; 95% CI 1.28–5.80). Incidences of liver cancer or biliary tract cancers among the male workers (588,047 person-years) were not significantly elevated. For overall trichloroethylene exposure, meta-analysis using results from this study and eight other occupational cohort studies considered to meet standards of epidemiologic design and analysis and with a high likelihood of trichloroethylene exposure in individual subjects, the meta-analysis resulted in a summary RR of 1.29 (95% CI 1.07–1.56) for liver and biliary tract cancer. The NRC evaluated available information regarding possible associations between exposure to trichloroethylene and risk for hepatobiliary cancer and concluded that the information is inadequate to determine whether a significant positive association exists.

A population that drank contaminated well water in Woburn, Massachusetts, was reported to have an increase in childhood leukemia. This was supported by a second study of New Jersey communities, which were served by a community water system, where an increase in the standardized mortality ratio for leukemia was found in females exposed to trichloroethylene. Further expansion of the New Jersey population showed a significant elevation of total leukemias, childhood leukemias, acute lymphatic leukemias, and non-Hodgkin's lymphoma in females exposed to >5.0 ppb trichloroethylene. Diffuse large cell/reticulosarcoma non-Hodgkin's lymphoma was significantly elevated in males as well. A relationship between trichloroethylene exposure in drinking water and cancer including non-Hodgkin's lymphoma, multiple myeloma, and leukemia was not observed in a Finnish study. Problems associated with these studies, including exposure to a mixture of chemical contaminants, particularly in one study and the use of statistical methods, have been elucidated by others. Thus, the associations drawn from these studies between the incidence of leukemia and other cancers and the oral exposure to trichloroethylene are suggestive, but not definitive.

Animal studies have shown increases in various types of cancer following high-dose chronic inhalation or oral exposure to trichloroethylene, including cancer of the liver in mice and cancer of the kidney in rats. There is some evidence for trichloroethylene-induced testicular cancer and leukemia in rats and

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lymphomas and lung tumors in mice. It should be noted that the rodent bioassays employed relatively high (maximally-tolerated) chronic exposure levels.

In a Toxicological Review of Trichloroethylene, the EPA concluded that trichloroethylene is “carcinogenic to humans by all routes of exposure” based on convincing evidence of a causal association between trichloroethylene exposure of humans and kidney cancer. Trichloroethylene is listed in the 13th Report on Carcinogens (RoC) as reasonably anticipated to be a human carcinogen. Since the report was released in October 2014, the National Toxicology Program (NTP) has completed its reevaluation of trichloroethylene for a possible change in its listing status in the RoC. The NTP recommends that trichloroethylene be listed in the 14th RoC as known to be a human carcinogen based on sufficient evidence from studies in humans. (See RoC Monograph on Trichloroethylene, available at <http://ntp.niehs.nih.gov/pubhealth/roc/candidates/tce.html>.) The next step is for the NTP to submit this listing recommendation for trichloroethylene to the Secretary of Health and Human Services to review and approve (<http://ntp.niehs.nih.gov/go/rocprocess>) for the 14th RoC. In 1995, the International Agency for Research on Cancer (IARC) concluded that trichloroethylene is “probably carcinogenic to humans”, based on sufficient evidence in experimental animals and limited evidence in humans. An IARC working group of 18 experts from seven countries recently reassessed the carcinogenicity of several chlorinated solvents (including trichloroethylene) and some of their metabolites, and reclassified trichloroethylene as carcinogenic to humans (Group 1). IARC considered trichloroethylene to be a multisite carcinogen (liver, kidney, lung, testes, and hematopoietic system) in rats and mice by inhalation and oral exposure routes. The NRC concluded that there is limited/suggestive evidence of an association between exposure to trichloroethylene and risk of kidney cancer and inadequate/insufficient evidence for determining whether associations exist between exposure to trichloroethylene and risk of cancer at other sites.

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.

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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 two 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-glucosaminidase (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 a significant association between end-stage renal disease and exposure to trichloroethylene (odds ratio [OR] 1.92; 95% CI 1.03–3.59). 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 meganucleocytosis 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

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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 resulted in a significant combined OR for any exposure in men (OR 2.5; 95% CI 1.1–5.4) and a nonsignificant OR in women (OR 1.2; 95% CI 0.58–2.6). 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. Seo and coworkers found that 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

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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.

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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 significant association between rates of spontaneous abortion and occupational or nonoccupational exposure of the women or their husbands to trichloroethylene. However, these studies are limited by small numbers of spontaneous abortion. The Agency for Toxic Substances and Disease Registry 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, a significantly elevated risk of low birth weight, small for gestational age, term low birth weight, cardiac defects, and conotruncal defects was reported. A significant (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 significantly 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. No significant associations between exposure to trichloroethylene and other contaminants from the drinking water and heart defects were observed in other populations.

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A small effect on birth weight was noted in a report on adverse birth outcomes for a population living at Camp LeJeune, North Carolina. Statistical significance was achieved for all births within the trichloroethylene-exposed group and all male births, but not for all female births. 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, neural tube defects, 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 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 pre-mating 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 gestation days 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

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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, poisoning, or anesthesia. Accidental oral exposure to trichloroethylene has resulted in cardiac arrhythmias. 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, statistically significant 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

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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.

