ADDENDUM TO THE TOXICOLOGICAL PROFILE FOR TRICHLOROETHYLENE

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ADDENDUM for TRICHLOROETHYLENE

Supplement to the 1997 Toxicological Profile for Trichloroethylene

Background Statement

This addendum to the Toxicological Profile for Trichloroethylene supplements the profile that was released in 1997.

Toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). CERCLA mandates that the Administrator of ATSDR prepare toxicological profiles on substances on the CERCLA Priority List of Hazardous Substances and that the profiles be revised "no less often than once every three years". CERCLA further states that the Administrator will "establish and maintain inventory of literature, research, and studies on the health effects of toxic substances" [Title 42, Chapter 103, Subchapter I, § 9604 (i)(1)(B)].

The purpose of this addendum is to provide, to the public and federal, state, and local agencies a non-peer reviewed supplement of the scientific data that were published in the open peer-reviewed literature since the release of the profile in 1997.

Chapter numbers in this addendum coincide with the Toxicological Profile for Trichloroethylene (1997). This document should be used in conjunction with the profile. It does not replace the profile.

2. HEALTH EFFECTS

Health effects information made available to the public subsequent to publication of the Toxicological Profile for Trichloroethylene dated September 1997 is summarized in this section. Levels of significant exposure (LSE) to trichloroethylene are summarized in Tables 2-1 and 2-1 and Figures 2-1 and 2-2 of the LSE Attachment to this Addendum and include LSE data from the 1997 Toxicological Profile for Trichloroethylene as well as the updated LSE data presented in this Addendum for Trichloroethylene.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

2.2.1 Inhalation Exposure

2.2.1.1 Death

Reported human deaths have been associated with accidental breathing of unusually high levels of trichloroethylene vapors in the workplace (Coopman et al. 2003; Pantucharoensri et al. 2004; Thorburn et al. 2004). Other human deaths were the result of presumed intentional inhalation of concentrated fumes from trichloroethylene-containing substances (Jones and Singer 2008; Takaki et al. 2008).

2.2.1.2 Systemic Effects

Respiratory Effects. In a cohort mortality study of 14,457 aircraft maintenance workers employed for at least 1 year between 1952 and 1956, a significant excess of death from asthma (standardized mortality ratio [SMR] 160; 95% confidence interval [CI] 102–251) was reported for a group of 6,153 workers with reported occupational exposure to trichloroethylene compared to a referent group of workers not exposed to any chemical (Blair et al. 1998). The followup period was 1952–1990 and the trichloroethylene-exposed workers were likely exposed to other chemicals as well. Asthma-related symptoms and lung function decrements were reported in studies of gun manufacturing workers exposed to solvents including trichloroethylene (Cakmak

et al. 2004; Saygun et al. 2007), but the specific role of trichloroethylene in causation of these symptoms could not be established.

Kumar et al. (2002b) reported bronchiolitis and alveolitis in rats exposed to trichloroethylene vapors at 376 ppm, 4 hours/day, 5 days/week for 28 or 90 days; marked edema, presence of mononuclear cells, and unspecified emphysematous changes were noted after 90 days. These rats also exhibited signs of nasal irritation during exposures.

Cardiovascular Effects. In a cohort mortality study of 14,457 aircraft maintenance workers employed for at least 1 year between 1952 and 1956, a significant excess of death from ischaemic heart disease (SMR 108; 95% CI 103–113) was reported for a group of 6,153 workers with reported occupational exposure to trichloroethylene compared to a referent group of workers not exposed to any chemical (Blair et al. 1998). The followup period was 1952–1990, and the trichloroethylene-exposed workers were likely exposed to other chemicals as well.

Hematological Effects. Hematological effects were not observed in rats exposed to trichloroethylene vapors at 1,000 ppm for 6 hours/day, 5 days/week for 28 days (Woolhiser et al. 2006).

Musculoskeletal Effects. Muscle necrosis was reported within 3 hours following the collapse of a 36-year-old female factory worker who was overcome by trichloroethylene vapors used to degrease metal; the exposure included a dermal component (Thorburn et al. 2004).

Hepatic Effects. Liver effects such as jaundice, hepatomegaly, hepatosplenomegaly, hepatitis, and liver failure have been reported in patients with occupational or nonoccupational exposure to trichloroethylene (Anagnostopoulos et al. 2004; Caprioli et al. 2001; Chittasobhaktra et al. 1997; Goon et al. 2001; Huang et al. 2002, 2006; Kamijima et al. 2007; Pantucharoensri et al. 2004). Changes in levels of serum liver enzymes (Xu et al. 2009) and bile acids (Neghab et al. 1997) among individuals exposed to trichloroethylene in the workplace were indicative of liver toxicity.

Kumar et al. (2001a) reported significantly increased liver weight and hepatocellular fatty and necrotic liver lesions in male rats exposed to trichloroethylene vapors at 376 ppm for 4 hours/day 5 days/week for 8, 12, or 24 weeks; the liver lesions became progressively more severe with duration, but quantitative data were not included in the study report. Ramdhan et al. (2008) reported concentration-related increased liver weight (43–64% higher than controls) and minimal to moderate hepatocellular necrosis in male wild type (CYP2E1+/+) mice exposed to trichloroethylene vapors at 1,000 or 2,000 ppm for 8 hours/day on 7 consecutive days; similarly-exposed CYP2E1 null mice exhibited no signs of exposure-related liver effects, indicating that the liver effects in the wild type mice are associated with CYP2E1-mediated metabolism. Only slightly (but statistically significant) increased liver weight was observed in female rats exposed to trichloroethylene vapors at 1,000 ppm for 6 hours/day, 5 days/week for 4 weeks (Woolhiser et al. 2006) or pregnant rats exposed for 6 hours/day on gestation days 6–20 at 600 ppm (Carney et al. 2006); histopathologic liver examinations were not performed.

Renal Effects. Renal toxicity, as indicated by changes in urinary proteins, including N-acetyl-β-d-glucosaminidase (NAG), α□-microglobulin and glutathione S-transferase α, was reported in persons exposed to trichloroethylene and other chemcials (Bolt et al. 2004; Brüning et al. 1999; Carrieri et al. 2007). Green et al. (2004) assessed renal dysfunction in a cross-sectional study of 70 workers exposed to trichloroethylene and 54 age- and sex-matched individuals without trichloroethylene exposure by measuring urinary levels of NAG and albumin. Urinary trichloroacetic acid (TCA) concentration was used to estimate trichloroethylene exposure level (mean 32 ppm; range 0.5–252 ppm). Although urinary levels of NAG and albumin were higher in the trichloroethylene-exposed workers, the values were within the normal range.

Radican et al. (2006) performed a retrospective cohort study of end-stage renal disease in aircraft workers exposed to trichloroethylene and other hydrocarbons by matching an occupational database to the U.S. Renal Data System and examining the all-cause end-stage renal disease using multivariate Cox regression. Among 6,532 aircraft workers with reported trichloroethylene exposure and a group of 3,327 referents with no reported chemical exposure, an approximately 2-fold increased risk of end-stage renal disease was observed for the

trichloroethylene-exposed aircraft workers (odds ratio [OR] 1.92; 95% CI 1.03–3.59) for the period of 1973–1999.

Mensing et al. (2002) reported increased urinary levels of high-molecular-weight proteins and albumin (biomarkers of glomerular damage) and NAG and low-molecular-weight proteins (biomarkers of proximal tubule damage) in male rats exposed to trichloroethylene vapors at 500 ppm, 6 hours/day, 5 days/week for 6 months. Histopathologic examinations of the kidneys revealed perivascular, interstitial inflammation and glomerulonephritis. Increased kidney weight was reported in female rats exposed to trichloroethylene vapors at 1,000 ppm for 6 hours/day, 5 days/week for 4 weeks (Woolhiser et al. 2006).

Endocrine Effects. In occupational studies of men who used trichloroethylene to degrease electronic equipment, increasing years of exposure to trichloroethylene was associated with increased serum dehydroepiandrosterone sulphate and decreases in serum levels of testosterone, follicle-stimulating hormone, and sex-hormone binding globulin (Chia et al. 1997; Goh et al. 1998). Serum androstenedione, cortisol, and aldosterone levels were in normal ranges.

Significantly decreased serum testosterone (31–48% less than that of controls) and decreased testicular 17β-hydroxy steroid dehydrogenase were noted in rats exposed to trichloroethylene vapors at 376 ppm, 4 hours/day, 5 days/week for 12 or 24 weeks (Kumar et al. 2000a).

Dermal Effects. Generalized skin disorders, manifested as irritation and rashes, have resulted from occupational exposure to trichloroethylene (Chittasobhaktra et al. 1997; Huang et al. 2006; Kamijima et al. 2007; Pantucharoensri et al. 2004; Xu et al. 2009). Eosinophilic fasciitis (Hayashi et al. 2000), thought to have immune components, was reported in a 50-year-old Japanese male who had reported occupational exposure to trichloroethylene for 8 years as a young adult. In one group of patients who were occupationally exposed to trichloroethylene and diagnosed with hypersensitivity dermatitis, workplace concentrations were estimated at 18–683 mg/m^3 and the average exposure time was 38.2 days (range 5–90 days) (Xu et al. 2009). Stevens-Johnson syndrome, a severe erythema, was diagnosed in a 36-year-old Chinese male

who worked in a factory where trichloroethylene was used in degreasing machines; the man subsequently died (Goon et al. 2001).

Ocular Effects. Ocular irritation was observed during repeated exposures of rats to trichloroethylene vapors at 376 ppm (Kumar et al. 2002a, 2002b).

Body Weight Effects. Kumar et al. (2001b) reported >20% depressed body weight gain in male rats exposed to trichloroethylene vapors at 376 ppm, 4 hours/day, 5 days/week for 12 or 24 weeks. In other rat studies, no body weight effects were observed following intermittent or continuous exposure to trichloroethylene vapors at exposure levels in the range of 400–2,500 ppm for 2–13 weeks (Albee et al. 2006; Carney et al. 2006; Kaneko et al. 2000; Woolhiser et al. 2006; Xu et al. 2004).

2.2.1.3 Immunological and Lymphoreticular Effects

Dermal effects in persons occupationally exposed to trichloroethylene may be hypersensitivity reactions in some cases (Hayashi et al. 2000; Raşcu et al. 2003; Xu et al. 2009). Iavicoli et al. (2005) reported alterations of the immune system, expressed as significantly altered serum inflammatory cytokine levels (increased interleukin-2 and interferon-γ and decreased interleukin-4), in a group of factory workers who were exposed to trichloroethylene at a mean workplace air concentration of 35±14 mg/m^3 (6.3 ppm) for at least 3 years during degreasing processes. The exposed group was compared to a group of workers not directly involved in the degreasing process and a group of nonexposed office workers. Immune function was not tested in this study.

There is some evidence for an association between occupational exposure to trichloroethylene and the occurrence of scleroderma (systemic sclerosis) (Diot et al. 2002; Garabrant et al. 2003; Nietert et al. 1998). A meta-analysis of these studies, performed by the EPA (2011e) 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). EPA (2011e) noted that the incidence rate of scleroderma in the general population is approximately 5–10 times higher in women

compared with men, in which case, increased risk of scleroderma in male workers may be easier to detect.

Lan et al. (2010) examined lymphocyte subsets among 80 trichloroethylene-exposed workers at factories in China that used trichloroethylene for cleaning a variety of materials and products and 96 unexposed controls (age and sex matched) from other industries. Full-shift personal air monitoring was performed to assess trichloroethylene exposure levels. The trichloroethylene-exposed workers exhibited significantly lower total numbers of lymphocytes, T cells, CD4+ T cells, CD8+ T cells, B cells, and natural killer (NK) cells. When the trichloroethylene-exposed workers were categorized according to exposure level, those in the higher exposure category (≥12 ppm; mean 38 ppm) exhibited more marked decreases in total lymphocytes and lymphocyte subsets than those in the lower exposure category (<12 ppm; mean 5 ppm).

A 64% reduction in splenic anti-sheep red blood cell (SRBC) IgM response was observed in female rats exposed to trichloroethylene vapors at 1,000 ppm, 6 hours/day, 5 days/week for 4 weeks; the no-observed-adverse-effect level (NOAEL) for immunological effects was 300 ppm (Woolhiser et al. 2006). Kaneko et al. (2000) reported dose-related decreased serum IgG levels, liver inflammation, splenomegaly, and hyperplasia of lymphatic follicles in male mice of an autoimmune-prone strain repeatedly exposed to trichloroethylene at concentrations ≥500 ppm for 8 weeks.

2.2.1.4 Neurological Effects

Neurological effects such as unconsciousness and amnesia were described in case reports of acute accidental or intentional overexposure to trichloroethylene vapors, (Adamek and Krupiński 2007; Carrieri et al. 2007; Miller et al. 2002). Caprioli et al. (2001) reported loss of strength and polyneuropathy in a woman who had been exposed to trichloroethylene during a 3-month period of degreasing and antiquing processes (7–8 hours/day) in a poorly-ventilated garage. Sanz et al. (2008) reported a case of disabling myoclonic encephalopathy with progression to thalamic and cerebellar involvement in a 25-year-old woman with a history of 18 months of occupational exposure to trichloroethylene; neurological symptoms persisted after the woman left the job.

Murata et al. (2010) found a significant association between eyes open static postural sway and urinary trichloroethanol in an investigation of 57 workers exposed to trichloroethylene at maximum estimated ambient concentrations <22 ppm; a control group consisted of 60 subjects. Total tremor intensities in nondominant hands differed significantly among three groups of the workers divided according to cumulative exposure index. Ambient trichloroethylene air concentrations were estimated using the equation Y=8.37X+17.12, where X is trichloroethylene in air and Y is total trichloro-compounds (TTC; sum of the trichloroethylene urinary metabolites trichloroethanol and trichloroacetic acid) (Ogata et al. 1971). Murata et al. (2010) reported a mean TTC level of 4.2 mg/L (range 0.6–192.6 mg/L) in the urine from exposed workers; TTC was not detected in the urine of the control subjects. The results of Murata et al. (2010) indicate that even relatively low occupational exposure levels of trichloroethylene may affect neuromotor function.

Bushnell and Oshiro (2000) trained rats to perform a visual signal detection task and assessed their performance when exposed to trichloroethylene during testing. The rats initially exhibited disruption of the task performance, which abated during 9 days of testing. Boyes et al. (2003, 2005) reported trichloroethylene-induced decreased amplitude of visual evoked potentials in rats repeatedly exposed to trichloroethylene vapors at concentrations in the range of 1,000–5,000 ppm; these studies also assessed the effects of exposure concentration and time (Boyes et al. 2003) or predicted brain trichloroethylene levels (Boyes et al. 2005) on the response.

Assessment of relationships between exposure concentration and duration in the observed trichloroethylene-induced hearing loss in rats included exposures to trichloroethylene vapors using 6-hour exposures and either single exposure, repeated exposures for 5 days, or exposures 5 days/week for 4 or 13 weeks (Boyes et al. 2000; Crofton and Zhao 1997). Following the final exposure period, the auditory threshold to a 16 kHz tone was measured and compared to that of a group of air-exposed rats. A single 6-hour exposure at 6,000 ppm resulted in a 14 dB increase in the 16 kHz threshold (NOAEL 4,000 ppm). A significantly increased 16 kHz threshold was noted at 3,200 ppm in the groups exposed for 5 days or 4 weeks, and 13 weeks of exposures at 2,400 ppm resulted in a 21 dB increase in the 16 kHz threshold (NOAEL 1,600 ppm).

F344 rats exposed to 2,500 ppm trichloroethylene for 13 weeks (5 days/week, 6 hours/day) exhibited a decrease in tone pip auditory response primarily at 16 kHz, along with a loss of cochlear hair cells (NOAEL 800 ppm) (Albee et al. 2006). Similar ototoxic effects were reported by Muijser et al. (2000) following exposure of rats to trichloroethylene at 3,000 ppm for 18 hours/day, 5 days/week for 3 weeks. Fechter et al. (1998) reported that the ototoxicity of trichloroethylene in rats could be accounted for by loss of spiral ganglion cells in the middle turn of the cochlea.

Waseem et al. (2001) exposed rats to trichloroethylene vapors at 376 ppm, 4 hours/day, 5 days/week for 180 days and noted significantly increased spontaneous locomotor activity.

2.2.1.5 Reproductive Effects

Studies in men include assessments of reproductive behavior, sperm quality, and fertility. Within two groups of men (n=85) exposed to trichloroethylene during degreasing of electronics at a mean trichloroethylene air concentration of 29.6 ppm (range 9–131 ppm, determined by 8-hour personal air sampling for 12 of the men), a decreased percentage of normal sperm morphology was reported for 48 of the workers with higher levels of trichloroethylene exposure compared to 37 of the workers with lower levels of trichloroethylene exposure (Chia et al. 1996; 1997; Goh et al. 1998). There was no effect on sperm volume, density, or motility; however, prevalence of hyperzoospermia increased with increasing urinary TCA level. Sallmén et al. (1998) found no effect on male fertility in a study that examined paternal occupational exposure to trichloroethylene and time-to-pregnancy among wives. Levels of exposure were determined by questionnaire and urinary TCA levels; however, the presentation of data regarding exposure categories and fertility outcomes precludes meaningful dose-response assessment. Forkert et al. (2003) identified trichloroethylene and its metabolites in the seminal fluid of eight mechanics exposed to trichloroethylene for at least 2 years and diagnosed with clinical infertility. Neither trichloroethylene nor its metabolites were detected in the seminal fluid of five other clinically infertile men at the same clinic who had not been occupationally exposed to trichloroethylene. The study did not include controls exhibiting normal fertility.

Studies in animals demonstrate the toxicity of trichloroethylene to the male reproductive system. Repeated exposures of male rats at trichloroethylene concentrations of 376–1,000 ppm for as little as 1–2 weeks resulted in effects that included degeneration of epididymal epithelium (Kan et al. 2007), increases in abnormal sperm and decreased reproductive success (Kumar et al. 2000b), and decreased numbers of sperm capable of attaching to eggs *in vitro* (Xu et al. 2004). Kumar et al. (2000a, 2000b, 2001b) exposed male rats to trichloroethylene at 376 ppm for 4 hours/day, 5 days/week for up to 24 weeks and noted testicular atrophy and decreases in sperm count and motility. Forkert et al. (2002) reported epididymal epithelium damage in mice exposed to trichloroethylene vapors at 1,000 ppm, 6 hours/day, 5 days/week for 4 weeks.

2.2.1.6 Developmental Effects

No significant associations were observed between occupational exposure to trichloroethylene and rates of spontaneous abortion among women who reported occupational exposure to organic solvents including trichloroethylene (Lindbohm et al. 1990), or women whose husbands were exposed to trichloroethylene (Taskinen et al. 1989). However, these studies are limited by small incidences of spontaneous abortion. No significant associations were observed between occupational exposure to trichloroethylene and time-to-pregnancy.

Yauck et al. (2004) reported results of a case-control study of 4,025 infants born to mothers in Milwaukee, Wisconsin, between 1997 and 1999 (Yauck et al. 2004). The study included a trichloroethylene-exposed group (defined as residing within a 1.32-mile radius of a trichloroethylene-emitting site) and a nonexposed group (residing outside a 1.32-mile radius of a trichloroethylene-emitting site. Using nonexposed mothers <38 years of age as the referent, a 6.2-fold increased risk of congenital heart defects was noted in children of trichloroethylene-exposed mothers who were ≥38 years of age at delivery (OR 6.2; 95% CI 2.6–14.5), but not for children of trichloroethylene-exposed mothers who were <38 years of age at delivery (OR 0.9; 95% CI 0.6–1.2). A 1.9-fold increased risk of congenital heart defects was also noted for children of unexposed mothers who were ≥38 years of age at delivery (OR 1.9; 95% CI 1.1–3.5). These results indicate that maternal age at delivery and trichloroethylene exposure may be a factor in increasing the risk of congenital heart defects.

The Agency for Toxic Substances and Disease Registry (2006, 2008) conducted a cancer and birth outcome analysis in the Endicott, New York, area where residents may have been exposed to volatile organic compounds (VOCs) via soil vapor intrusion (migration of contamination through the soil into structures through cracks in building foundations). Total cardiac defects were twice as prevalent as expected (standardized prevalence ratio [SPR] 2.02; 95% CI 1.23–3.11). There were no cases of neural tube defects, orofacial clefts, or choanal atresia in the study area and results of spontaneous fetal death analysis did not support an association between living in the exposure area and increased risk of fetal death. The findings were not attributable to exposure to trichloroethylene *per se*, although VOCs found in the soil gas included trichloroethylene and perchloroethylene.

There were no indications of trichloroethylene exposure-related developmental effects in pups of rat or mouse dams exposed to trichloroethylene vapors at up to 600 ppm for 6 hours/day, on gestation days (GD) 6–20 (Carney et al. 2006).

2.2.1.8 Cancer

The EPA (2011e) summarized >50 epidemiological studies and selected those studies considered to have been of adequate quality and with a high probability for trichloroethylene exposure to individual subjects for inclusion in meta-analysis exercises designed to assess possible associations between exposure to trichloroethylene and selected cancers. EPA (2011e) focused on kidney cancer, liver cancer, and non-Hodgkin's lymphoma because most studies reported RRs for these cancer sites. Refer to the EPA IRIS Toxicological Review for Trichloroethylene (EPA 2011e) for a detailed discussion of available epidemiological data for trichloroethylene. Some studies reported RRs for cancer at other sites, but the weight of evidence for trichloroethylene-induced cancer at these sites is weaker than that for kidney and liver cancer and non-Hodgkin's lymphoma.

The most convincing evidence for an association between exposure to trichloroethylene and cancer in humans is for kidney cancer. Upon critical review of the available epidemiological

data regarding the possible carcinogenicity of trichloroethylene, the National Research Council (NRC 2006) and the EPA (2011e) determined that there is convincing evidence for a causal association between trichloroethylene exposure and kidney cancer. The EPA (2011e) performed a meta-analysis using up to 15 cohort and case-control studies considered to be of adequate quality and with a high probability for trichloroethylene exposure to individual subjects (Antilla et al. 1995; Axelson et al. 1994; Boice et al. 1999; Brüning et al. 2003; Charbotel et al. 2006; Dosemeci et al. 1999; Greenland et al. 1994; Hansen et al. 2001; Moore et al. 2010; Morgan et al. 1998; Pesch et al. 2000; Raaschou-Nielsen et al. 2003; Radican et al. 2008; Siemiatycki 1991; Zhao et al. 2005). Five of these studies reported significantly increased risk for kidney cancer (Brüning et al. 2003 [OR 2.47; 95% CI 1.36–4,49]; Charbotel et al. 2006 [OR 2.16; 95% CI 1.02–4.60 for highest cumulative dose group]; Dosemeci et al. 1999 [OR 1.96; 95% CI 1.0–4.0 for women]; Raaschou-Nielsen et al. 2003 [standardized incidence ratio (SIR) 1.4; 95% CI 1.0–1.8]; Zhao et al. 2005 (RR 4.90; 95% CI 1.23–19.6). For overall trichloroethylene exposure, primary random effects meta-analysis using all 15 studies resulted in a summary relative risk (RRm) estimate of 1.27 (95% CI 1.13–1.43) for kidney cancer (EPA 2011e). No single study was overly influential, statistically significant RRm values were obtained following the removal of individual studies from the analysis, and there was no significant heterogeneity across the 15 studies. Ten of the 15 studies included in the meta-analysis reported risks for what were considered higher exposure groups (Boice et al. 1999; Brüning et al. 2003; Charbotel et al. 2006; Moore et al. 2010; Morgan et al. 1998; Pesch et al. 2000; Raaschou-Nielsen et al. 2003; Radican et al. 2008; Siemiatycki 1991; Zhao et al. 2005). Meta-analysis using RRs for these studies and null RR estimates (i.e., RR=1.0) for three studies that did not report risk ratios for kidney cancer by “higher exposure” (Antilla et al. 1995; Axelson et al. 1994; Hansen et al. 2001) resulted in a higher RRm value (1.58; 95% CI 1.28–1.96) than the RRm of 1.27 (95% CI 1.13–1.43) from the 15 studies that assessed overall trichloroethylene exposure and suggests that higher-level exposure to trichloroethylene increases the risk of kidney cancer.

Other investigators have performed meta-analyses using published studies regarding trichloroethylene exposure and risk of kidney cancer. Wartenberg et al. (2000) reported RRm values of 1.7 (95% CI 1.1–2.7) for kidney cancer incidence among four trichloroethylene-exposed cohorts (Antilla et al. 1995; Axelson et al. 1994; Blair et al. 1998; Henschler et al. 1995)

and 1.2 (95% CI 0.8–1.7) for kidney cancer mortality among five trichloroethylene-exposed cohorts (Antilla et al. 1995; Axelson et al. 1994; Blair et al. 1998; Henschler et al. 1995; Ritz 1999). Kelsh et al. (2010) reported RRm values of 1.34 (95% CI 1.07–1.67) for what was described as group I cohort studies (Antilla et al. 1995; Axelson et al. 1994; Blair et al. 1998; Boice et al. 1999, 2006; Hansen et al. 2001; Morgan et al. 1998; Raaschou-Nielsen et al. 2003) and 0.88 (95% CI 0.8–1.33) for group II cohort studies in which trichloroethylene exposure was not documented and heterogeneity was not observed (Blair et al. 1998; Chang et al. 2003; Costa et al. 1989; Garabrant et al. 1988; Sélden and Ahlborg 1991). An RRm of 1.33 (95% CI 1.02–1.73) was reported for renal cancer from meta-analysis of renal cancer case-control studies (Charbotel et al. 2006; Dosemeci et al. 1999; Greenland et al. 1994; Pesch et al. 2000; Siemiatycki 1991) for which there was no evidence of heterogeneity (Kelsh et al. 2010). Finally, meta-analysis of selected cohort studies and case-control studies combined with no evidence of heterogeneity resulted in an RRm of 1.24 (95% CI 1.06–1.45) (Kelsh et al. 2010).

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 two cohort studies (Hansen et al. 2001 [SIR 3.5; 95% CI 1.5–6.9 for men]; Raaschou-Nielsen et al. 2003 [SIR 1.24; 95% CI 1.01–1.52]) and one case-control study (Hardell et al. 1994 [OR 7.2; 95% CI 1.3–42]). EPA (2011e) performed a meta-analysis using results from these 3 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 (Antilla et al. 1995; Axelson et al. 1994; Boice et al. 1999; Cocco et al. 2010; Greenland et al. 1994; Miligi et al. 2006; Morgan et al. 1998; Nordstrom et al. 1998; Persson and Fredriksson 1999; Purdue et al. 2011; Radican et al. 2008; Siemiatycki 1991; Wang et al. 2009; Zhao et al. 2005). For overall trichloroethylene exposure, the meta-analysis resulted in an RRm of 1.23 (95% CI 1.07–1.42) for non-Hodgkin's lymphoma (EPA 2011e). NRC (2009) evaluated the epidemiological data and concluded tehre continued to be inadequate/insufficient evidence to determine whether an association exists between trichloroethylene exposure and non-Hodkin's lymphoma.

Evidence for trichloroethylene-induced liver cancer in humans is less convincing. Reliable information is limited to a few cohort studies, most of which reported RRs 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 (SIR 2.8; 95% CI 1.13–5.80) and 9 cases of cancer of the biliary tract cancer were observed compared to 3.2 expected (SIR 2.8; 95% CI 1.28–5.80) (Raaschou-Nielsen et al. 2003). Incidences of liver cancer or biliary tract cancers among the male workers (588,047 person-years) were not significantly elevated. EPA (2011e) performed a meta-analysis using results from nine cohort studies considered to meet standards of epidemiologic design and analysis and with a high likelihood of trichloroethylene exposure in individual subjects (Antilla et al. 1995; Axelson et al. 1994; Boice et al. 1999, 2006; Greenland et al. 1994; Hansen et al. 2001; Morgan et al. 1998; Raaschou-Nielsen et al. 2003; Radican et al. 2008). For overall trichloroethylene exposure, the meta-analysis resulted in a RRm of 1.29 (95% CI 1.07–1.56) for liver and biliary tract cancer (EPA 2011e).

Within the cohort of Danish blue-collar workers assessed by Raaschou-Nielsen et al. (2003), male workers exhibited significantly increased incidences of esophageal adenocarcinomas (23 observed versus 12.7 expected; SIR 1.8 [95% CI 1.15–2.73]) and lung cancer (559 observed versus 401.7 expected; SIR 1.4 [95% CI 1.28–1.51]). Female workers exhibited significantly increased incidences of cervical cancer (62 observed versus 33.5 expected; SIR 1.9 [95% CI 1.42–2.37]) and lung cancer (73 observed versus 39.0 expected; SIR 1.9 [95% CI 1.48–2.35]). However, the NRC (2009) concluded there was inadequate/insufficient evidence to determine whether there was an association between chronic exposure to trichloroethylemne and esophageal cancer.

The National Toxicology Program (NTP) concluded that trichloroethylene is reasonably anticipated to be a human carcinogen based on limited evidence in humans and sufficient evidence in animals (NTP 2005). 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 in humans and kidney cancer (EPA 2011e; IRIS 2011). EPA calculated an adult-based inhalation unit risk of $4x10^{-6}$ per $\mu g/m^3$ (0.02 per ppm) based on human kidney cancer risks reported by Charbotel et al. (2006) and adjusted for potential risk for tumors at multiple sites using human epidemiologic data (EPA 2011e; IRIS 2011). EPA stated that the inhalation unit risk of $4.1x10^{-6}$ per $\mu g/m^3$, calculated from adult exposure data, does not reflect presumed increased early-life susceptibility to trichloroethylene-induced kidney tumors (EPA 2011e; IRIS 2011). For risk assessments based on specific exposure assessments, EPA (2011e; IRIS 2011) recommends the application of age-dependent adjustment factors (ADAFs) of 10 for <2 years of age, 3 for 2–<16 years of age, and 1 for ≥16 years of age (EPA 2005). For full lifetime exposure to a constant exposure level, EPA notes that the ADAF-adjusted unit risk estimate for trichloroethylene is $4.8x10^{-6}$ per $\mu g/m^3$. Based on exposure from age 0 to 70 years, the lower bound estimates on the trichloroethylene air concentrations associated with risk of $1x10^{-4}$, $1x10^{-5}$, $1x10^{-6}$, and $1x10^{-7}$ are 20, 2, 0.2, and 0.02 $\mu g/m^3$, respectively ($4x10^{-3}$, $4x10^{-4}$, $4x10^{-5}$, and $4x10^{-6}$ ppm, respectively) (EPA 2011e; IRIS 2011). These risk levels are presented in Figure 2-1 (see the LSE Attachment).

2.2.2 Oral Exposure

2.2.2.1 Death

Human studies have reported hepatorenal failure as the cause of death following accidental or intentional ingestion of trichloroethylene (De Baere et al. 1997; Liotier et al. 2008; Vattemi et al. 2005).

2.2.2.2 Systemic Effects

Respiratory Effects. Pulmonary congestion and edema were observed in a 43-year-old male who died following an oral overdose of trichloroethylene (De Baere et al. 1997).

Cardiovascular Effects. Cardiac arrhythmia was reported in a 70-year-old woman who supposedly ingested 1 L of 90% trichloroethylene (Moritz et al. 2000). Sinus tachycardia was

observed in a man who ingested approximately 70 mL of trichloroethylene (Brüning et al. 1998) and another man who ingested an unknown amount of trichloroethylene (Vattemi et al. 2005).

Gastrointestinal Effects. Vomiting, diarrhea, hemorrhagic gastritis, and abdominal perforation and necrosis have been reported in people who ingested large amounts of trichloroethylene (De Baere et al. 1997; Liotier et al. 2008; Moritz et al. 2000; Vattemi et al. 2005).

Musculoskeletal Effects. Vattemi et al. (2005) reported skeletal muscle damage in a man who ingested an unknown amount of trichloroethylene.

Hepatic Effects. Davis et al. (2005) reported a significant excess of liver ailments in a cohort of 4,006 white registrants of the ATSDR National Exposure Registry during 1989–2000 with drinking water exposure during the years 1989–2000 in Michigan, Indiana, Illinois, Pennsylvania, and Arizona.

Liver weight was not increased in female mice administered trichloroethylene in the drinking water for 30 weeks; however, the highest dose tested was 3.5 mg/kg/day (Keil et al. 2009).

Body Weight Effects. No treatment-related effects were found on body weight in rats (Waseem et al. 2001) administered trichloroethylene in the drinking water for 16 weeks at concentrations resulting in estimated doses as high as 206 mg/kg/day (Waseem et al. 2001) or in autoimmune-prone female MRL+/+ mice administered trichloroethylene in the drinking water for up to 22 weeks at concentrations resulting in estimated doses as high as 734 mg/kg/day (Griffin et al. 2000a).

DuTeaux et al. (2004) reported mean body weight gains of only 18–19 g in groups of male rats receiving trichloroethylene from the drinking water at 143 or 270 mg/kg/day for 14 days; the control group exhibited a mean body weight gain of 78 g. However, nonstatistically significant differences in mean initial body weight may have influenced the weight gain (mean initial body weight of controls was only 553 g compared to 573 and 606 g for the low- and high-dose groups,

respectively). Cai et al. (2008) reported 26% decreased body weight gain during the first 11 weeks of a 48-week study in which female mice were administered trichloroethylene in the drinking water at concentrations resulting in an author-estimated average trichloroethylene intake of 60 mg/kg/day. As much as 30% depressed mean body weight gain was noted in young mice that received trichloroethylene in the drinking water at 122 mg/kg/day during 4 weeks of postweaning treatment; the mice had also been exposed via their mothers during gestation and lactation (Blossom and Doss 2007). There were no effects on body weight among similarly-treated mice that received trichloroethylene in the drinking water at 31 mg/kg/day (Blossom et al. 2008). A 12% depression in mean terminal body weight was noted in a group of male mice administered trichloroethylene in the drinking water for 12 months at a concentration resulting in an estimated trichloroethylene dose of 3.3 mg/kg/day; there were no effects on terminal body weight of similarly-exposed female rats (Peden-Adams et al. 2008). However, these rats had also been exposed to trichloroethylene via their mothers during gestation.

2.2.2.3 Immunological and Lymphoreticular Effects

Immunosuppression has been studied to some extent in animals orally-exposed to trichloroethylene. The potential for trichloroethylene to accelerate autoimmune diseases has been investigated as well. The MRL+/+, MRL-*lpr*, and NZB x NZW mouse strains spontaneously develop conditions that resemble the human disease, systemic lupus erythematosus (SLE). The MRL-*lpr* and NZB x NZW strains exhibit a high degree of susceptibility with early disease development (6–8 months); the MRL+/+ strain is less severely affected and exhibits later disease development (12 months). The MRL+/+ strain has been used in most studies.

Keil et al. (2009) reported 30% decreased thymus weight and increased serum levels of IgG and selected autoantibodies in female B6C3F1 mice administered trichloroethylene in the drinking water at 1.4 or 14 ppm (estimated trichloroethylene doses of 0.35 and 3.5 mg/kg/day, respectively) for up to 30 weeks. Trichloroethylene did not significantly alter body, spleen, thymus, liver, or kidney weight of NZBWF1 female mice. There was no significant change in overall splenic cellularity of trichloroethylene-exposed mice. Serum autoantibodies to double-

stranded deoxyribonucleic acid (dsDNA) were significantly increased only at 19, 32, and 34 weeks of age (10, 22, and 24 weeks of treatment) in the 1.4 ppm treatment group and at 19 weeks of age in the 14 ppm group of NZBWF1 mice. Significant increases in single-stranded DNA (ssDNA) autoantibodies were detected only in the 1.4 ppm group and only at 23 weeks of age. Levels of serum anti-glomerular antigen autoantibodies increased steadily in control NZWBF1 mice from 11 to 36 weeks of age (as expected for this strain of autoimmune disease-prone mice), and significant changes in trichloroethylene-treated mice occurred during the time period of 11–19 weeks of age. Total serum IgG levels were significantly increased in the 14 ppm group of NZBWF1 at 11 and 36 weeks of age. Trichloroethylene did not alter splenic NK cell activity or T- and B-cell proliferation. There were no indications of trichloroethylene treatment-related pathological lesions of the kidney of either strain. The results suggest that trichloroethylene did not accelerate the onset of autoimmune disease.

Female MRL+/+ mice (Gilbert et al. 1999; Griffin et al. 2000a) were exposed to trichloroethylene in the drinking water for 4, 8, or 22 weeks at concentrations of 0, 2.5, or 5.0 mg/mL (estimated doses of 0, 455, and 734 mg/kg/day, respectively). Significant increases in antinuclear antibodies and total serum immunoglobulins were observed in the trichloroethylene-treated mice, suggestive of an accelerated autoimmune response. A subsequent study (Griffin et al. 2000b) employed lower trichloroethylene concentrations (0, 0.1, 0.5, and 2.5 mg/mL; estimated doses of 0, 21, 100, and 400 mg/kg/day) for 32 weeks and reported peak T-cell activation at 32 weeks.

Cai et al. (2008) exposed female MRL+/+ mice to trichloroethylene in the drinking water at 0 or 0.5 mg/mL (estimated doses of 0 or 60 mg/kg/day) for up to 48 weeks and reported increased serum concentrations of antinuclear antibodies after 36 and 48 weeks, accompanied by histopathological evidence of lymphocyte infiltration in the liver at 36 and 48 weeks and in the pancreas, lung, and kidney at 48 weeks. Immunoglobulin deposits were detected in kidney glomeruli at 48 weeks as well. The results suggest that trichloroethylene promoted inflammation in these organs.

2.2.2.4 Neurological Effects

Among persons in the ATSDR exposure subregistry, a statistically significant increase in impairment of hearing was reported in children <10 years old (Agency for Toxic Substances and Disease Registry 2003; Burg and Gist 1999).

Tremor, general motor restlessness, and coma have been observed in people who ingested large amounts (500–1,000 mL) of trichloroethylene (Liotier et al. 2008; Moritz et al. 2000).

Nunes et al. (2001) reported 25% increased foot splay in rats administered trichloroethylene by gavage (in corn oil) at 2,000 mg/kg/day for 7 days. Degenerative changes in dopaminergic neurons were observed in the substantia nigra from rats administered trichloroethylene by gavage at 1,000 mg/kg/day 5 days/week for 6 weeks; dopamine levels were significantly decreased in the substantia nigra, but not in the striatum (Gash et al. 2008).

2.2.2.5 Reproductive Effects

No treatment-related effects on fertility were seen in female rats receiving trichloroethylene from the drinking water during gestation at estimated doses as high as 129 mg/kg/day (Johnson et al. 1998, 2003). DuTeaux et al. (2004) reported decreased *in vitro* fertilization capacity in sperm from male rats that had been exposed to trichloroethylene in the drinking water for 14 days at concentrations resulting in estimated doses of 143 and 270 mg/kg/day. There were no significant effects on reproductive organ weights, sperm concentration, or percentage of motile sperm, although histopathologic evaluations of testes revealed slight (unspecified) changes in efferent ductile epithelium.

2.2.2.6 Developmental Effects

White et al. (1997) reported verbal naming/language impairment in 6/13 children from the Woburn, Massachusetts population and similar indicators of cognitive impairment in children from two other communities with reported high levels of trichloroethylene in the drinking water

(from 3.3 ppb to as much as 2,440 ppb) for time periods up to 12–25 years. However, these results are based on clinical examination and diagnostic procedures performed on limited numbers of subjects.

Rodenbeck et al. (2000) found no significant association between trichloroethylene in the drinking water and birth weight outcomes in a section of the Tucson, Arizona, area where the trichloroethylene contamination in the drinking water was estimated to have ranged from <5 to 107 µg/L during the period of 1978–1981. In this study, a comparison group without trichloroethylene-contaminated drinking water was selected to match the socioeconomic status of the trichloroethylene-exposed population.