A preferred chronic reference dose (RfD) of 0.0005 mg/kg/day and a preferred chronic reference concentration (RfC) of 0.0004 ppm were derived for trichloroethylene (EPA 2011e; IRIS 2011); these values have been adopted as the ATSDR chronic-duration oral MRL and chronic-duration inhalation MRL, respectively. Potential points of departure (PODs) for candidate chronic RfD and RfC 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 (Carney et al. 2006; 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 internal dose POD (idPOD) for plausible internal dose-metrics based on present understanding of the role that different trichloroethylene metabolites play in

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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 (HED₉₉) or human equivalent concentration (HEC₉₉) for candidate critical effects. 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 subsequently exposed via their drinking water (Peden-Adams et al. 2006) because no adequate model parameters were available for this exposure scenario.

Oral MRLs*Chronic-Duration Oral MRL*

ATSDR adopts the preferred chronic RfD of 0.0005 mg/kg/day for trichloroethylene that was derived by EPA (2011e) as the chronic-duration oral MRL for trichloroethylene.

EPA (2011e) determined that the lowest candidate RfDs fall within a narrow range of 0.0003–0.0005 mg/kg/day and are based on results from three studies. Among these three critical studies, the lowest candidate RfD value of 0.0004 mg/kg/day is based on the applied dose LOAEL (the dataset was not amenable to BMD analysis and PBPK modeling was not attempted due to lack of appropriate models/parameters to account for the complicated fetal/pup exposure scenario) and the critical effect is developmental immunotoxicity (decreased plaque-forming cell response and increased delayed-type hypersensitivity) in mice (Peden-Adams et al. 2006). The lowest PBPK model-based candidate RfD value is 0.0005 mg/kg/day for both heart malformations in rats (Johnson et al. 2003) and decreased thymus weights in mice (Keil et al. 2009). EPA determined that these estimates support a preferred chronic RfD of 0.0005 mg/kg/day. EPA elected not to select the most sensitive candidate RfD to represent the RfD for trichloroethylene, but rather selected an RfD that could be supported by multiple effects because individual candidate RfD values are somewhat imprecise, and similar candidate RfD values were obtained for multiple critical effects. This approach is less sensitive to limitations of individual studies. EPA noted that the preferred chronic RfD of 0.0005 mg/kg/day is within 20% of the estimates for the critical effects. EPA also noted that the preferred chronic RfD of 0.0005 mg/kg/day is within approximately a factor of two of the supporting effect estimates of 0.0003 mg/kg/day for toxic

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nephropathy in rats (NTP 1988) and 0.0008 mg/kg/day for increased kidney weight in rats derived using route-to-route extrapolation from an inhalation study (Boverhof et al. 2013).

Intermediate-Duration Oral MRL

No adequate human data are available regarding the effects of intermediate-duration oral exposure to trichloroethylene. The basis for adoption of the preferred chronic RfD of 0.0005 mg/kg/day as the chronic-duration oral MRL is applicable to intermediate-duration oral exposure as well. As noted earlier, the preferred chronic RfD of 0.0005 mg/kg/day is based, in part, on results of PBPK modeling exercises that simulated 100 weeks of exposure for humans. The 100-week simulation 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. 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 (within the range of an ATSDR-defined chronic-duration exposure [≥ 365 days]). Thus, an intermediate-duration oral MRL derived in the same manner as the preferred chronic RfD of 0.0005 mg/kg/day would result in the same value. Therefore, the preferred chronic RfD of 0.0005 mg/kg/day for trichloroethylene derived by EPA (2011e) and adopted as the ATSDR chronic-duration oral MRL is adopted as the intermediate-duration oral MRL as well. 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 EPA (2011e) preferred chronic RfD for trichloroethylene, each employed intermediate-duration oral exposure.

The basis for the adoption of the preferred chronic RfD as the intermediate-duration oral MRL of 0.0005 mg/kg/day is supported by the results of an oral study in mice. Peden-Adams et al. (2006) exposed groups of mouse dams (5/group) to trichloroethylene in the drinking water (0, 1,400, or 14,000 ppm) throughout gestation and lactation and continued exposing the pups to trichloroethylene in the drinking water until pups were 3 or 8 weeks of age at the same concentrations as their mothers. The estimated dam doses were 0, 0.37, and 37 mg/kg/day, respectively. The lowest dose level resulted in decreased plaque-forming cell responses in 3- and 8-week-old pups and increased delayed-type hypersensitivity in 8-week-old pups. A LOAEL approach was used to derive a candidate RfD from the results of Peden-Adams et al. (2006) because BMD analysis of the critical effect data resulted in inadequate model fit caused by supralinear dose-response shape (EPA 2011e). PBPK modeling was not attempted on the results of Peden-Adams et al. (2006) due to lack of appropriate model parameters to

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account for gestational and lactation exposure via the trichloroethylene-exposed dams and additional postnatal exposure of the pups directly from the drinking water (EPA 2011e). The resulting candidate RfD was 0.00037 mg/kg/day based on the LOAEL of 0.37 mg/kg/day (estimated daily dam dose) and application of a total uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for interspecies extrapolation, and 10 for human variability).