A small effect on birth weight was noted in a report on adverse birth outcomes for a population living at Camp LeJeune, North Carolina (Agency for Toxic Substances and Disease Registry 1997, 1998). The women were exposed some time during gestation. Statistical significance ($p \leq 0.05$) was achieved for all births (n=31) within the trichloroethylene-exposed group (mean birth weight 3,361 kg; standard error [SE] 71.8) compared to 997 unexposed births (mean birth weight 3,469 kg; SE 16.9) and all male births (trichloroethylene-exposed mean birth weight 3,213 kg; SE 113.2; n=12 versus trichloroethylene-unexposed birth weight 3,527 kg; SE 25.2; n=497). The trichloroethylene-exposed female birth weight (n=19) was not significantly different from that of controls (n=500). The study authors cautioned that the small trichloroethylene-exposed group size weakens the causal association.

Johnson et al. (2003) reported results from rat dams administered trichloroethylene in the drinking water at 0.0025, 0.25, 1.5, or 1,100 ppm during gestation (estimated doses of 0.00045, 0.048, 0.218, and 129 mg/kg/day, respectively). The study authors stated that there were no statistically significant differences between controls and trichloroethylene-treated groups regarding maternal and fetal variables other than congenital cardiac abnormalities. Control data were pooled from multiple studies; the study report did not include concurrent control data. Incidences of control fetuses with cardiac abnormalities were 13/606 (2.15%). Incidences of fetuses with cardiac abnormalities in the 0.0025, 0.25, 1.5, and 1,100 ppm groups were 0/144 (0%), 5/110 (4.5%), 9/181 (5.0%), and 11/105 (10.48%), respectively. Compared to the

pooled controls, the incidences of fetuses with cardiac abnormalities were significantly increased only at the 1.5 and 1,100 ppm exposure levels ($p=0.044$ and $p<0.001$, respectively). The study authors also reported results on a per-litter basis (number of litters with at least one fetus that exhibited a cardiac malformation per number of litters). Nine of 55 control litters had one or more fetuses with a cardiac malformation; incidences in the 0.0025, 0.25, 1.5, and 1,100 ppm groups were 0/12, 4/9, 5/13, and 6/9, respectively.

No trichloroethylene-related effect on incidence of cardiac malformations was observed among fetuses of rat dams administered trichloroethylene by gavage (in soybean oil vehicle) on gestation days 6–15 at doses of 0 or 500 mg/kg/day (Fisher et al. 2001). The incidences of fetuses with heart malformations were 13/290 (4.5%) for the trichloroethylene-treated group and 24/367 (6.5%) for the controls. On a litter basis, 12 of 20 litters from the trichloroethylene-treated dams exhibited at least one cardiac malformation compared to 12 of 25 control litters.

Blossom and Doss (2007) assessed the effects of trichloroethylene on the immune system of young MRL+/+ mice that had been exposed via their mothers during gestation and lactation (maternal doses of 123 and 684 mg/kg/day) and for an additional 4 weeks via their drinking water (offspring doses of 122 and 553 mg/kg/day). Significantly increased cytokine IFN-γ production by splenic CD4+ cells, decreased splenic CD8+ and B220+ lymphocytes, increased IgG2a and histone, and altered thymocyte profiles were observed at the low-dose level. At the high dose, increased IFN-γ production by splenic CD4+ cells; decreased splenic CD+4, CD8+, and B220+ lymphocytes; and altered thymocyte profiles were noted. In a subsequent study that employed a single trichloroethylene exposure level (0.1 mg/mL) resulting in a 25.7 mg/kg/day maternal dose and a 31 mg/kg/day dose to the offspring, trichloroethylene treatment resulted in altered immunoregulation as evidenced by increased thymocyte cellularity associated with increased thymocyte subset distribution, increased reactive oxygen species generation in total thymocytes, and increased splenic CD4+ T-cell production of cytokines IFN-γ and IL-2 in females and TNF-α in males (Blossom et al. 2008).

Peden-Adams et al. (2006) administered trichloroethylene to male and female B6C3F1 mice (not prone to autoimmune disease) via the drinking water at 0, 1.4, or 14 ppm during mating,

gestation, and lactation (estimated doses to the dams of 0, 0.37, and 3.7 mg/kg/day). Selected pups were assessed at 3 weeks of age for effects on the immune system (thymus and spleen weights, splenic lymphocyte proliferation, NK cell activity, plaque-forming cell [PFC] response to SRBC, numbers of splenic B220+ cells, and thymic and splenic T-cell immunophenotypes). Other pups were similarly assessed at 8 weeks of age with additional assessments of autoantibodies to dsDNA and delayed-type hypersensitivity response (indicated by foot pad swelling following subcutaneous injection of SRBC). Thymus weights were not affected by trichloroethylene exposure. Spleen weight was depressed by 15% in the 1.4 ppm exposure group of pups at 3 weeks of age. Splenic lymphocyte proliferation and NK cell activity were not affected in pups at either time point. The PFC response was significantly decreased in male and female pups at both trichloroethylene exposure levels; the hypersensitivity response was increased in male pups of both exposure levels. Splenic numbers of B220+ cells were decreased only in 3-week-old pups of the 14 ppm treatment level.

2.2.2.8 Cancer

EPA calculated an adult-based oral slope factor of 4.6×10^{-2} per mg/kg/day (rounded to 5×10^{-2} per mg/kg/day) resulting from PBPK model-based route-to-route extrapolation of the inhalation unit risk estimate based on human kidney cancer risks reported by Charbotel et al. (2006) and adjusted for potential risk for tumors at multiple sites using human epidemiologic data (EPA 2011e; IRIS 2011). EPA stated that the oral slope factor for trichloroethylene should not be used with exposures exceeding 10 mg/kg/day, because above this level, the route-to-route extrapolation relationship is no longer linear (EPA 2011e; IRIS 2011). EPA also stated that the oral slope factor of 4.6×10^{-2} per mg/kg/day, calculated from adult exposure data, does not reflect presumed increased early-life susceptibility to trichloroethylene-induced kidney tumors (EPA 2011e; IRIS 2011). For risk assessments based on specific exposure assessments, EPA (2011e; IRIS 2011) recommends the application of ADAFs of 10 for <2 years of age, 3 for 2–<16 years of age, and 1 for ≥16 years of age (EPA 2005). Based on exposure from age 0 to 70 years with age-specific 90^{th} percentile water consumption rates, rounded to one significant figure, the lower bound estimates (lower 95% confidence limits) on the drinking water concentrations associated

with risk of $1x10^{-4}$, $1x10^{-5}$, $1x10^{-6}$, and $1x10^{-7}$ are 50, 5, 0.5, and 0.05 µg/L, respectively (EPA 2011e; IRIS 2011). These risk levels are presented in Figure 2-2 (see the LSE Attachment).

2.3 TOXICOKINETICS

2.3.1 Absorption

2.3.1.3 Dermal Exposure

Exposure of the forearm and hand of volunteers to 1.3 mmol/L ($3.18x10^4$ ppm) of trichloroethylene in a dynamic exposure cylinder for 20 minutes resulted in peak concentrations of trichloroethylene in the exhaled air at about 30 minutes after the initiation of exposure (Kezic et al. 2000). The calculated average dermal penetration rate was 0.049 cm/hour for trichloroethylene vapor.

Maximum penetration rates for 1 minute exposure of the volar forearm to liquid trichloroethylene occurred within 5 minutes of the start of exposure (modeled based on the time course of trichloroethylene in expired air following dermal versus inhalation exposure) (Kezic et al. 2001). The estimated dermal flux was 430 nmol/cm^2/minute.

To simulate environmental exposures, studies of absorption of trichloroethylene from water and soil were performed in two to four volunteers per exposure scenario (Poet et al. 2000). The estimated dermal permeability coefficients for trichloroethylene in water for 2-hour exposures were 0.015 cm/hour for immersion of the hand (exposed area in the range of 418–581 cm^2) in 4 L of 810–1,300 mg/L of trichloroethylene solution and 0.019 cm/hour for application of a total of 80 mL of 850–1,000 mg/L trichloroethylene solution in occluded patches (exposed area of 50.2 cm^2). The estimated dermal permeability coefficients for trichloroethylene in soil for 2-hour exposures were 0.0074 cm/hour for immersion of the hand in 4 kg of the 4,000–4,200 mg/kg trichloroethylene/soil mixture and 0.0043 cm/hour for application of a total of 80 g of the 3,200–21,000 mg/kg trichloroethylene/soil mixture in occluded patches. The total amounts of trichloroethylene absorbed were estimated at 27–56 g for the hand immersion in

water, 2.8–3.4 g for the water patches, 19–21 g for the hand immersion in soil, and 1.2–11 g for the soil patches. The high level for the soil patches was for the highest trichloroethylene concentration in soil.

Similar experiments with rats indicated that rat skin was significantly more permeable to trichloroethylene in water and soil than was human skin (Poet et al. 2000). Permeability coefficients for rats were estimated at 0.31 cm/hour for exposure to 5 mL of 600–1,600 mg/L solution of trichloroethylene in water for 5 hours in an occluded patch (exposed area of 2.5 cm^2), 0.086 cm/hour for exposure to 1 g of a 5,000–40,600 mg/kg mixture of trichloroethylene in soil for 3 hours in a non-occluded patch (exposed area of 8 cm^2), and 0.09 cm/hour for exposure to 5 g of a 5,300–15,600 mg/kg mixture of trichloroethylene in soil for 5 hours in an occluded patch (exposed area of 8 cm^2). Total amounts of trichloroethylene absorbed were estimated at 2.7–7.5 mg for the occluded water patches, 1.7–15 mg for the non-occluded soil patches, and 14–40 mg for the occluded soil patches, with the higher amounts corresponding to the higher exposure concentrations.

2.3.2 Distribution

Trichloroethylene readily crosses biological membranes, resulting in rapid distribution to tissues regardless of route of exposure (EPA 2011e; NRC 2006). Route of exposure may result in greater initial distribution to portal-of-entry and first-pass organs, and higher distribution of trichloroethylene and its metabolites has been noted to organs involved in metabolism and excretion (liver, kidney, lung). Another important factor in determining distribution is the solubility of trichloroethylene in each organ, as indicated by its partition coefficient (EPA 2011e.) In humans, the tissue having the highest tissue:blood partition coefficient is fat (63.8–70.2) and the organ having the lowest is lung (0.48–1.7). Although adipose tissue also has the highest partition coefficient in rodents, it is smaller (22.7–36.1 in rats and 36.4 in mice) than in humans, indicating lower potential for storage of trichloroethylene in rodent fat than in human fat. A compilation of partition coefficients in these three species is available (EPA 2011e).

2.3.2.1 Inhalation Exposure

Solubility in blood is a major factor determining the trichloroethylene concentration in blood leaving the lungs during inhalation exposure, as indicated by the blood:air partition coefficient. The blood:air partition coefficient has been reported to be 8.1–11.7 in humans, 13.3–25.82 in rats, and 13.4–15.91 in mice (EPA 2011e). Higher tissue concentrations of trichloroethylene were found in accidental occupational inhalation fatalities (12, 21, and 72 mg/kg in kidney, lung, and liver; 40–84 mg/L in blood [Coopman et al. 2003]; 174 mg/L in blood and 809 mg/kg in brain [Ford et al. 1995]).

2.3.2.2 Oral Exposure

Case studies of oral exposure have found measurable levels of trichloroethylene in the blood (De Baere et al. 1997; Yoshida et al. 1996) and lung, kidney, and liver (De Baere et al. 1997).

2.3.3 Metabolism

Although dichloroacetic acid (DCA, a trichloroethylene metabolite) has not been reported in human urine, it has been detected in the urine of rats and in the blood of humans exposed to trichloroethylene (Fisher et al. 1998). Oxygenated trichloroethylene-P450 intermediate can generate trichloroethylene oxide, resulting in the formation of dichloroacetyl chloride, which rearranges to DCA (Cai and Guengerich 2000). DCA also may be formed from the dechlorination of TCA and oxidation of trichloroethanol (Lash et al. 2000a). DCA can be further metabolized to monochloroacetic acid or glyoxylic acid, resulting in the formation of oxalic acid and CO_2 (Lash et al. 2000a; Saghir and Schultz 2002; Tong et al. 1998).

Evidence for DCA formation is equivocal because the use of strong acids in the analytical procedures can produce *ex vivo* conversion of TCA to DCA in blood, thus potentially resulting in an artifactual appearance or augmentation of DCA levels (EPA 2011e; Ketcha et al. 1996; Templin et al. 1995). The rapid metabolism of DCA at low exposure levels *in vivo* (Saghir and Schultz 2002) poses another difficulty in assessing DCA formation. Nevertheless, DCA is

known to be formed from trichloroethylene oxide in aqueous systems (Cai and Guengerich 1999), and has been detected in the serum of mice orally dosed with trichloroethylene using a method that confirmed the absence of artifactual formation of DCA from TCA during sample preparation and analysis (Kim et al. 2009a, 2009b).

The NRC (2006) and the EPA (2011e) have concluded, based on this and other evidence, that oxidative metabolism of trichloroethylene includes the formation of an oxygenated trichloroethylene-P450 complex as well as the epoxide as transient intermediates. Regardless of route of exposure, the majority of oxidative metabolism of trichloroethylene occurs in the liver in humans and animals (EPA 2011e; NRC 2006).

Additional cytochrome P450 isoforms identified as having a role in the oxidative metabolism of trichloroethylene are CYP1A1/2 and CYP2C11/6 (Lipscomb et al. 1997), CYP2F and CYP2B1 (Forkert et al. 2005, 2006), and CYP3A4 (Lipscomb et al. 1997). The overall contribution of these cytochrome P450 isoforms is thought to be small, although CYP2F may be important in bioactivation of trichloroethylene in Clara cells in the mouse lung (Forkert et al. 2006). In addition, although trichloroethylene oxidation is decreased in CYP2E1 knockout mice exposed via inhalation, these knockout mice still had substantial capacity for trichloroethylene oxidation (Kim and Ghanayem 2006).

Oxidation of trichloroethylene to chloral was demonstrated in microsomal fractions from lung of rodents (Green et al. 1997) and from kidney of rodents and humans (Cummings et al. 2001). Pulmonary P450 isoforms important in metabolizing trichloroethylene in the Clara cells were CYP2E1 and CYP2F (Forkert et al. 2005, 2006).

Although the GSH conjugation of many compounds is associated with detoxification, trichloroethylene is bioactivated through the formation of reactive species downstream from the initial GSH conjugation; this process is thought to result in cytotoxic and carcinogenic effects, particularly in the kidney (EPA 2011e; Lash et al. 2000b; NRC 2006). The conjugation of trichloroethylene with GSH produces S-dichlorovinyl-glutathione isomers (DCVG, collectively). These isomers are S-(1,2-dichlorovinyl)glutathione (1,2-DCVG) (EPA 2011e; Lash et al. 2000a,

2000b, 2006; NRC 2006) and S-(2,2-dichlorovinyl)glutathione (2,2-DCVG) (Bernauer et al. 1996; Commandeur and Vermeulen 1990; EPA 2011e). 1,2-DCVG has been identified as a product of trichloroethylene metabolism in rat liver microsomes incubated with GSH (Dekant et al. 1990) and in isolated human and rat liver and kidney cells (Cummings and Lash 2000; Lash et al. 1995, 1999a). Following *in vivo* exposure to trichloroethylene, 1,2-DCVG was detected in human blood (Lash et al. 1999b) and in rat serum, blood, bile, liver, and kidney (Dekant et al. 1990; Kim et al. 2009a; Lash et al. 2006).

The enzymes that mediate the conjugation of trichloroethylene with GSH, glutathione S-transferases, are present in various tissues, including renal tissues, but total amounts are highest in the liver, leading to the assumption that the majority of DCVG is produced in the liver (Lash et al. 2000a, 2000b). Conjugation of trichloroethylene with GSH to form 1,2-DCVG was demonstrated in hepatic and renal subcellular fractions from humans, rats, and mice (Lash and Anders 1989; Lash et al. 1998, 1999a) and in isolated hepatocytes, renal cortical cells, and renal proximal tubule cells from rats (Lash and Anders 1989; Lash et al. 1998).

DCVG formed in the liver can be transported to serum and bile, taken up by the renal brush border, and metabolized to the corresponding S-dichlorovinylcysteine isomers (collectively DCVC). Metabolism of DCVG to S-(1,2-dichlorovinyl)cysteine (1,2-DCVC) or S-(2,2-dichlorovinyl)cysteine (2,2-DCVC) occurs as a two-step process by γ-glutamyl transpeptidase and dipeptidases (Elfvaara and Anders 1984; Goeptar et al. 1995; Lash et al. 1988). The activities of these enzymes (measured with an alternative substrate) are much higher in the kidney than in the liver of humans, rats, and mice (EPA 2011e; Lash et al. 1998). Conversion of DCVG to DCVC also can occur in the bile or gut (EPA 2011e). Any DCVC that is formed in the gut can be reabsorbed into the bloodstream.

Evidence of β-lyase activity has been reported in extrarenal tissues, such as rat and human liver and rat brain, and in intestinal microflora (EPA 2011e).

An additional bioactivating pathway involves the sulfoxidation of DCVC by flavin mono-oxygenase 3 (FMO3) and of its mercapturic acid conjugates by CYP3A. Sulfoxidation of DCVC

by FMO3 was observed in microsomes from rabbit liver (Ripp et al. 1997) and human liver (Krause et al. 2003). Sulfoxidation of DCVC was not detected in microsomes from human kidney, but FMO3 expression was lower in renal microsomes than in hepatic microsomes (Krause et al. 2003).

The relative flux of trichloroethylene through the P450-dependant oxidative pathway versus the GSH-dependent conjugation pathway is uncertain. These pathways are in competition with each other; inhibition of P450 mediated oxidation *in vitro* with renal preparations increases the GSH conjugation of trichloroethylene (Cummings and Lash 2000). The quantitative reliability of reported concentrations of metabolites of either pathway and of rates of GSH conjugation have been questioned because they vary greatly across studies; it has been suggested that the variance in rates of GSH conjugation may be related to different analytical methods (EPA 2011e).

There is evidence to suggest that trichloroethylene is metabolized in the male reproductive tract, primarily in the epididymal epithelium, but also in testicular Leydig cells, by CYP2E1 to chloral, trichloroethanol, and TCA (Forkert et al. 2002, 2003). Furthermore, DCA protein adducts have been detected in the epididymis and efferent ducts of rats administered trichloroethylene (DuTeaux et al. 2003, 2004).

2.3.4 Elimination and Excretion

2.3.4.1 Inhalation Exposure

Following exposure of human subjects to 1 ppm for 6 hours, terminal half-lives for trichloroethylene in alveolar air of 14–23 hours were determined (Chiu et al. 2007).

2.3.4.3 Dermal Exposure

Peak concentrations of trichloroethylene in expired air (approximately 7 nmol/L) occurred approximately 30 minutes following the initiation of exposure of the forearm and hand (1,000 cm^2) of volunteers to trichloroethylene vapor at 1.3 mmol/L ($3.18x10^4$ ppm) in a dynamic

exposure cylinder for 20 minutes (Kezic et al. 2000). Trichloroethylene also was excreted in the breath of volunteers who were exposed dermally to trichloroethylene in water or soil as described previously in Section 2.3.1.3, generally with a slight delay (0.1–0.55 hours) thought to be due to loading of the chemical into the stratum corneum, and reaching peak levels within about 1 hour after the start of exposure (Poet et al. 2000). Volunteers exposed dermally to pure trichloroethylene liquid for 1 minute expired trichloroethylene into the air; the expired air data were used to model permeation rates and were not reported (Kezic et al. 2001).

Rats exposed dermally to trichloroethylene in water and soil as described in Section 2.3.1.3 excreted trichloroethylene in the expired air with peak concentrations occurring within 2 hours of the initiation of exposure to trichloroethylene in water and 1–2 hours of exposure to trichloroethylene in soil (Poet et al. 2000).

2.3.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Numerous PBPK models of trichloroethylene have been reported that have evolved in complexity to address specific problems in toxicokinetics extrapolation (Chiu et al. 2009; EPA 2011e; Evans et al. 2009; Fisher 2000; Hack et al. 2006; Keys et al. 2003; Poet et al. 2000; Simmons et al. 2002; Thrall and Poet 2000). In the early models applied to dosimetry extrapolations, absorbed trichloroethylene was distributed into four flow-limited tissue compartments (liver, fat, rapidly perfused tissue, and slowly perfused tissue), and elimination was attributed to metabolism of trichloroethylene (K_m, V_{max}) in liver (Allen and Fisher 1993; Fisher and Allen 1993; Fisher et al. 1991). Metabolic production of TCA was represented as a fixed proportion of total metabolism, and plasma kinetics of TCA was represented by a single-compartment, first-order model. Subsequent models extended the metabolism simulation to include more complete simulations of metabolism and the metabolites formed (Abbas and Fisher 1997; Fisher et al. 1998; Greenberg et al. 1999). Trichloroethylene metabolism was attributed to conversion to chloral in liver (K_m, V_{max}), and formation of downstream metabolites (DCA, trichloroethylene to TCA, trichloroethanol, and trichloroethanol-glucuronide conjugate) were presented with first-order rate constants (k_i). These included conversion of chloral to TCA, interconversion of chloral and trichloroethanol, conjugation of trichloroethanol to

trichloroethanol-glucuronide conjugate, and conversion of TCA to DCA. Kinetics of each metabolite were simulated with multi-compartment submodels (e.g., flow-limited liver, fat, rapidly perfused and slowly perfused tissue compartments). The models also included first-order excretion in urine of chloral, TCA, trichloroethanol, and trichloroethanol-glucuronide conjugate, and fecal excretion (i.e., biliary) of trichloroethanol-glucuronide conjugate.

An alternative to models of Fisher and colleagues was developed by Clewell et al. (2000) to specifically address dosimetry predictions for carcinogenicity target tissues (lung, kidney, and liver). The Clewell et al. (2000) model distributes absorbed trichloroethylene into seven flow-limited tissue compartments (tracheobronchial region of the respiratory tract, gastrointestinal tract, kidney, liver, fat, and rapidly perfused and slowly perfused tissues). Metabolism is assumed to occur in the respiratory tract, kidney, and liver. Metabolism occurring in the respiratory tract includes oxidation of trichloroethylene to chloral (K_m, V_{max}) and metabolic elimination of chloral (K_m, V_{max}). In the kidney, trichloroethylene is converted to DCVC (first order) and activated to a cytotoxic product (first order) or eliminated by conversion to NAcDCVC (first order). Liver metabolism is assumed to produce three metabolites (TCA, trichloroethanol-glucuronide conjugate, and DCA), which are excreted in urine (first order). These three metabolites are also assumed to be distributed in volumes of distribution (fraction of body weight), which provides for computation of their respective concentrations in blood and plasma. In the liver, trichloroethylene is converted to chloral (K_m, V_{max}), which is instantly and completely converted to TCA and trichloroethanol (proportionality constant). TCA is partially converted to DCA (K_m, V_{max}). Trichloroethanol undergoes three competing reactions consisting of conversion to TCA (K_m, V_{max}), trichloroethanol-glucuronide conjugate (K_m, V_{max}), or DCA (K_m, V_{max}). Trichloroethanol-glucuronide conjugate, in addition to being excreted in urine, is transferred to the gastrointestinal tract (first order), representing biliary secretion, from where it can be reabsorbed as trichloroethanol (first order), representing enterohepatic circulation. DCA, in addition to being excreted in urine, undergoes metabolic elimination (K_m, V_{max}).

The Halogenated Solvents Industry Alliance (HSIA) suggested to ATSDR that some of the priority data needs for trichloroethylene might be satisfied by extrapolating the results of inhalation toxicity studies to oral (drinking water) exposure through the use of existing, peer-

reviewed PBPK models. In response to this suggestion, Clewell (2011) applied a modified version of the Clewell et al. (2000) model to results from inhalation studies of rats that identified NOAELs and lowest-observed-adverse-effect levels (LOAELs) for neurological (Albee et al. 1993; Arito et al. 1994) or developmental (Carney et al. 2006) end points to estimate human drinking water concentrations resulting in similar NOAELs and LOAELs. The most conservative estimates of equivalent drinking water concentrations of 27.65 mg/L (rat brain area under the curve [AUC] trichloroethanol based on the LOAEL for neurotoxicity, Arito et al. [1994]) or 23.22 mg/L (fetal AUC TCA based on the NOAEL for developmental effects, Carney et al. [2006]) were determined to be 5,500- and 4,600-fold greater than the maximum concentration limit (MCL) of 5 µg trichloroethylene/L (EPA 2009a).

Although the Clewell et al. (2000) and Fisher (2000) models differ in many ways, the major differences are the inclusion of separate tissue compartments for metabolism in respiratory tract, kidney, and liver in the Clewell et al. (2000) model, the inclusion of DCVC production, activation, and elimination in the Clewell et al. (2000) model, and flow-limited distribution of trichloroethylene metabolites from blood to tissue compartments in the Fisher (2000) models. The two groups also used different data sets and approaches to estimating model parameters and evaluating model performance. Various statistical analyses, including Bayesian probabilistic approaches to parameter value estimation and uncertainty analyses have been performed on both models (Bois 2000a, 2000b). In 2006, the results of an EPA-U.S. Air Force (USAF) working group included a proposed structure for a harmonized model based on data included in the development of the Fisher (2000) and Clewell et al. (2000) models, along with newer data available at that time (AFRL 2004). Hack et al. (2006) also applied a Bayesian probabilistic approach to estimate parameter values for the harmonized model. The EPA reevaluated the Hack et al. (2006) model and derived a model based on newer data (Chiu et al. 2009; Evans et al. 2009). EPA re-estimated parameter values for the Chiu et al. model (Chiu et al. 2009; Evans et al. 2009) and applied the updated model to dosimetry extrapolations in support of its Toxicological Review of Trichloroethylene (EPA 2011e). The model described in EPA (2011e represents the most recent elaboration of a PBPK model for trichloroethylene for application in risk assessment. It is essentially identical to that described in Chiu et al. (2009) with small

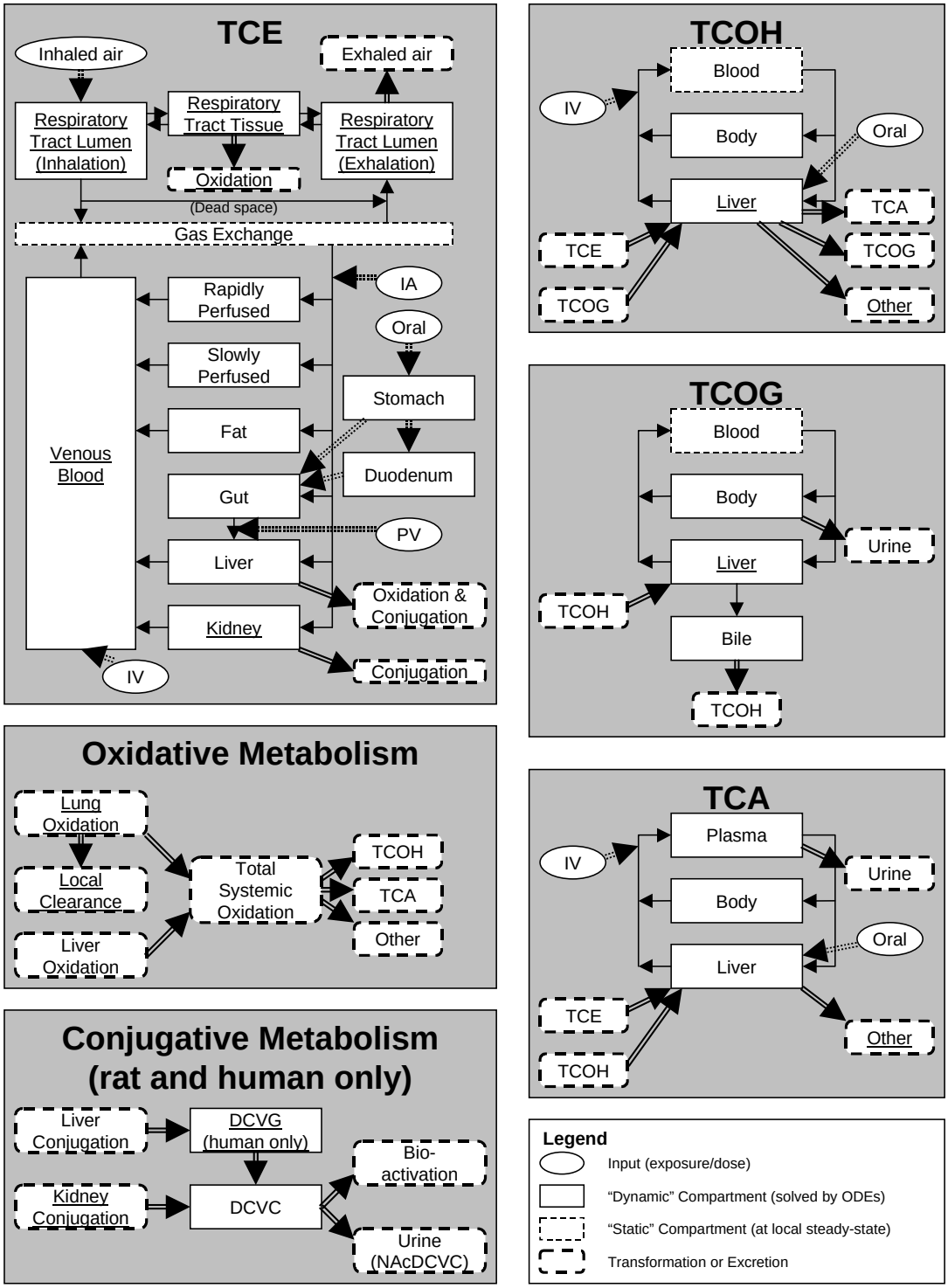
differences in the prior and posterior distributions for the central estimates (i.e., median) of parameters.

EPA Model (Chiu et al. 2009; EPA 2011e; Evans et al. 2009)

Description of the Model. The structure of the EPA (2011e) model is shown in Figure 2-3. This model includes eight tissue compartments; it retains the seven-compartment structure of the Clewell et al. (2000) model (tracheobronchial region of the respiratory tract, gastrointestinal tract, kidney, liver, fat, and rapidly perfused and slowly perfused tissues) with the addition of a separate venous blood compartment. Similar to the Clewell et al. (2000) model, metabolism is assumed to occur in the respiratory tract, kidney, and liver. Metabolism occurring in the respiratory tract consists of trichloroethylene oxidation (K_m, V_{max}), with a fraction of oxidative flux undergoing instantaneous elimination within the respiratory tract or translocation to liver where further metabolism to TCA or trichloroethanol occurs. In kidney, trichloroethylene is converted to the GSH conjugate DCVG (K_m, V_{max}), which undergoes conversion to DCVC (first order), which can be activated to a cytotoxic product (first order) or eliminated by conversion to N-acetyl-S-dichlorovinyl-L-cysteine (NAcDCVC) and excreted in urine (first order). Inclusion of DCVG as a distinct intermediate in the production of DCVC distinguishes the kidney metabolism model in the EPA (2011e) model from other previous models and enables the use of data on DCVG kinetics in parameter estimation (Chiu et al. 2009). Unlike previous models that assume that DCVC production is limited to the kidney, the liver metabolism in the EPA (2011e) model includes a GSH conjugation pathway as well as oxidation pathways, which compete for trichloroethylene as a substrate. The total rate of oxidation of trichloroethylene in liver (K_m, V_{max}) is split into fractions leading to TCA and trichloroethanol or to other oxidative pathways (e.g., leading to DCA but not via trichloroethanol). TCA formed in the liver is eliminated by conversion in the liver to downstream oxidative products (first order). Trichloroethanol undergoes three competing reactions in the liver consisting of conversion to TCA (K_m, V_{max}), trichloroethanol-glucuronide conjugate (K_m, V_{max}), or elimination to other products (e.g., DCA, first order). Trichloroethanol-glucuronide conjugate in liver is transferred to the gastrointestinal tract (first order) representing biliary secretion, from where it can be reabsorbed as trichloroethanol (first order) representing enterohepatic circulation. The hepatic GSH pathway

leads to formation of DCVC from DCVG in liver. Activation of DCVC is assumed to occur in kidney, but not in liver. The hepatic oxidation products, TCA, trichloroethanol, and trichloroethanol-glucuronide conjugate, enter systemic blood and undergo flow-limited

Figure 2-3. Overall Structure of PBPK Model for TCE and Metabolites



Boxes with underlined labels are additions or modifications of the Hack et al. (2006) model.

Sources: EPA 2011e; Chiu et al. 2009

distribution to liver and to a lumped tissue compartment representing tissues other than liver (body). Urinary metabolites include TCA transferred from plasma (first order), trichloroethanol-glucuronide conjugate transferred from the lumped body compartment (first order), and NAcDCVC transferred after formation in kidney (first order).

Validation of the Model. Parameter values for the EPA (2011e) model were estimated by applying a hierarchical Bayesian approach (Markov Chain Monte Carlo, MCMC). Initial (*prior*) central estimates (median) and variance (geometric standard deviation) were made for each parameter. These estimates represent initial expectations of variability in each parameter value, based on data applied to the estimate, or scientific judgment, if no data were available. Prior estimates were updated by applying MCMC using data from approximately 30 rodent studies and 8 human studies to direct the Markov chain towards convergence with observations (e.g., a distribution of parameter values that yield distributions of model predictions in agreement with observations). In MCMC, a Markov chain is produced in which each step of the chain consists of repeated (e.g., n=1,000) random draws from each parameter distribution. Each draw from all parameters yields a single set of model predictions of observations (e.g., blood TCA concentration, urinary NAcDCVC). Each step in the chain (n draws) yields a distribution for each prediction (e.g., n=1,000). The distributions of model predictions are compared to observations available for each prediction. Based on acceptance or rejection criteria (i.e., whether or not the new predictions improve agreement with observations), the randomly drawn parameter values are accepted or rejected. If accepted, they establish the prior distributions for the next step in the Markov chain. The process is repeated many times (e.g., n=100,000) until the Markov chain achieves a stable probability of predicting observations (known as *convergence*, usually an oscillation about a central likelihood). The resulting distributions of parameter values are referred to as *posterior* distributions and represent estimates of the distributions of parameter values in the population of subjects that achieve the highest agreement possible with observations, given measurement error and variability within the population and other unspecified sources of error in the model. The MCMC is repeated several times to evaluate stability of the outcomes.

Some model parameters were allometrically scaled across species using standard scaling assumptions (e.g., volumes, BW^{1}, first-order rates, $BW^{-0.25}$, whole-body flows V_{max}, $BW^{0.75}$). However, because these standard scaling factors are only approximations and because data were available for rats, mice, and humans, the scaled parameter values were also updated in sequential MCMC analyses to account for residual error not reduced by standard allometric scaling assumptions (EPA 2011e). The sequence began with the MCMC analysis of the mouse model. Posterior distributions of the parameters to be scaled then served, along with a "scaling" error term, as priors for the MCMC analysis of the rat model. Posterior distributions for scaled parameters for the mouse and rat were combined and, with an additional error term, used as priors for the MCMC of the human model.

EPA (2011e) utilized approximately 30 data sets from rodent studies and 8 data sets from human studies to estimate posterior distributions for parameter values. The resulting calibrated model, with parameter values assigned from the posterior distributions, was evaluated against a validation set consisting of six data sets from rodent studies and 10 human studies, not used in the calibration. Rodent data included oral gavage, intravenous, and inhalation studies of rats (predominantly) and mice. Human studies were all inhalation exposures.

Predictions of the calibrated model were compared at two levels. The first level was a comparison of model predictions of posterior parameter distributions derived for subjects representing specific observation data sets with the observation from the same data sets (i.e., predictions based on calibration with data set *i* compared to observations in data set *i*). Since these data sets were used to establish the posterior parameter distributions, as expected, posterior parameter distributions achieved good agreement when compared to data used in the calibration (i.e., in general, residuals were <2). This comparison confirmed success of the calibration. The second level was a validation of the calibrated model in which population posterior distributions were compared to observations that were not used to inform the MCMC calibration, using the 95% CI on predictions as a metric for evaluating agreement with observation (i.e., whether or not observations fell within the 95% CI of predictions). This validation analysis was possible only for the rat and human models; all available data were needed and used in the calibration of the mouse model. In general, the rat model predicted observations not included in calibration of the

rat model, with the observations of trichloroethylene concentrations in blood and tissues (liver, gastrointestinal tract, skeletal muscle, venous blood) within the 95% CI of predictions (EPA 2011e). The only exception reported was an under-prediction of observed kidney levels of trichloroethylene during an inhalation exposure to 500 ppm trichloroethylene, although post-exposure levels were accurately predicted. The human model also performed well against observations not included in model calibration, although observations were limited to trichloroethylene concentrations in blood and exhaled air and TCA and trichloroethanol in blood and urine. The human model showed a tendency (not in all studies) to over-predict trichloroethylene concentrations in exhaled air.

Risk Assessment. The EPA (2011e) applied the trichloroethylene model for extrapolating external dose response relationships for cancer and noncancer end points observed in rats to humans in derivation of a chronic reference concentration (RfC), chronic reference dose (RfD), inhalation cancer unit risk, and oral cancer slope factor for trichloroethylene. Candidate inhalation exposure-response and oral dose-response relationships and corresponding BMDLs or NOAELs and LOAELs were derived from rodent bioassay data. For each candidate critical effect, internal dose metrics were selected that would be expected to relate to each response. The rodent PBPK models were used to predict internal doses that corresponded to the inhalation exposures or oral doses used in the rodent bioassay. The median of the distribution of predicted internal doses was selected to represent the typical rodent internal dose. A point of departure (POD) for internal dose (idPOD) was derived from internal dose-response analyses (e.g., benchmark dose [BMD] analysis or selection of NOAELs and/or LOAELs). The rodent idPOD was extrapolated to a human equivalent concentration (HEC, mg/m^3) for inhalation exposures or human equivalent dose (HED, mg/kg/day) for oral exposures, where the HEC and HED represent the continuous inhalation or oral exposure, respectively, corresponding to the idPOD in the human. Interspecies extrapolation was based on application of the human PBPK model, using posterior parameter distributions for humans to derive human internal dose distributions for a range of inhalation or oral exposures. The internal dose distributions at each exposure level were based on 500 random draws from the posterior parameter distributions (represented a sample of n=500) from the human population. The posterior parameter distributions in the human model represent predicted population variability in parameter values. Therefore, the

model predicts distributions of internal doses corresponding to a given human exposure that reflect population variability in toxicokinetics of trichloroethylene. The median of this distribution was assumed to represent the typical internal dose corresponding to a given exposure, while the 99th percentile was assumed to represent a sensitive subpopulation. Based on the predicted median and 99th percentile internal doses, HECs or HEDs representing the typical internal dose and (HEC_{50}, HED_{50}) and sensitive subpopulation (HEC_{99}, HEC_{99}) were derived. The model-based derivation of the 99th percentile values was used as a rationale for eliminating the need for application of uncertainty factors to adjust the HEC_{99} or HED_{99} to account for interspecies toxicokinetics variability ($10^{0.5}$) and for human variability in toxicokinetics ($10^{0.5}$). Uncertainty factors applied to the HEC_{99} or HED_{99} were $10^{0.5}$ to account for possible interspecies variability in toxicodynamics, and $10^{0.5}$ to account for possible human population variability in toxicodynamics.