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. In particular, available assessments of sensitive developmental effects (e.g., cardiac malformations, developmental immunotoxicity) employed gestational exposure or gestational and early postnatal development periods that exceeded 14 days in duration. An acute-duration oral MRL was not derived because these effects could potentially be elicited by trichloroethylene exposure for <15 days if exposure were to occur during critical periods of development, and such studies are not available. Derivation of an acute-duration oral MRL based on a less sensitive effect might underestimate the health concern.

*Inhalation MRLs**Chronic-Duration Inhalation MRL*

ATSDR adopts the preferred chronic RfC of 0.0004 ppm (0.002 mg/m³) for trichloroethylene that was derived by EPA (2011e) as the chronic-duration inhalation MRL for trichloroethylene.

EPA determined that the lowest PBPK model-based candidate RfCs fall within a narrow range of 0.0003–0.0006 ppm. These candidate RfCs are values derived from route-to-route extrapolation using the PBPK model. For each of the candidate RfCs, the PBPK model was used for interspecies and intraspecies extrapolation, based on the preferred dose metric for each end point. The PBPK model-based candidate RfC values are 0.00037 ppm for cardiac malformations in rat fetuses (Johnson et al. 2003) and 0.00033 ppm for decreased thymus weight in adult mice (Keil et al. 2009). EPA determined that these estimates support a preferred chronic RfC of 0.0004 ppm. EPA elected not to select the most sensitive candidate RfC to represent the preferred chronic RfC for trichloroethylene, but rather selected an RfC that could be supported by multiple effects because individual candidate RfC values are somewhat imprecise and similar candidate RfC values were obtained for multiple critical effects. This approach is less

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sensitive to limitations of individual studies. EPA noted that the preferred chronic RfC of 0.0004 ppm represents the midpoint of the model-based candidate RfC values of 0.00033 and 0.00037 ppm (i.e., 0.00035 ppm, or 0.0004 ppm rounded to one significant digit). EPA also noted that the preferred chronic RfC of 0.0004 ppm is <2-fold different from the supporting effect PBPK model-based candidate RfC of 0.0006 ppm for toxic nephropathy in rats (NTP 1988). The lowest PBPK model-based candidate RfC (for a primary dose-metric) from inhalation studies is 0.001 ppm for kidney effects, which is higher than the route-to-route extrapolated PBPK model-based candidate RfC from the most sensitive oral study. Therefore, the preferred chronic RfC of 0.0004 ppm based on route-to-route extrapolation from studies that employed the oral exposure route is considered protective of immunological and developmental effects from inhalation exposure.

Intermediate-Duration Inhalation MRL

No adequate human data are available regarding the effects of intermediate-duration inhalation exposure to trichloroethylene. The basis for adoption of the preferred chronic RfC of 0.0004 ppm (0.002 mg/m³) derived by EPA (2011e) for trichloroethylene as the chronic-duration inhalation MRL is applicable to intermediate-duration oral exposure to trichloroethylene as well. As noted previously, EPA (2011e) performed PBPK model-based route-to-route extrapolation from the oral studies of Johnson et al. (2003) and Keil et al. (2009) and to derive a preferred chronic RfC of 0.0004 ppm for trichloroethylene. The PBPK model exercise included an adjustment from less-than-lifetime to lifetime continuous exposure by which dose-metrics were converted to daily or weekly averages based on simulations for 100 weeks of exposure for humans. The 100-week exposure period 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 HEC). Sample simulations for a 52-week exposure (within the range of an ATSDR-defined intermediate-duration exposure [15–364 days]) result in the same idPOD as the idPOD from simulations for a 100-week exposure (within the range of an ATSDR-defined chronic duration exposure [≥ 365 days]). Thus, an intermediate-duration inhalation MRL derived in the same manner as the preferred chronic RfC of 0.0004 ppm would result in the same value. Therefore, the preferred chronic RfC of 0.0004 ppm for trichloroethylene derived by EPA (2011e) and adopted as the ATSDR chronic-duration inhalation MRL is adopted as the intermediate-duration inhalation MRL as well. It should be noted that the co-critical studies (Johnson et al. 2003; Keil et al. 2009), which served as basis for the EPA (2011e) preferred chronic RfC for trichloroethylene, employed intermediate-duration oral exposure.

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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. In particular, available assessments of sensitive developmental effects (e.g., cardiac malformations, developmental immunotoxicity) employed gestational exposure or gestational and early postnatal development periods that exceeded 14 days in duration. An acute-duration inhalation MRL was not derived because these effects could potentially be elicited by trichloroethylene exposure for < 15 days if exposure were to occur during critical periods of development, and such studies are not available. Derivation of an acute-duration inhalation MRL based on a less sensitive effect might underestimate the health concern.