Several internal dose metrics were used in analyses supporting the derivation of the RfC, RfD, inhalation cancer unit risk, and oral cancer slope factor (EPA 2011e). These included the AUC for trichloroethylene, TCA, or trichloroethanol concentrations in blood, amounts of trichloroethylene metabolized (to GSH conjugates, oxidized) per unit body weight of metabolizing tissue weight (liver or kidney), and amount of DCVC activated per unit of body weight or kidney weight. The RfC was ultimately based on production of developmental heart defects and immunological effects as critical effects, supported by dose-response relationships for nephropathy. The internal dose metric selected to represent the developmental heart effects was the total amount of trichloroethylene metabolized through oxidative pathways in all metabolizing tissues per unit of body weight. The internal dose metric selected to represent the immunological effects was the total amount of trichloroethylene metabolized through all pathways in all metabolizing tissues per unit of body weight. Internal dose metrics used to represent kidney effects were the amount of DCVC activated per unit of body weight or the amount of trichloroethylene conjugated with GSH per unit of body weight. The RfD was also based on developmental heart defects and immunological effects as critical effects, supported by nephropathy. Internal dose metrics selected to represent these effects were the same as those used in the derivation of the RfC. A variety of internal dose metrics were evaluated in support

for the derivation of the inhalation cancer unit risk and oral cancer slope factor, which depended on the tissue location of the cancers observed (e.g., lung, liver, kidney, or other tissues).

Target Tissues. The trichloroethylene model (EPA 2011e) was calibrated to predict blood trichloroethylene, TCA, and trichloroethanol kinetics; rates of metabolism of trichloroethylene in lung, liver, and kidney; and excretion of trichloroethylene metabolites following inhalation or oral exposures to trichloroethylene. As noted above, the model has been used to predict various internal dose metrics of trichloroethylene exposure in rats and humans (EPA 2011e). These include the AUC for trichloroethylene, TCA, or trichloroethanol concentrations in blood; amounts of trichloroethylene metabolized (to GSH conjugates, oxidized) formed per unit body weight or metabolizing tissue weight (liver or kidney); and amount of DCVC activated per unit of body weight or kidney weight.

Species Extrapolation. As described above, models simulating toxicokinetics in mice, rats, and humans have been used in interspecies extrapolation of external-internal dose response relationships (EPA 2011e). Models for the above species were developed by a combination of allometric scaling across species and optimization of scaled model parameters (metabolism V_{max} and rate constants) using hierarchical Bayesian analyses. The scaled rat and human models have been evaluated against independent observations not used to estimate model parameter values (EPA 2011e).

Interroute Extrapolation. The trichloroethylene PBPK model (EPA 2011e), as it is currently configured, simulates trichloroethylene kinetics associated with inhalation, oral, and intravenous dosing. Simulation of other potential routes of exposure (e.g., dermal) would require development of models for the absorption of trichloroethylene deposited on the skin. EPA (2011e) used the human model to extrapolate an inhalation cancer unit risk to an oral cancer slope factor. The basis of the inhalation cancer unit risk was epidemiological evidence of cancers in humans exposed to trichloroethylene along with supporting evidence from rodent bioassays. The interroute extrapolation was based on the internal dose metrics considered to be related to cancer, the amount of DCVC activated in kidney per unit of body weight, or the total amount of trichloroethylene metabolized per unit of body weight.

2.4 MECHANISMS OF ACTION

2.4.2 Mechanisms of Toxicity

Target Organ Toxicity. Based on effects reported in humans and/or animals, the primary targets for trichloroethylene toxicity appear to be the nervous system, liver, kidney, immune system, male reproductive system, and developing fetus.

Neurological Effects. Although mechanistic studies of trichloroethylene neurotoxicity have been performed, the mechanisms for this toxicity are not well established (EPA 2011e; NRC 2006). Trichloroethylene and some of its metabolites such as chloral hydrate and trichloroethanol are central nervous system depressants and this property, mediated through effects on inhibitory neuronal receptors, may account for some of the behavioral changes associated with trichloroethylene exposure (EPA 2011e). Although it has been suggested that changes in trigeminal nerve function may be due to dichloroacetylene, which is produced under non-biological conditions (high alkalinity or temperature) during volatilization of trichloroethylene, exposure to this chemical has not been identified or measured in epidemiologic studies. In addition, changes in trigeminal nerve function also have been reported in humans exposed orally (EPA 2011e), and changes in trigeminal nerve morphology have been reported in rats exposed orally (Barret et al. 1991, 1992). Oral exposures are not expected to involve generation of dichloroacetylene. Dopamine neuron disruption, including degeneration of dopamine neurons in the substantia nigra, has been reported in animal studies (Gash et al. 2008; Guehl et al. 1999) and has been suggested as a potential mechanism for clinical psychomotor effects from trichloroethylene exposure (EPA 2011e). A possible mechanism of hearing impairment was hypothesized, by analogy to aromatic hydrocarbons such as toluene, to involve toxicity to supporting cells in the cochlea, which then alters structural elements, ultimately resulting in hair cell displacement and death (EPA 2011e). Another potential mechanism is blockade in neuronal nicotinic receptors on the auditory cells and changes in calcium transmission seen with toluene and speculated to be relevant to trichloroethylene (EPA 2011e).

Hepatic Effects. The oxidative metabolites of trichloroethylene, particularly chloral hydrate, TCA, and DCA, are thought to contribute to liver toxicity in humans and animals and to liver cancer in animals (EPA 2011e; NRC 2006). This conclusion is based on the studies in animals showing the potentiation of liver effects by pretreatment with cytochrome P450 inducers and the similarity of effects, such as increased liver weight, peroxisome proliferation, and liver cancer, produced by trichloroethylene and these metabolites. The potential mechanisms or modes of action for liver cancer are (1) that trichloroethylene's metabolite chloral hydrate is mutagenic, causing mutations, DNA damage, and/or micronuclei induction, or (2) that trichloroethylene's metabolite, TCA, activates the peroxisome proliferator activated receptor alpha (PPARα) in the liver, which causes alterations in cell proliferation and apoptosis, and clonal expansion of initiated cells (EPA 2011e). Additional proposed hypotheses for modes of action for liver cancer include polyploidization, changes in glycogen storage, and inhibition of glutathione-S-transferase zeta. EPA (2011e), however, concluded that the data are inadequate to support the conclusion that any of these hypotheses are operant, and that therefore, the mode of action for trichloroethylene induction of liver tumors is unknown.

Renal Effects. The GSH-dependent metabolites of trichloroethylene, DCVC, and related GSH conjugation metabolites are considered to be the active agents of trichloroethylene renal toxicity and carcinogenicity (EPA 2011e). *In vivo* and *in vitro* studies show that 1,2-DCVC causes renal effects that are similar to those of trichloroethylene, and that it is formed in sufficient amounts after trichloroethylene exposure to account for these effects. EPA (2011e) concluded that the mechanism for renal carcinogenicity is a mutagenic mode of action mediated by the GSH-conjugation metabolites of trichloroethylene, predominantly DCVC. This conclusion is based on evidence that these metabolites are genotoxic, including *in vivo* evidence of renal-specific genotoxicity from exposure to trichloroethylene or 1,2-DCVC. An additional potential mode of action is cytotoxicity resulting in compensatory cellular proliferation, also due to DCVC. Again, the evidence was primarily from studies with 1,2-DCVC. A combination of these mechanisms, with increased rates of mutation and regenerative proliferation (Vaidya et al. 2003a; Vaidya et al. 2003b; Vaidya et al. 2003c; Korrapati et al. 2005; Korrapati et al. 2006; Korrapati et al. 2007), enhancing cell survival or clonal expansion is considered biologically plausible. The possible

implication of formic acid formation in the renal toxicity has been suggested and reviewed (Dow and Green 2000; Green et al. 2003; Green et al. 2004; Lock et al. 2007; Lock and Reed 2006)."

Immunological Effects. The mechanism of action for immunological effects, including autoimmune disease and lymphoma, is not known (EPA 2011e). Some mechanistic studies have focused on oxidative stress as a potential mechanism for induction of immune effects (Khan et al. 2001; Wang et al. 2008, 2007b). Studies in mice susceptible to autoimmune disease indicate that trichloroethylene oxidative metabolites such as chloral (also known as trichloroacetaldehyde) or dichloroacetyl chloride may be responsible, at least in part, for activating T-cells or altering T-cell regulation and survival associated with polyclonal disease (Blossom and Gilbert 2006; Blossom et al. 2007; Cai et al. 2006; Gilbert et al. 2004).

Male Reproductive Effects. The evidence suggests that trichloroethylene is metabolized in the male reproductive tract, primarily in the epididymal epithelium, but also in testicular Leydig cells, by CYP2E1 to chloral, trichloroethanol, and TCA (Forkert et al. 2002, 2003). The finding of dichloroacetyl protein adducts in the epididymis and efferent ducts of rats administered trichloroethylene and of oxidized proteins on the surface of their spermatozoa suggested that male reproductive toxicity was initiated by metabolic activation of trichloroethylene to reactive metabolites (DuTeaux et al. 2003, 2004).

Developmental Effects. A number of studies of the potential mechanisms for trichloroethylene-induced fetal cardiac defects have focused on disruptions in cardiac valve formation in chickens as a model. The use of an avian model is supported by the similarity in the stages and events of cardiac valve formation between mammals and birds (NRC 2006). These studies demonstrated alterations in endothelial cushion development, which could be associated with defects in septal and valvular morphogenesis (e.g., Boyer et al. 2000; Mishima et al. 2006). The proposed mechanism is inhibition of endothelial separation and formation of mesenchymal cells (from which the septum and valves are formed). An additional study in bovine coronary endothelial cells (Ou et al. 2003) supported a mechanism of interference with the role of endothelial nitric oxide synthase in endothelial cell proliferation. In contrast, Watson et al. (2006) in their review of the literature did note that there were some differences between mammalian and avian

development (Section 6.2, page 141). A thorough review of this topic is presented in the EPA Toxicological Review (2011e) Section 4.8.3.3.2 titled Cardiac Malformations.

2.5 RELEVANCE TO PUBLIC HEALTH

Genotoxic Effects. Oxidative DNA damage was reported in liver cells from rats administered a single intraperitoneal injection of trichloroethylene (Toraason et al. 1999). Increased incidences of micronuclei and ssDNA breaks were observed in kidney cells of rats given a single oral dose of trichloroethylene (Robbiano et al. 1998). Sujatha and Hegde (1998) reported increased micronucleus formation and C-mitotic changes (increased mitotic index, decreased frequencies of anaphases) in bone marrow cells from mice administered trichloroethylene intraperitoneally, but no effect on incidence of chromosomal aberrations. Covalent binding to hepatic DNA and/or proteins from mice after intraperitoneal injection has been observed (Halmes et al. 1997; Kautiainen et al. 1997). Trichloroethylene gave a clearly negative response in a comet assay designed to assess whether trichloroethylene was involved in DNA breakage in the proximal tubules of rat kidneys; the study author indicated that the result supports an overall conclusion that renal tumors observed in trichloroethylene-exposed rats are non-genotoxic in origin (Clay 2008). Trichloroethylene was not mutagenic to the *Salmonella typhimurium* strain YG7108pin3ERb$_5$ (a strain expressing cytochrome P450) in the absence of exogenous metabolic activation (Emmert et al. 2006). Robbiano et al. (2004) reported increased incidences of micronuclei and ssDNA breaks in primary cultures of rat and human kidney cells exposed to trichloroethylene. Covalent binding of trichloroethylene to proteins was observed in hepatocytes from rats and humans (Griffin et al. 1998). A possible association between TCE exposure and mutations in the von Hippel-Lindau (VHL) gene in humans has been suggested (Brauch 1999; Brauch 2004). However, some findings have been inconsistent (Charbotel 2007).

Minimal Risk Levels for Trichloroethylene

ATSDR did not derive chronic MRLs in the 1997 Toxicological Profile for Trichloroethylene. Recently, EPA has derived a preferred chronic RfD and a preferred chronic RfC for trichloroethylene (EPA 2011e; IRIS 2011). The preferred chronic RfD of 0.0005 mg/kg/day is

adopted as the ATSDR chronic-duration oral Minimal Risk Level (MRL) and the preferred chronic RfC of 0.0004 ppm is adopted as the ATSDR chronic-duration inhalation MRL. EPA determined potential PODs for candidate chronic RfD and RfC values for numerous studies by utilizing the LOAEL/NOAEL approach, BMD analysis, and/or PBPK modeling of human and animal data considered suitable for dose-response assessment. Candidate critical effects included trichloroethylene-induced neurological effects in humans and animals; effects on kidney, liver, and body weight in animals; immunological effects in animals; reproductive effects in humans and animals; and developmental effects in animals.

EPA employed a PBPK model 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 99^{th} percentile estimates of human equivalent dose (HED_{99}) or human equivalent concentration (HEC_{99}) for candidate critical effects. The PBPK modeling exercises simulated 100 weeks of exposure for humans, which 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.

Previously, three MRLs were derived in the 1997 Toxicological Profile for Trichloroethylene: an acute-duration inhalation MRL, an intermediate-duration inhalation MRL and an acute-duration oral MRL. No intermediate-duration oral MRL was derived in the 1997 Toxicological Profile for Trichloroethylene. All three MRLs are rescinded at this time as discussed below. Also, all three of these MRLs, along with a potential intermediate-duration oral MRL, are presently under futher review.

Oral MRLs

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

The EPA (2011e) preferred chronic RfD is supported by candidate RfD values derived from three principal studies. In brief, a candidate RfD of 0.00048 mg/kg/day was based on decreased thymus weight in female B6C3F1 mice administered trichloroethylene in the drinking water for 30 weeks (Keil et al. 2009). A candidate RfD of 0.00037 mg/kg/day was based on increased delayed-type hypersensitivity (at 8 weeks of age) in B6C3F1 mouse pups whose mothers were administered trichloroethylene in the drinking water throughout gestation and lactation; the pups were postnatally exposed to trichloroethylene-treated drinking water as well (Peden-Adams et al. 2006). A candidate RfD of 0.00051 mg/kg/day was based on fetal heart malformations in Sprague-Dawley rat fetuses whose mothers were administered trichloroethylene in the drinking water throughout gestation (Johnson et al. 2003). EPA noted that the preferred chronic RfD of 0.0005 mg/kg/day is within 20% of the individual candidate RfDs that range from 0.0004 to 0.0005 mg/kg/day (rounded from 0.00037 to 0.00051 mg/kg/day) (EPA 2011e; IRIS 2011). See Appendix A for additional details regarding EPA's methodology used to derive the chronic RfD for trichloroethylene, including a summary of the three studies (Keil et al. 2009, Peden-Adams et al. 2006, Johnson et al. 2003).

Previously, no intermediate-duration oral MRL was derived in the 1997 Toxicological Profile for Trichloroethylene due to the lack of adequately designed studies examining suitable end points. No change in the intermediate-duration oral MRL is proposed at this time, although it is presently under further review. Furthermore, based upon newer data the chronic-duration oral MRL of 0.0005 mg/kg/day is considered to be protective for intermediate-duration oral exposure to trichloroethylene.

The basis for adoption of the preferred chronic RfD of 0.0005 mg/kg/day derived by EPA (2011e) for trichloroethylene as the chronic-duration oral MRL is applicable to intermediate-duration oral exposure to trichloroethylene 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 weeks 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 human equivalent dose, HED). Sample simulations for a 52-week exposure (within the range of an ATSDR-defined intermediate-duration exposure [15–364 days]) did not result in a substantially different HED (Weihsueh Chiu, personal communication, August 22, 2011). Therefore, the preferred chronic RfD of 0.0005 mg/kg/day derived by EPA (2011e) and adopted as the ATSDR chronic-duration oral MRL is considered protective for intermediate-duration oral exposure to trichloroethylene.

The consideration that the chronic-duration oral MRL of 0.0005 mg/kg/day is protective for the intermediate-duration exposure 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 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). See Appendix A for additional details regarding the Peden-Adams et al. 2006 study.

Previously, an acute-duration oral MRL of 0.2 mg/kg/day was derived in the 1997 Toxicological Profile for Trichloroethylene. This MRL is rescinded based upon newer data that demonstrate

that it is not adequately protective. The potential derivation of a new, replacement MRL value is under further review.

The basis for adoption of the preferred chronic RfD of 0.0005 mg/kg/day derived by EPA (2011e) for trichloroethylene as the chronic-duration oral MRL is applicable to rescinding the acute-duration oral exposure MRL for trichloroethylene. Two of the studies (Peden-Adams et al. 2006, Johnson et al. 2003) used to support the RfD derivation had assessed sensitive developmental effects (e.g., cardiac malformations, developmental immunotoxicity) identified in animal studies that employed gestational exposure or gestational and early postnatal development periods that were just greater than 15 days in duration. It is possible these effects could potentially be elicited by trichloroethylene exposure for less than15 days, if adequately examined. Based upon this newer data, the 1997 acute-duration oral MRL of 0.2 mg/kg/day is no longer adequately protective.

Inhalation MRLs

The preferred chronic RfC of 0.0004 ppm (0.002 mg/m^3) for trichloroethylene derived by EPA (2011e) is adopted as the ATSDR chronic-duration inhalation MRL for trichloroethylene.

The chronic RfC is supported by candidate RfC values derived from two principal studies that employed the oral exposure route and application PBPK model-based route-to-route extrapolation. In brief, a candidate RfC of 0.00033 ppm (0.0019 mg/m^3) was derived based on decreased thymus weight in female B6C3F1 mice administered trichloroethylene in the drinking water for 30 weeks (Keil et al. 2009). A candidate RfC of 0.00037 ppm (0.002 mg/m^3) was derived based on fetal heart malformations in Sprague-Dawley rat fetuses whose mothers were administered trichloroethylene in the drinking water throughout gestation (Johnson et al. 2003). 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 lowest PBPK-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-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. See Appendix A for additional details regarding EPA's methodology used to derive the preferred chronic RfC for trichloroethylene.

Previously, an intermediate-duration inhalation MRL of 0.1 ppm was derived in the 1997 Toxicological Profile for Trichloroethylene. This MRL is rescinded based upon newer data that demonstrate that it is not adequately protective. The potential derivation of a new, replacement MRL value is under further review. Furthermore, based upon newer data the chronic-duration inhalation MRL is considered to be protective for intermediate-duration oral exposure to trichloroethylene.

The basis for adoption of the preferred chronic RfC of 0.0004 ppm (0.002 mg/m^3) derived by EPA (2011e) for trichloroethylene as the chronic-duration inhalation MRL is applicable to rescinding the intermediate-duration inhalation exposure to trichloroethylene. As noted elsewhere, EPA (2011e) performed PBPK model-based route-to-route extrapolation from the oral studies of Johnson et al. (2003) and Keil et al. (2009) in order 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 lasting 10 weeks for rats and mice and 100 weeks for humans. Sample simulations for a 52-week inhalation exposure in humans, which is within the range of an ATSDR-defined intermediate-duration exposure (15–364 days), did not result in a substantially different value from the 100 week inhalation exposure simulation (Weihsueh Chiu, personal communication, August 22, 2011).

The consideration that the chronic-duration inhalation MRL of 0.0004 ppm is protective for the intermediate-duration exposure is supported by the results from original studies used by the EPA (2011e) in the route-to-route extrapolation to derive the RfC. The details of those studies are presented in Appendix A.

Previously, an acute-duration inhalation MRL of 2 ppm was derived in the 1997 Toxicological Profile for Trichloroethylene. This MRL is rescinded based upon newer data that demonstrate that it is not adequately protective. The potential derivation of a new, replacement MRL value is under further review.

The basis for adoption of the preferred chronic RfC of 0.0004 ppm (0.002 mg/m^3) derived by EPA (2011e) for trichloroethylene as the chronic-duration inhalation MRL is applicable to rescinding the acute-duration inhalation exposure to trichloroethylene. The Johnson et al study (2003) assessed sensitive developmental effects (e.g., cardiac malformations) identified in animal studies that employed gestational exposure. When combined with the results from the Peden-Adams et al study (2006) that assessed developmental and early postnatal developmental exposure of immunotoxicity at a three week end point, it is possible that these effects could potentially be elicited by trichloroethylene exposure for less than 15 days, if adequately examined. Based upon this newer data, the 1997 acute-duration inhalation MRL of 2 ppm is no longer adequately protective.

2.6 BIOMARKERS OF EXPOSURE AND EFFECT

2.6.1 Biomarkers Used to Identify or Quantify Exposure to Trichloroethylene

Lash et al. (1999a) detected the GSH-derived conjugate of trichloroethylene (DCVG) in the blood of all male and female subjects from 30 minutes after the start of a 4-hour exposure to trichloroethylene vapors at 50 or 100 ppm to up to 8 hours after the end of the exposure period. DCVG levels were approximate 3.5-fold higher in males than females.

Tabrez and Ahmad (2009) observed increased glutathione-*S*-activity in the liver and kidneys (50 and 218% greater than that of controls) of rats administered trichloroethylene by gavage at 1,000 mg/kg/day for 15 days. However, these increases are not unique to trichloroethylene exposure.

2.6.2 Biomarkers Used to Characterize Effects Caused by Trichloroethylene

Bolt et al. (2004) reported increased urinary α_1-microglobulin in trichloroethylene-exposed renal cancer patients compared to renal cancer patients and healthy controls without trichloroethylene exposure. Although increased urinary α_1-microglobulin may serve as an indicator of renal toxicity, it is not unique to trichloroethylene exposure.

Brüning et al. (1999) reported increased glutathione transferase alpha (a marker of distal renal tubular damage) in the urine of 39 workers exposed to high levels of trichloroethylene for up to 19 years compared to a group of 46 male office and administrative workers without known exposure to trichloroethylene. Although glutathione transferase alpha urinary levels may serve as biomarkers of effects caused by trichloroethylene, this effect is not unique to trichloroethylene exposure.

2.7 INTERACTIONS WITH OTHER SUBSTANCES

Coexposure to mercury was reported to increase trichloroethylene-induced autoimmune hepatitis in autoimmune-prone MRL+/+ mice (Gilbert et al. 2011). Co-exposure to trichloroethylene and mercury also generated a liver-specific antibody response in the mice that was not observed in mice exposed to mercury or trichloroethylene alone.

Muijser et al. (2000) reported that mice exposed to trichloroethylene vapors (3,000 ppm) and noise (95 dB) experienced significantly greater hearing loss at the 4 kHz frequency than mice exposed to either trichloroethylene or noise alone; the results were considered indicative of an interaction between exposures to trichloroethylene and noise in combination.

2.8 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

Infants and young children may be more susceptible than adults to trichloroethylene toxicity based on age-related differences in the pharmacokinetics of trichloroethylene. For example,

trichloroethylene may be absorbed in greater amounts in children exposed by inhalation due to increased ventilation rates per kg body weight and the fact that alveolar surface area is 2-fold higher in infants compared to adults (EPA 2008). Intake from trichloroethylene-contaminated drinking water is expected to be greater in children than adults because children tend to drink more water on a per kg body weight basis than adults. Nursing infants can be exposed to trichloroethylene via the breast milk. Household dust and dirt are potential sources of greater potential dermal contact and ingestion exposure in small children. Infants and small children have a higher concentration of lipophilic compounds in their fat (NRC 1993), which may result in a higher concentration of absorbed trichloroethylene in the fat. If the metabolic products are more toxic than the parent compound, an individual with higher metabolic rates (such as some children and adolescents) would be expected to have greater toxicity.

Results of a study in which trichloroethylene-exposed workers with generalized skin disorders accompanied by hepatic dysfunction and healthy trichloroethylene-exposed workers were assessed for possible risk factors for rash and hepatitis indicated that those with human herpesvirus 6 were more likely to suffer trichloroethylene-induced skin disorders and hepatic dysfunction (Huang et al. 2006). Diets deficient in selected essential elements may contribute to increased sensitivity to trichloroethylene toxicity. Giovanetti et al. (1998) found increased numbers of vacuolated Clara cells in the lungs of mice administered copper-deficient diet and exposed to trichloroethylene vapors.

Lash et al. (1999a) reported that trichloroethylene-exposed male subjects produced approximately 3.5-fold higher levels of DCVG in the blood than similarly-exposed female subjects, indicating that males may be more susceptible to trichloroethylene-induced renal toxicity.

There is some indication of gene-related susceptibility to trichloroethylene toxicity. Selected genotypes/phenotypes may be more sensitive to trichloroethylene based on altered metabolic rates (Brüning et al. 1997; Dai et al. 2009; Moore et al. 2010). Li et al. (2007) reported an association between the presence of a particular allele for human leucocyte antigen (HLA-B*1301) and hypersensitivity dermatitis among trichloroethylene-exposed workers.

2.9 METHODS FOR REDUCING TOXIC EFFECTS

The following texts provide specific information about treatment following exposures to trichloroethylene:

Dart RC. 2004. Medical toxicology. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins, 1339-1341.

Leikin JB, Paloucek FP. 2002. Poisoning & toxicology handbook. 3rd ed. Hudson, OH: Lexi-Comp, Inc., 1212-1213.

Palmer RB, Phillips SD. 2007. Chlorinated hydrocarbons. In: Shannon MW, Borron SW, Burns MJ, eds. Haddad and Winchester's clinical management of poisoning and drug overdose. 4th ed. Philadelphia, PA: Saunders Elsevier, 1347-1361.

2.9.1 Reducing Peak Absorption Following Exposure

Human exposure to trichloroethylene may occur by inhalation, ingestion, or dermal contact. Mitigation methods for reducing exposure to trichloroethylene have included the general recommendations of separating contaminated food, water, air, and clothing from the exposed individual. Externally, trichloroethylene can produce mild irritation; chronic exposure may produce a rash and chapped skin (HSDB 2011).

The following recommendations for monitoring and treating trichloroethylene poisoning are contained in the Hazardous Substances Data Bank (HSDB 2011). For oral intake of hazardous amounts of trichloroethylene, use of an activated charcoal slurry (240 mL water/30 g charcoal) at age-related recommended doses is recommended to diminish absorption. Any attempt to reduce absorption must be initiated soon after ingestion has occurred. Ipecac-induced emesis is not recommended due to the potential for cardiovascular instability and central nervous system depression. Gastric lavage may be considered after ingestion of a potentially life-threatening amount of trichloroethylene if it can be performed within 1 hour following ingestion.
In cases of overexposure to trichloroethylene vapors, the patient should be moved to fresh air and monitored for respiratory difficulty.

In cases of dermal exposure, contaminated clothing should be removed and exposed skin should be washed thoroughly with soap and water. Exposed eyes should be flushed with copious amounts of room temperature water for at least 15 minutes. If ocular or dermal symptoms persist, then the patient should be evaluated at a health care facility.

2.9.3 Interfering with the Mechanism of Action for Toxic Effects

Administration of antioxidants such as curcumin diminished trichloroethylene-induced oxidative stress in mouse liver cells (Watanabe and Fukui 2000); however, this response was only demonstrated *in vitro*. Trichloroethylene has been shown to decrease methylation of the *c-jun* and *c-myc* protooncogenes and increase levels of their messenger ribonucleic acid (mRNA) in the livers of mice (Tao et al. 2000). Co-treatment with methionine prevented both decreased methylation and increased levels of the mRNA and proteins of the *c-jun* and *c-myc* protooncogenes. The study authors hypothesized that trichloroethylene may act as a carcinogen by depleting the availability of S-adenosylmethionine and that methionine could prevent DNA hypomethylation by maintaining sufficient S-adenosylmethionine. However, methionine treatment has not been suggested as a method for protecting against trichloroethylene carcinogenicity.

2.10 ADEQUACY OF THE DATABASE

2.10.3 Ongoing Studies

Under the auspices of ATSDR's Voluntary Research Program (VPR), the Halogenated Solvents Industry Alliance (HSIA) has planned to study PBPK dose route conversion for immunological effects described in a rat inhalation study (Woolhiser et al. 2006). The HSIA has also planned an oral developmental neurotoxicity study in rats. These studies are designed to address priority data needs identified by the Agency for Toxic Substances and Disease Registry (2011a) and as cited in the Federal Register (FR Doc. 05-23361; FR Doc. 96-7852).

Ongoing studies identified in the Federal Research in Progress database (FEDRIP 2011) are presented in Table 2-3.

Table 2-3. Ongoing Studies of Health Effects of Trichloroethylene

Principal Investigator	Study topic	Institution	Sponsor
Selmin, O	Susceptibility to trichloroethylene and chlorinated acids in heart development; folic acid supplementation	University of Arizona, Tucson, Arizona	Not specified
Blossom, SJ	Neuroimmune dysregulation with developmental exposure to trichloroethylene	Arkansas Children's Hospital Research Institute, Little Rock, Arkansas	National Institute of Environmental Health Sciences
Gilbert, KM	Determining how trichloroethylene alters CD4+ T cell function	Arkansas Children's Hospital Research Institute, Little Rock, Arkansas	National Institute of Environmental Health Sciences
Stacpoole, PW	Pharmacotoxicology of trichloroethylene metabolites	University of Florida, Gainesville, Florida	National Institute of Environmental Health Sciences
Buffler, PA	Examination of the potential roles that environmental exposure to selected Superfund chemicals, including trichloroethylene, play in the etiology of childhood leukemia	University of California Berkeley, Berkeley, California	National Institute of Environmental Health Sciences

3. CHEMICAL AND PHYSICAL INFORMATION

No updated data.

4. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

4.1 PRODUCTION

Use of acetylene as a feedstock for trichloroethylene production declined significantly during the 1970s, and this method is no longer used (Rossberg 2006; Snedecor et al. 2004).

The trichloroethylene production demand in the United States was 192 million pounds in the year 2000 and 218 million pounds in 2004 (CMR 2005). According to the U.S. EPA Inventory Update Reporting database, the annual production of trichloroethylene during 2006 was between 100 and 500 million pounds (EPA 2010a).

The only U.S. manufacturers of trichloroethylene are DOW Chemical in Freeport, Texas, and PPG Industries in Lake Charles, Louisiana (CMR 2005; SRI 2011). These two manufacturers had estimated combined annual production capacities of 320 million pounds in 2005 (SRI 2005) and 270 million pounds 2011 (SRI 2011).

Table 4-1 summarizes the number of facilities in each state that manufactured or processed trichloroethylene in 2009, the ranges of maximum amounts on site, if reported, and the activities and uses as reported in the Toxics Release Inventory (TRI) (TRI09 2011).

Table 4-1. Facilities that Produce, Process, or Use Trichloroethylene

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AL	35	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 13
AR	23	100	999,999	2, 3, 5, 7, 8, 9, 10, 11, 12
AZ	10	100	99,999	2, 4, 7, 9, 11, 12
CA	49	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
CO	14	0	99,999	1, 2, 3, 5, 6, 7, 9, 10, 11, 12
CT	30	0	99,999,999	1, 2, 3, 6, 7, 9, 10, 11, 12
DE	9	1,000	999,999	2, 3, 6, 7, 8, 9, 10, 12
FL	25	0	499,999,999	2, 3, 7, 9, 10, 11, 12
GA	40	0	499,999,999	2, 3, 4, 6, 7, 8, 9, 10, 11, 12, 14
IA	14	0	99,999	1, 2, 3, 7, 9, 10, 11, 12
ID	1	1,000	9,999	8, 11
IL	80	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
IN	63	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14
KS	34	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
KY	33	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12
LA	51	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 13, 14
MA	37	0	49,999,999	1, 2, 3, 4, 7, 8, 9, 10, 11, 12
MD	11	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13
ME	7	0	99,999	2, 3, 8, 11, 12, 14

Table 4-1. Facilities that Produce, Process, or Use Trichloroethylene

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
MI	52	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14
MN	36	0	999,999	2, 3, 6, 7, 9, 10, 11, 12
MO	41	0	49,999,999	1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12
MS	16	0	999,999	1, 2, 4, 8, 9, 11, 12, 13
MT	5	1,000	99,999	10, 12
NC	30	0	999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12
NE	7	1,000	999,999	10, 11, 12
NH	8	1,000	99,999	6, 7, 10, 11, 12
NJ	35	0	99,999,999	1, 2, 3, 4, 6, 7, 8, 9, 10, 11, 12
NM	3	100	99,999	11, 12
NV	8	100	99,999	1, 3, 7, 12
NY	48	0	49,999,999	2, 3, 6, 7, 8, 9, 10, 11, 12
OH	70	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 13
OK	17	0	99,999	1, 2, 3, 4, 7, 9, 10, 11, 12
OR	19	0	9,999,999	2, 7, 9, 10, 11, 12
PA	55	0	9,999,999	1, 2, 3, 4, 6, 7, 8, 9, 10, 11, 12
PR	4	100	99,999	2, 3, 12
RI	27	0	999,999	2, 3, 7, 9, 10, 11, 12, 14
SC	23	0	9,999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12
SD	5	1,000	99,999	11, 12
TN	36	0	999,999,999	2, 3, 6, 7, 8, 9, 10, 11, 12
TX	99	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
UT	6	100	999,999	9, 11, 12
VA	32	0	99,999,999	1, 2, 3, 6, 7, 8, 9, 10, 11, 12
VT	4	1,000	99,999	10, 12
WA	25	0	999,999	1, 2, 3, 4, 6, 7, 8, 9, 10, 11, 12, 14
WI	51	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12
WV	9	1,000	999,999	7, 10, 11, 12
WY	1	10,000	99,999	12

[a]Post office state abbreviations used.
[b]Amounts on site reported by facilities in each state.
[c]Activities/Uses:

1. Produce
2. Import
3. Onsite use/processing
4. Sale/Distribution
5. Byproduct
6. Impurity
7. Reactant
8. Formulation Component
9. Article Component
10. Repackaging
11. Chemical Processing Aid
12. Manufacturing Aid
13. Ancillary/Other Uses
14. Process Impurity

Source: TRI09 2011 (data are from 2011)

4.2 IMPORT/EXPORT

Reported U.S. imports during the years 2000, 2002, and 2004 were 10, 19, and 20 million pounds, respectively (CMR 2005). Reported U.S. exports during these same 3 years were 76, 52, and 55 million pounds, respectively (CMR 2005). The continued strength of U.S. exports during this time period was most likely due to the high global demand for trichloroethylene as a feedstock for the refrigerant HFC-134a (CMR 2002, 2005; Snedecor et al. 2004). More recent data regarding U.S. imports and exports of trichloroethylene have not been located.

4.3 USE

The end-use pattern of trichloroethylene in the United States during 2004 was estimated as follows (CMR 2005): hydrofluorocarbon (HFC-134a) intermediate, 73%; metal degreasing, 24%; and miscellaneous uses, 3%. The use of trichloroethylene vapors for degreasing of metal parts has declined over the past decade due to increased environmental regulations governing trichloroethylene emissions (CMR 2000, 2002, 2005). During the same time period, trichloroethylene found increasing use as a feedstock for HFC-134a, a refrigerant that was introduced as a replacement for CFC-12 during the 1990s (CMR 1995, 1997, 2000, 2002, 2005; Snedecor et al. 2004). Production of HFC-134a is expected to level off as CFC-12 becomes largely replaced (Snedecor et al. 2004).

4.4 DISPOSAL

There has been an emphasis on recovery and recycling of trichloroethylene to reduce emissions of this photoreactive chemical to the atmosphere (CMR 2002; Snedecor et al. 2004).

5. POTENTIAL FOR HUMAN EXPOSURE

5.2 RELEASES TO THE ENVIRONMENT

5.2.1 Air

Estimated releases of 1.4 million pounds (618 metric tons) of trichloroethylene to the atmosphere from 252 domestic manufacturing and processing facilities in 2009, accounted for about 89% of the estimated total environmental releases from facilities required to report to the TRI (TRI09 2011).

Millet et al. (2009) estimated a trichloroethylene emission rate of 7.6 Gg/year based on aircraft measurements collected over the United States from 2004 to 2006. Modeling of the distribution of trichloroethylene releases in the global atmosphere suggested much lower levels than are actually observed in the southern hemisphere, far from areas of release, indicating that oceanic emissions may be important (Olaguer 2002). Pratt et al. (2004) estimated that 87 metric tons of trichloroethylene were released from publicly owned treatment works located in the Minneapolis-St. Paul, Minnesota metropolitan area in 1999.

5.2.2 Water

Estimated releases of <0.001 million pounds (0.29 metric tons) of trichloroethylene to surface water from 252 domestic manufacturing and processing facilities in 2009, accounted for about 0.04% of the estimated total environmental releases from facilities required to report to the TRI (TRI09 2011). An additional 0.135 million pounds (61 metric tons) were released off site, which includes releases to publicly owned treatment works (POTWs) (TRI09 2011).

5.2.3 Soil

Estimated releases of 0.077 million pounds (35 metric tons) of trichloroethylene to soils from 252 domestic manufacturing and processing facilities in 2009, accounted for about 5% of the

estimated total environmental releases from facilities required to report to the TRI (TRI09 2011). An additional 0.038 million pounds (17 metric tons), constituting about 2.5% of the total environmental emissions, were released via underground injection (TRI09 2011).

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

Based on a measured Henry's law constant of 9.85×10^{-3} atm-m^3/mol at 25 °C, the estimated volatilization half-life of trichloroethylene is 1.2 hours from a model river (1 m deep, flowing 1 m/second, with a wind velocity of 5 m/second) and 4.6 days from a model lake (1 m deep, flowing 0.05 m/second, with a wind velocity of 0.5 m/second) (EPA 2010b).

Experimentally measured soil organic carbon sorption coefficients (K_{oc} values) for trichloroethylene generally range from 49 to 460 (Brigmon et al. 1998; Chiou and Kile 1998; Sahoo and Smith 1997; USGS 1998).

Uptake of trichloroethylene in apple and peach trees and wheat, corn, and tomato seedlings has been demonstrated (Chard et al. 2006; Doucette et al. 2007; Su et al. 2010).

5.3.2 Transformation and Degradation

5.3.2.2 Water

A microcosm study of trichloroethylene biotransformation in aquifers indicated that reductive dehalogenation is the primary degradation reaction (Dong et al. 2009). Squillace and Moran (2007) reported that concentrations of trichloroethylene in oxic groundwater sampled across the United States were approximately 2 orders of magnitude larger than in anoxic groundwater and cited a slower rate of biodegradation under oxic conditions.

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.1 Air

The U.S. EPA reports the annual mean concentrations of trichloroethylene measured at approximately 300 locations across the United States between 1998 and 2008. Annual mean trichloroethylene concentrations at most of these locations were between 0.01 and 0.3 ppb. Some locations had annual mean levels as high as 0.7–3.4 ppb (EPA 2011f). McCarthy et al. (2006) have estimated the upper limit for the remote background concentration of trichloroethylene in North America to be 0.02 $\mu g/m^3$.

The mean and median concentrations of trichloroethylene in air samples collected at 25 sites across Minnesota between 1991 and 1998 were 0.43 and 0.21 $\mu g/m^3$ (0.08 and 0.04 ppb), respectively (Pratt et al. 2000). Gordon et al. (1999) detected trichloroethylene in the indoor air of two out of 185 homes in Arizona with a maximum concentration of 24 $\mu g/m^3$ (4.39 ppb). Weisel et al. (2008) detected trichloroethylene in the air of 8 out of 100 homes located in both suburban and rural areas of New Jersey with maximum and 95th percentile values of 13 and 2.74 $\mu g/m^3$ (2.38 and 0.50 ppb), respectively.

Loh et al. (2006) measured geometric mean and maximum trichloroethylene concentrations of 0.43 and 115 $\mu g/m^3$ (0.08 and 21.1 ppb), respectively, in the air of over 100 stores in the greater Boston, Massachusetts area and 0.23 and 118 $\mu g/m^3$ (0.04 and 21.6 ppb), respectively, in the air of 20 dining establishments in the same region. Martin et al. (2007) measured the concentrations of trichloroethylene at buildings located near an industrial facility in Clark County, Georgia. Levels in indoor were 0.92 $\mu g/m^3$ (0.17 ppb) at an elementary school, 0.59–1.85 $\mu g/m^3$ (0.11–0.34 ppb) at a local business, and 0.21–4.66 µg/m3 (0.04–0.85 ppb) in three homes. Levels measured in outdoor air at these same locations were 0.72 $\mu g/m^3$ (0.13 ppb), 1.30–4.59 $\mu g/m^3$ (0.24–0.84 ppb), and 0.03–0.05 $\mu g/m^3$ (0.005–0.009 ppb), respectively.

Mean concentrations of trichloroethylene measured during the Minnesota Children's Pesticide Exposure Study (MCPES) were 0.8 $\mu g/m^3$ (0.15 ppb) in 73 personal air samples, 0.6 $\mu g/m^3$

(0.11 ppb) in 101 indoor air samples, and 0.6 μg/m^3 (0.11 ppb) in 100 outdoor air samples collected from households with children (Adgate et al. 2004a). During the School Health Initiative: Environment, Learning, Disease (SHIELD) study, the concentrations of trichloroethylene were measured in the outdoor home air, indoor school air, indoor home air, and personal air of 113 children from two inner-city schools in Minneapolis, Minnesota (Adgate et al. 2004b). Median concentrations of trichloroethylene in each of these sampling groups during both summer and winter were between 0.1 and 0.3 μg/m^3 (0.02–0.05 ppb). The mean concentrations of trichloroethylene measured in the winter during the Toxic Exposure Assessment, Columbia/Harvard (TEACH) study were 0.36 μg/m^3 (0.07 ppb) in home outdoor air, 1.26 μg/m^3 (0.23 ppb) in home indoor air, and 2.62 μg/m^3 (0.48 ppb) in personal air associated with 36 students from west central Harlem in New York City (Kinney et al. 2002). Trichloroethylene concentrations measured in the summer were 0.24 μg/m^3 (0.04 ppb) in home outdoor air, 0.32 μg/m^3 (0.06 ppb) in home indoor air, and 0.51 μg/m^3 (0.09 ppb) in personal air associated with 31–40 students from the same area. Clayton et al. (1999) reported mean trichloroethylene levels of 5.27 μg/m^3 (0.96 ppb) in 386 personal air samples, 2.84 μg/m^3 (0.52 ppb) in 402 indoor air samples, and 1.11 μg/m^3 (0.20 ppb) in 97 outdoor air samples collected in EPA Region 5.

Brenner (2010) measured median and maximum trichloroethylene concentrations of 0.895 and 1.69 μg/m^3 (0.16 and 0.31 ppb), respectively, in the indoor air of four large buildings at the National Aeronautics and Space Administration (NASA) Ames Research Center at the southern end of San Francisco Bay. The levels were attributed to vapor intrusion from underlying contaminated groundwater. Some elevated outdoor air levels of trichloroethylene reported are associated with waste disposal sites. Average trichloroethylene levels of 0.08–2.43 ppb were detected in ambient air at six landfill sites in New Jersey; the maximum concentration was 12.3 ppb (Harkov et al. 1985).

Sapkota et al. (2005) measured median and maximum trichloroethylene concentrations of 3.11 and 6.89 μg/m^3 (0.57 and 1.26 ppb), respectively, in the indoor air of a tollbooth at the Baltimore Harbor Toll Plaza and 0.06 and 0.56 μg/m^3 (0.01 and 0.10 ppb), respectively, in the air outside the tollbooth.

5.4.2 Water

The EPA (2011d) conducts yearly monitoring of the concentrations of trichloroethylene in public water systems (PWS) located across the United States. During 2005, trichloroethylene was detected in 2,292 out of 46,937 samples (4.9%) collected from groundwater supplied PWS and 1,874 out of 12,705 samples (14.8%) collected from surface water supplied PWS. The median, 95th percentile, and maximum concentrations of the positive samples were 1.1, 13.0, and 159 ppb, respectively, in groundwater supplied PWS and 1.6, 28.0, and 50.0, respectively, in the surface water supplied PWS. Rowe et al. (2007) detected trichloroethylene in 41 out of 1,207 U.S. domestic well samples collected between 1996 and 2002, a detection frequency of 3.4%.

Williams et al. (2002) reported annual levels of trichloroethylene measured in 3,447–4,226 California drinking water sources between 1995 and 2001. Trichloroethylene was detected in 9.6–11.7% of the sources over the time period with an average detected concentration ranging from 14.2 to 20.7 µg/L (ppb). Trichloroethylene was detected in groundwater samples from approximately 55% of 30 public supply wells and 10% of 95 monitoring wells located in a region of southern New Jersey (Stackelberg et al. 2001). The maximum concentrations of trichloroethylene measured in community water systems near Dayton, Ohio during 2004 were 3.29 µg/L (ppb) in source water and 0.21 µg/L (ppb) in finished water (Rowe et al. 2007).

Average trichloroethylene concentrations measured in groundwater at different locations at a Superfund site (former auto parts manufacturing) located on the shore of Lake Michigan ranged from 14.6 to 6,554 µg/L (ppb) (An et al. 2004). The average concentration measured in sediment water collected 100 m offshore from the site was 1.37 µg/L (ppb). Brusseau et al. (2007) reported concentrations of trichloroethylene ranging from 100 to approximately 12,000 µg/L in groundwater collected at the Tucson International Airport Area federal Superfund site in Southern Arizona.

Asher et al. (2007) measured trichloroethylene concentrations ranging from 0.15 to 0.32 µg/L (ppb) in a section of the Aberjona River near Woburn, Massachusetts.

5.4.4 Other Environmental Media

Trichloroethylene was detected in 30 table-ready food items collected from supermarkets across the United States during a 5-year study (1996–2000) conducted by the U.S. FDA (Fleming-Jones and Smith 2003). Minimum and maximum concentrations are listed in Table 5-1. Reported concentrations were between 2 and 10 ppb in most items. However, maximum levels were much higher in beef frankfurters (105 ppb), chocolate cake with icing (57 ppb), raw avocado (75 ppb), and potato chips (140 ppb).

Table 5-1. Levels of Trichloroethylene Measured in Table-Ready Foods from Across the United States During a 5-Year Study (1996–2000)

Type of food	Positive detections	Minimum (ppb)	Maximum (ppb)
American cheese	2	2	2
Cheddar cheese	1	2	2
Mixed nuts	2	2	5
Ground beef	2	3	6
Banana raw	1	2	2
Cream cheese	2	2	3
Frankfurters, beef	5	2	105
Chocolate cake with icing	3	3	57
Tuna, canned in oil	2	9	11
Fruit-flavored cereal	1	3	3
Peanut butter	3	4	70
Avocado, raw	6	2	75
Popcorn, popped in oil	2	4	8
Blueberry muffin	2	3	4
Orange, raw	1	2	2
Coleslaw with dressing	1	3	3
Sweet roll/danish	3	3	4
Potato chips	4	4	140
Quarter pound hamburger, cooked	2	5	9
Margarine	3	2	21
Butter	2	7	9
Chocolate chip cookies	2	2	4
Apple pie, fresh/frozen	2	2	4
Chicken nuggets, fast food	3	2	5

Table 5-1. Levels of Trichloroethylene Measured in Table-Ready Foods from Across the United States During a 5-Year Study (1996–2000)

Type of food	Positive detections	Minimum (ppb)	Maximum (ppb)
French fries, fast food	2	3	3
Cheeseburger, quarter pound	1	7	7
Cheese pizza	1	2	2
Bologna	5	2	20
Cheese and pepperoni pizza	2	2	2
Cake doghnuts with icing	1	3	3

Source: Fleming-Jones and Smith 2003

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

The Fourth National Report on Human Exposure to Environmental Chemicals (CDC 2009) includes results from assessment of trichloroethylene levels in blood samples from 2,150 members of the U.S. general population surveyed during the years 2001–2004. As shown in Table 5-2, trichloroethylene was below the detection limit of 0.012 ng/mL (ppb).

Table 5-2. Geometric Mean and Selected Percentiles of Blood Concentrations (in ng/mL) for the U.S. Population from the National Health and Nutrition Examination Survey

	Survey years[a]	Geometric mean (95% confidence interval)	Selected percentiles (95% confidence interval)				Sample size
			50th	75th	90th	95th	
Total	01–02	*[b]	<LOD[c]	<LOD	<LOD	<LOD	922
	03–04	*	<LOD	<LOD	<LOD	<LOD	1,228
Age group							
20–59 years	01–02	*	<LOD	<LOD	<LOD	<LOD	922
	03–04	*	<LOD	<LOD	<LOD	<LOD	1,228
Gender							
Males	01–02	*	<LOD	<LOD	<LOD	<LOD	434
	03–04	*	<LOD	<LOD	<LOD	<LOD	604
Females	01–02	*	<LOD	<LOD	<LOD	<LOD	488
	03–04	*	<LOD	<LOD	<LOD	<LOD	624

Table 5-2. Geometric Mean and Selected Percentiles of Blood Concentrations (in ng/mL) for the U.S. Population from the National Health and Nutrition Examination Survey

	Survey years[a]	Geometric mean (95% confidence interval)	Selected percentiles (95% confidence interval)				Sample size
			50th	75th	90th	95th	
Race/ethnicity							
Mexican Americans	01–02	*	<LOD	<LOD	<LOD	<LOD	228
	03–04	*	<LOD	<LOD	<LOD	<LOD	224
Non-Hispanic blacks	01–02	*	<LOD	<LOD	<LOD	<LOD	191
	03–04	*	<LOD	<LOD	<LOD	<LOD	266
Non-Hispanic whites	01–02	*	<LOD	<LOD	<LOD	<LOD	441
	03–04	*	<LOD	<LOD	<LOD	<LOD	644

[a]Survey period 2001–2002 is a one-third subsample of 20–59 year olds; survey period 2003–2004 is a one-half subsample of 20–59 year olds.
[b]Not calculated; the proportion of results below limit of detection was too high to provide a valid result.
[c]<LOD means less than the limit of detection of 0.012 ng/mL.

Source: CDC (2009)

The majority of data regarding worker exposure to trichloroethylene derive from degreasing operations, which is the primary industrial use of trichloroethylene (Bakke et al. 2007; Franco et al. 2007; Green et al. 2004; Murata et al. 2010; Raaschou-Nielson et al. 2001; Rosa 2003; von Grote et al. 2003). von Grote et al. (2003) reviewed historical occupational exposure measurements at facilities in Europe and reported average workplace air concentrations measured between 1980 and 2000 generally between <1.0 and 15.4 ppm with 95th percentile values of <170 ppm.

5.7 ADEQUACY OF THE DATA BASE

5.7.2 Ongoing Studies

As part of the National Health and Nutrition Examination Survey (NHANES), the Division of Laboratory Sciences in the National Center for Environmental Health, Centers for Disease Control, continues to analyze human blood samples for trichloroethylene and other volatile

organic compounds. These data provide estimates regarding frequency of occurrence and background levels of these compounds in the general population.

The Agency for Toxic Substances and Disease Registry (2011b) is conducting a survey of more than 300,000 people who lived or worked at Camp Lejeune or Camp Pendleton in the 1970s and 1980s.

6. ANALYTICAL METHODS

6.1 BIOLOGICAL SAMPLES

The main analytical method used to analyze for the presence of trichloroethylene and its metabolites, trichloroethanol and TCA, in biological samples is separation by gas chromatography (GC) combined with detection by mass spectrometry (MS) or electron capture detection (ECD) (Delinsky et al. 2005). Additional information regarding methods for monitoring trichloroethylene in biological samples is available in the CDC fourth National Report on Human Exposure to Environmental Chemicals (CDC 2009).

6.2 ENVIRONMENTAL SAMPLES

The most common analytical methods for analysis of trichloroethylene in environmental samples are GC coupled to MS, ECD, a Hall's electrolytic conductivity detector (HECD), or a flame-ionization detector (FID) (Delinsky et al. 2005). Preconcentration of samples is usually done by sorption on a solid sorbent for air and by the purge-and-trap method for liquid and solid matrices.

6.3 ADEQUACY OF THE DATABASE

6.3.2 Ongoing Studies

The Division of Laboratory Sciences at the National Center for Environmental Health, Centers for Disease Control and Prevention continues to develop and refine methods for the analysis of

trichloroethylene and other volatile organic compounds in blood (CDC 2009). These methods use purge and trap methodology, high-resolution gas chromatography, and magnetic sector mass spectrometry, which give detection limits in the low parts per trillion (ppt) range.

7. REGULATIONS AND ADVISORIES

An acute-duration inhalation MRL of 2 ppm was derived in the 1997 Toxicological Profile for Trichloroethylene. This MRL has been rescinded and is under further review.

An intermediate-duration inhalation MRL of 0.1 ppm was derived in the 1997 Toxicological Profile for Trichloroethylene. This MRL has been rescinded and is under further review.

ATSDR has adopted the preferred chronic RfD of 0.0005 mg/kg/day derived by EPA as the chronic-duration oral MRL for trichloroethylene (EPA 2011e; IRIS 2011). Refer to Section 2.5 of this Addendum for detailed information regarding derivation of the preferred chronic RfD.

An acute-duration oral MRL of 0.2 mg/kg/day was derived in the 1997 Toxicological Profile for Trichloroethylene. This MRL has been rescinded and is under further review.

ATSDR has adopted the preferred chronic RfC of 0.0004 ppm (0.002 mg/m^3) derived by EPA as the chronic-duration inhalation MRL for trichloroethylene (EPA 2011e; IRIS 2011). Refer to Section 2.5 of this Addendum for detailed information regarding derivation of the preferred chronic RfC.

EPA has characterized trichloroethylene as “carcinogenic to humans” by all routes of exposure based on convincing evidence of a causal association between trichloroethylene exposure in humans and kidney cancer (EPA 2011e; IRIS 2011). The 12^{th} edition of the NTP Report on Carcinogens lists trichloroethylene as “reasonably anticipated to be a human carcinogen” based on limited evidence in humans and sufficient evidence in animals (NTP 2011). The International Agency for Research on Cancer (IARC) designated trichloroethylene as Group 2A, or probably carcinogenic to humans (IARC 2011). The American Conference of Governmental Industrial

Hygienists (ACGIH) has classified trichloroethylene as an A2 carcinogen (suspected human carcinogen) (ACGIH 2011).

The Occupational Safety and Health Administration (OSHA) has required employers of workers who are occupationally exposed to trichloroethylene to institute engineering controls and work practices to reduce and maintain employee exposure at or below permissible exposure limits (PELs), which are 100 ppm trichloroethylene as an 8-hour time weighted average, 200 ppm ceiling concentration for an 8-hour shift, or a maximum peak of 300 ppm during not more than 5 minutes in any 2 hours of an 8-hour shift (OSHA 2011).

EPA has designated trichloroethylene as a hazardous air pollutant (HAP) under the Clean Air Act (CAA) (EPA 2011b). Trichloroethylene is on the list of chemicals appearing in "Toxic Chemicals Subject to Section 313 of the Emergency Planning and Community Right-to-Know Act of 1986" and has been assigned a reportable quantity (RQ) limit of 100 pounds (EPA 2011j).

Table 7-1 lists regulations and guidelines applicable to trichloroethylene.

Table 7-1. Regulations and Guidelines Applicable to Trichloroethylene

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification	Group 2A[a]	IARC 2011
WHO	Air quality guidelines		WHO 2000
	Unit risk[b]	$4.3x10^{-7}$	
	Site of tumour	Lung and testis	
	Drinking water quality guidelines	No	WHO 2008
EU SCOEL	8-hour	10 ppm (54.7 mg/m^3)	EU 2009
	STEL (15 minute)	30 ppm (164.1 mg/m^3)	EU 2009
	BLV	20 mg TCA / liter urine	EU 2009
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (8-hour TWA)	10 ppm	ACGIH 2011
	STEL (15-minute TWA)	25 ppm	
	TLV-basis (critical effect)	Central nervous system impairment, cognitive decrements, and renal toxicity	
AIHA	ERPG-1[c,d]	100 ppm	AIHA 2011
	ERPG-2[c]	500 ppm	
	ERPG-3[c]	5,000 ppm	
DOE	TEEL-0[e]	10 ppm	DOE 2010
NATIONAL *(cont.)*			
EPA	AEGL-1[f]		EPA 2010d
	10 minutes	260 ppm	
	30 minutes	180 ppm	
	60 minutes[g]	130 ppm	
	4 hours	84 ppm	
	8 hours	77 ppm	
	AEGL-2[f]		
	10 minutes	960 ppm	
	30 minutes	620 ppm	
	60 minutes[g]	450 ppm	
	4 hours	270 ppm	
	8 hours	240 ppm	
	AEGL-3[f]		
	10 minutes	6,100 ppm	
	30 minutes	6,100 ppm	
	60 minutes[g]	3,800 ppm	
	4 hours	1,500 ppm	
	8 hours	970 ppm	
	Hazardous air pollutant	Yes	EPA 2011b 42 USC 7412
	Urban hazardous air pollutant for the Integrated Urban Air Toxics Strategy	Yes	EPA 1999 64 FR 38706

Table 7-1. Regulations and Guidelines Applicable to Trichloroethylene

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
NIOSH	REL (potential occupational carcinogen)	2 ppm (1-hour ceiling as anesthetic gas) 25 ppm (10-hour TWA for all other exposures)	NIOSH 2011
	IDLH	1,000 ppm (potential occupational carcinogen)	NIOSH 1994
	Target organs	Eyes, skin, respiratory system, heart, liver, kidneys, central nervous system	NIOSH 2011
OSHA	PEL (8-hour TWA)	100 ppm	OSHA 2011
	Acceptable ceiling concentration	200 ppm	29 CFR 1910.1000, Table Z-2
	Acceptable maximum peak above the acceptable ceiling concentration for an 8-hour shift for a maximum duration of 5 minutes in any 2 hours	300 ppm	
b. Water			
EPA	Designated as hazardous substances in accordance with Section 311(b)(2)(A) of the Clean Water Act	Yes	EPA 2011g 40 CFR 116.4
	Drinking water standards and health advisories		EPA 2011a
	1-day health advisory for a 10-kg child	No	
	10-day health advisory for a 10-kg child	No	
	DWEL	0.2 mg/L	
	Lifetime	No	
	10^{-4} Cancer risk	0.3 mg/L	
	National primary drinking water standards		EPA 2009a
	MCLG	0.1 mg/L	
	MCL	0.005 mg/L	
	Potential health effects from long-term exposure above the MCL	Liver problems; increased risk of cancer	
	Sources of contaminant in drinking water	Discharge from metal degreasing sites and other factories	
	National recommended water quality criteria—human health for the consumption of:		EPA 2009b
	Water + organism	2.5 µg/L	
	Organism only	30 µg/L	
	Reportable quantities of hazardous substances designated pursuant to Section 311 of the Clean Water Act	100 pounds	EPA 2011h 40 CFR 117.3

Table 7-1. Regulations and Guidelines Applicable to Trichloroethylene

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
c. Food			
FDA	Bottled drinking water	0.005 mg/L	FDA 2011a 21 CFR 165.110
	EAFUS	Yes[h]	FDA 2011c
	Indirect food additives: substances for use only as components of adhesives	Yes	FDA 2011b 21 CFR 175.105
d. Other			
ACGIH	Carcinogenicity classification	A2[i]	ACGIH 2011
	Biological exposure indices (end of shift at end of workweek)		
	Trichloroacetic acid in urine	15 mg/L	
	Trichloroethanol in blood (without hydrolysis)	0.5 mg/L	
EPA	Carcinogenicity classification	Carcinogenic to humans[j]	EPA 2011e
	RfC	$4x10^{-4}$ ppm	
	RfD	$5x10^{-4}$ mg/kg/day	
	Oral slope factor	$4.6x10^{-2}$ per mg/kg/day	
	Inhalation unit risk	$4x10^{-6}$ per µg/m^3 ($2x10^{-2}$ per ppm) ()	
	Master Testing List	Yes[k]	EPA 2011c
	Standards for owners and operators of hazardous waste TSD facilities; groundwater monitoring list	Yes	EPA 2011i 40 CFR 264, Appendix IX
	Superfund, emergency planning, and community right-to-know		
	Designated CERCLA hazardous substance	Yes[l]	EPA 2011i 40 CFR 302.4
	Reportable quantity	100 pounds	
	Effective date of toxic chemical release reporting	01/01/1987	EPA 2011k 40 CFR 372.65
	Toxic pollutant designated pursuant to Section 307(a)(1) of the Clean Water Act	Yes	EPA 2010c 40 CFR 401.15
NIOSH	Pesticide	Group 1[m]	NIOSH 1992

Table 7-1. Regulations and Guidelines Applicable to Trichloroethylene

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
NTP	Carcinogenicity classification	Reasonably anticipated to be a human carcinogen	NTP 2011

[a]Group 2A: probably carcinogenic to humans (IARC 2011).
[b]Cancer risk estimates for lifetime exposure to a concentration of 1 µg/m^3 trichloroethylene (WHO 2000).
[c]ERPG-1 is the maximum airborne concentration below which nearly all individuals could be exposed for up to 1 hour without experiencing other than mild, transient health effects; ERPG-2 is the maximum airborne concentration below which nearly all individuals could be exposed for up to 1 hour without experiencing irreversible or other serious adverse effects; and ERPG-3 is the maximum airborne concentration below which nearly all individuals could be exposed for up to 1 hour without life-threatening health effects (AIHA 2011).
[d]Odor should be detectable near ERPG-1 (AIHA 2011).
[e]TEEL-0 is the threshold concentration below which most people will experience no adverse health effects (DOE 2010).
[f]AEGL-1 is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic nonsensory effects; however, the effects are not disabling and are transient and reversible upon cessation of exposure; AEGL-2 is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape; and AEGL-3 is the airborne concentration of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death (EPA 2010d).
[g]60-minute AEGL-1, -2, and -3 values correspond to PAC-1 (mild, transient health effects), PAC-2 (irreversible or other serious health effects that could impair the ability to take protective action), and PAC-3 (life-threatening health effects) values, respectively (DOE 2010).
[h]The EAFUS list of substances contains ingredients added directly to food that FDA has either approved as food additives or listed or affirmed as GRAS (FDA 2009).
[i]A2: suspected human carcinogen (ACGIH 2011).
[j]Carcinogenic to humans by all routes of exposure based on convincing evidence of a causal association between trichloroethylene exposure in humans and kidney cancer (EPA 2011e).
[k]Trichloroethylene was recommended to the MTL by the U.S. EPA's Office of Pollution Prevention and Toxics on the basis of the SIDS. Styrene was added to the MTL in 1994 and the chemical testing program is currently underway by way of a VTA. The testing needs include health effects, environmental effects, and environmental fate and exposure.
[l]Designated CERCLA hazardous substance pursuant to Section 311(b)(2) of the Clean Water Act, Section 307(a) of the Clean Water Act, Section 112 of the Clean Air Act, and Section 3001 of RCRA.
[m]Group 1: pesticide that poses a significant risk of: (1) adverse acute health effects at low concentrations, or (2) carcinogenic, teratogenic, neurotoxic, or reproductive effects; trichloroethylene is a suspected carcinogen (NIOSH 1992).

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = acute exposure guideline levels; AIHA = American Industrial Hygiene Association; CERCLA = Comprehensive Environmental Response, Compensation, and Liability Act; CFR = Code of Federal Regulations; DOE = Department of Energy; DWEL = drinking water equivalent level; EAFUS = Everything Added to Food in the United States; EPA = Environmental Protection Agency; ERPG = emergency response planning guidelines; EU = European Union; FDA = Food and Drug Administration; FR = Federal Register; GRAS = Generally Recognized As Safe; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; MCL = maximum contaminant level; MCLG = maximum contaminant level goal; MTL = Master Testing List; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PAC = Protective Action Criteria; PEL = permissible exposure limit; RCRA = Resource Conservation and Recovery Act; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; SCOEL = Scientific Committee on Occupational Exposure Limits; SIDS = Screening Information Data Sets; STEL = short-term expsoure limit; TEEL = Temporary Emergency Exposure Limit; TLV = threshold limit values; TSD = treatment, storage, and disposal; TWA = time-weighted average; USC = United States Code; VTA = Voluntary Testing Agreement; WHO = World Health Organization

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APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (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 for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point

considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Environmental Medicine, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology and Environmental Medicine, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-62, Atlanta, Georgia 30333.

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Trichloroethylene
CAS Number: 79-01-6
Date: March 2012
Route: [X] Inhalation [ ] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: Not applicable
Species: Not applicable

Minimal Risk Level: Rescinded [ ] mg/kg/day [ ] ppm

The previous acute-duration inhalation MRL of 2 ppm derived in the 1997 Toxicological Profile for Trichloroethylene is rescinded, because it is not adequately protective. It is presently under further review.

The basis for adoption of the preferred chronic RfC of 0.0004 ppm derived by EPA (2011e) for trichloroethylene as the chronic-duration inhalation MRL is applicable to rescinding the acute-duration oral exposure MRL for trichloroethylene.

As noted elsewhere, EPA (2011e) performed PBPK model-based route-to-route extrapolation from the oral studies of Johnson et al. (2003) and Keil et al. (2009) to derive a preferred chronic RfC of 0.0004 ppm for trichloroethylene. As noted elsewhere, modeling of those route-to-route extrapolations for 52 weeks in humans found that the previous 1997 intermediate-duration inhalation MRL is no longer adequately protective. Not only was the 1997 intermediate-duration inhalation MRL of 0.1 ppm found to be inadequately protective, but studies by Johnson et al. (2003) and Peden-Adams et al. (2006) suggest that the 1997 acute-duration MRL of 2 ppm is no longer adequately protective.

The Johnson et al. study (2003) assessed sensitive developmental effects (e.g., cardiac malformations) identified in animal studies that employed gestational exposure. When combined with the results from the Peden-Adams et al. study (2006) that assessed developmental and early postnatal developmental exposure of immunotoxicity at a three week end point, it was felt is possible that these effects could potentially be elicited by trichloroethylene exposure for <15 days, if adequately examined.

Based upon this newer data, the 1997 acute-duration inhalation MRL of 2 ppm is no longer adequately protective. The 1997 MRL is rescinded at this time and remains under futher review.

Agency Contact (Chemical Manager): G. Daniel Todd, Ph.D.

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Trichloroethylene
CAS Number: 79-01-6
Date: March 2012
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: Not applicable
Species: Not applicable

Minimal Risk Level: Rescinded [ ] mg/kg/day [ ] ppm

The previous intermediate-duration inhalation MRL of 0.1 ppm derived in the 1997 Toxicological Profile for Trichloroethylene is rescinded, because it is not adequately protective. It is presently under further review.

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 rescinding the intermediate-duration inhalation exposure to trichloroethylene. As noted elsewhere, EPA (2011e) performed PBPK model-based route-to-route extrapolation from the oral studies of Johnson et al. (2003) and Keil et al. (2009) in order 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 lasting 10 weeks for rats and mice and 100 weeks for humans.

Sample simulations for a 52-week inhalation exposure in humans, which is within the range of an ATSDR-defined intermediate-duration exposure (15–364 days), did not result in a substantially different value from the 100 week inhalation exposure simulation (Weihsueh Chiu, personal communication, August 22, 2011).

Based upon this newer data, the 1997 intermediate-duration inhalation MRL of 0.1 ppm is no longer adequately protective. The 1997 MRL is rescinded at this time and remains under futher review.

Agency Contact (Chemical Manager): G. Daniel Todd, Ph.D.

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Trichloroethylene
CAS Numbers: 79-01-6
Date: March 2012
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 61, 86
Species: Mouse, Rat

Minimal Risk Level: 0.0004 [ ] mg/kg/day [X] ppm

ATSDR has adopted the EPA (2011e) preferred chronic RfC of 0.0004 ppm for trichloroethylene as the chronic-duration inhalation MRL for trichloroethylene. The preferred chronic RfC of EPA is based on results of two critical studies for which individual candidate chronic RfCs were derived: A candidate chronic RfC of 0.00033 ppm for decreased thymus weight in female mice (Keil et al. 2009), and a candidate chronic RfC of 0.00037 ppm for fetal heart malformations in rats (Johnson et al. 2003). Derivation of the EPA preferred chronic RfC included route-to-route extrapolation. Selected details regarding EPA's methodology for derivation of the preferred chronic RfC using results from the two critical studies are presented below and summarized in Table A-1.

Study of Keil et al. (2009)

Reference: 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(5):443-453.

Experimental design: Groups of 9-week-old female B6C3F1 mice (9–10/group) were administered trichloroethylene in the drinking water at 0, 1,400, or 14,000 ppb (1.4 or 14 ppm) in 1% emulphor vehicle for 30 weeks. During the exposure period, serum levels of total IgG and autoantibodies (anti-ssDNA, -dsDNA, and -glomerular antigen [GA]) were monitored. Body weights were recorded 1 day prior to the initiation of trichloroethylene exposure and again at exposure termination. At sacrifice, spleen, thymus, liver, and kidney were weighed. Spleen and thymus were processed for assessment of cell counts and activity. Kidneys were processed for histopathologic evaluation; renal pathology was scored by grading glomerular inflammation, crescent formation, and necrosis in histopathology slides.

Effect noted in study and corresponding doses: Decreased thymus weight (30% lower than controls), increased serum levels of IgG and selected autoantibodies at 1.4 ppm trichloroethylene in the drinking water (EPA-estimated dose of 0.35 mg/kg/day).

Dose and end point used for MRL derivation: A PBPK model was used to calculate the internal dose point of departure (idPOD = 0.139 mg trichloroethylene metabolized/$kg^{3/4}$/day) from the applied dose LOAEL of 0.35 mg/kg/day. The mouse idPOD was converted to a 99^{th} percentile estimate of a human equivalent concentration (HEC_{99} = 0.033 ppm) for lifetime continuous exposure derived from combined interspecies, intraspecies, and route-to-route extrapolation using the PBPK model for trichloroethylene.

[ ] NOAEL [ ] LOAEL [X] HEC_{99}

Uncertainty Factors used in MRL derivation:

[10] for use of a LOAEL
[3] because a PBPK model was used for interspecies extrapolation
[3] because a PBPK model was used to characterize human toxicokinetic variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? EPA estimated doses using the average of subchronic and chronic reference values for generic body weight and water consumption rates for female B6C3F1 mice.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Not applicable.

Study of Johnson et al. (2003)

Reference: Johnson PD, Goldberg SY, Mays MZ, et al. 2003. Threshold of trichloroethylene contamination in maternal drinking waters affecting fetal heart development in the rat. Environ Health Perspect 111(3):289-292.

Experimental design: Groups of pregnant Sprague-Dawley rats (9–13/exposure level) were administered trichloroethylene in the drinking water throughout gestation (GDs 1–22) at concentrations of 0, 0.0025, 0.25, 1.5, or 1,000 ppm. At termination on GD 22, dams and fetuses were examined for gross abnormalities and fetuses were weighed, measured for crown-rump length, and sexed. Fetal hearts and great vessels were examined for gross malformations and prepared for histopathologic evaluations.

Effect noted in study and corresponding doses: Increased incidences of fetuses with cardiac malformations at maternal exposure levels ≥0.25 ppm (estimated maternal doses ≥0.048 mg/kg/day).

Dose and end point used for MRL derivation: Using a benchmark response (BMR) of 1% extra risk that was preferred due to accounting for intralitter effects using a nested model and pups being the unit of measure, EPA (2011e) calculated a rat lower 95% confidence limit on the benchmark dose ($BMDL_{01}$) of 0.0207 mg/kg/day from the fetal heart malformation incidence data. The highest-dose group (1,000-fold higher than next highest) was dropped to improve model fit. The rat $BMDL_{01}$ was 0.0207 mg/kg/day. A PBPK model was used to calculate the idPOD of 0.0142 mg trichloroethylene metabolized by oxidation/kg body weight$^{3/4}$/day. The rat idPOD was converted to a HEC_{99} of 0.0037 ppm for continuous lifetime exposure derived from route-to-route extrapolation and combined interspecies and intraspecies extrapolation using the PBPK model.

[ ] NOAEL [ ] LOAEL [X] HEC_{99}

Uncertainty Factors used in MRL derivation:

[3] because a PBPK model was used for interspecies extrapolation
[3] because a PBPK model was used to characterize human toxicokinetic variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Not applicable.

Other additional studies or pertinent information that lend support to this MRL: EPA determined potential PODs for candidate chronic RfD and RfC values for numerous studies by utilizing the LOAEL/NOAEL approach, BMD analysis, and/or PBPK modeling of human and animal data considered suitable for dose-response assessment. EPA employed a PBPK model to calculate an idPOD for plausible internal dose-metrics based on present understanding of the role 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 HED_{99} or HEC_{99} values for candidate critical effects.

EPA determined that the lowest PBPK model-based candidate RfCs fall within a narrow range of 0.0003–0.0006 ppm. EPA selected the PBPK model-based candidate RfC values of 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) to represent the critical effects for deriving the preferred chronic RfC of 0.0004 ppm for trichloroethylene and noted that this value represents the midpoint of the model-based candidate RfC values of 0.00033 and 0.00037 ppm (0.00035 ppm, or 0.0004 ppm rounded to one significant digit). EPA also noted that the preferred RfC of 0.0004 ppm is less than 2-fold different from a supporting effect PBPK-based candidate RfC of 0.0006 ppm for toxic nephropathy in rats (NTP 1988). The lowest PBPK-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-based candidate RfC from the most sensitive oral study. Therefore, the preferred 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.

Table A-1. Derivation of Candidate RfCs from Critical Effects that Support the Preferred RfC for Trichloroethylene

Keil et al. (2009)—Decreased thymus weight in female B6C3F1 mice exposed for 30 weeks by drinking water.

- idPOD = 0.139 mg trichloroethylene metabolized/kg$^{3/4}$/day, which is the PBPK model-predicted internal dose at the applied dose LOAEL of 0.35 mg/kg/day (no BMD modeling due to inadequate model fit caused by supralinear dose-response shape).
- HEC_{99} = 0.033 ppm (lifetime continuous exposure)[a] derived from combined interspecies, intraspecies, and route-to-route extrapolation using PBPK model.
- UF_{loael} = 10 because POD is a LOAEL for an adverse effect.
- UF_{is} = 3.16 because the PBPK model was used for interspecies extrapolation.
- UF_h = 3.16 because the PBPK model was used to characterize human toxicokinetic variability.
- PBPK model-based candidate RfC = 0.033/100 = 0.00033 ppm.

Johnson et al. (2003)—Cardiac malformations in Sprague-Dawley rat fetuses whose mothers were exposed to trichloroethylene in the drinking water from GDs 1 to 22.

- idPOD = 0.0142 mg trichloroethylene metabolized by oxidation/kg$^{3/4}$/day, which is the BMDL from BMD modeling using PBPK model-predicted internal doses, with highest-dose group (1,000-fold higher than next highest-dose group) dropped, pup as unit of analysis, BMR = 1% (due to severity of defects, some of which could have been fatal), and a nested Log-logistic model to account for intralitter correlation.
- HEC_{99} = 0.0037 ppm (lifetime continuous exposure)[a] derived from combined interspecies, intraspecies, and route-to-route extrapolation using PBPK model.
- UF_{is} = 3.16 because the PBPK model was used for interspecies extrapolation.
- UF_h = 3.16 because the PBPK model was used to characterize human toxicokinetic variability.
- PBPK model-based candidate RfC = 0.0037/10 = 0.00037 ppm.

[a]Dose-metrics were converted to daily or weekly averages based on simulations lasting 10 weeks for rats and mice and 100 weeks for humans. These simulation times were the shortest for which additional simulation length did not add substantially to the average (i.e., less than a few percent change with a doubling of simulation time).

BMD = benchmark dose; BMDL = lower 95% confidence limit on the BMD; BMR = benchmark response; HEC_{99} = 99th percentile estimate of human equivalent concentration; idPOD = internal dose POD; LOAEL = lowest-observed adverse-effect-level; PBPK = physiologically-based pharmacokinetic; POD = point of departure; RfC = reference concentration; UF = uncertainty factor; UF_{is} = interspecies UF; UF_h = human variability UF; UF_{loael} = LOAEL-to-NOAEL UF

Source: EPA 2011e

Agency Contact (Chemical Manager): G. Daniel Todd, Ph.D.

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Trichloroethylene
CAS Number: 79-01-6
Date: March 2012
Route: [ ] Inhalation [X] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: Not applicable
Species: Not applicable

Minimal Risk Level: Rescinded [ ] mg/kg/day [ ] ppm

The previous acute-duration oral MRL of 0.2 mg/kg/day derived in the 1997 Toxicological Profile for Trichloroethylene is rescinded, because it is not adequately protective. It is presently under further review.

The basis for adoption of the preferred chronic RfD of 0.0005 mg/kg/day derived by EPA (2011e) for trichloroethylene as the chronic-duration oral MRL is applicable to rescinding the acute-duration oral exposure to trichloroethylene as well.

Recall that 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 weeks 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 oral exposure (within the range of an ATSDR-defined intermediate-duration exposure [15–364 days]) did not result in a substantially different value from the 100 week oral exposure simulation (Weihsueh Chiu, personal communication, August 22, 2011).

Two of the studies (Peden-Adams et al. 2006, Johnson et al. 2003) used to support the above derivation had assessed sensitive developmental effects (e.g., cardiac malformations, developmental immunotoxicity) identified in animal studies that employed gestational exposure or gestational and early postnatal development periods that were just >14 days in duration. It is possible these effects could potentially be elicited by trichloroethylene exposure for <15 days, if adequately examined.

Based upon this newer data, the 1997 acute-duration oral MRL of 0.2 mg/kg/day is no longer adequately protective. The 1997 MRL is rescinded at this time and remains under futher review.

Agency Contact (Chemical Manager): G. Daniel Todd, Ph.D.

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Trichloroethylene
CAS Number: 79-01-6
Date: March 2012
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Graph Key: Not applicable
Species: Not applicable

Minimal Risk Level: Not Applicable [ ] mg/kg/day [ ] ppm

The 1997 Toxicological Profile for Trichloroethylene did not derive an oral, intermediate-duration MRL. However, based upon newer data this MRL is under further review.

The basis for adoption of the preferred chronic RfD of 0.0005 mg/kg/day derived by EPA (2011e) for trichloroethylene as the chronic-duration oral MRL is applicable to further review of the intermediate-duration oral exposure to trichloroethylene as well.

Recall that 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 weeks 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 oral exposure (within the range of an ATSDR-defined intermediate-duration exposure [15–364 days]) did not result in a substantially different value from the 100 week oral exposure simulation (Weihsueh Chiu, personal communication, August 22, 2011).

Also, all three studies (Peden-Adams et al. 2006, Johnson et al. 2003, Keil et al. 2009) used to support the above derivation had assessed endpoints following exposures lasting for 15 days to not more than 365 days, within the range of an ATSDR-defined intermediate-duration exposure.

Based upon this newer data, the intermediate-duration oral MRL is under futher review.

Agency Contact (Chemical Manager): G. Daniel Todd, Ph.D.

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Trichloroethylene
CAS Numbers: 79-01-6
Date: March 2012
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Graph Key: 54, 56, 69
Species: Mouse, Rat

Minimal Risk Level: 0.0005 [X] mg/kg/day [ ] ppm

ATSDR has adopted 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. The preferred chronic RfD of EPA is based on results of three critical studies for which individual candidate chronic RfDs were derived: A candidate chronic RfD of 0.00048 mg/kg/day for decreased thymus weight in female mice exposed to trichloroethylene in the drinking water for 30 weeks (Keil et al. 2009), a candidate chronic RfD of 0.00037 mg/kg/day for decreased plaque forming cell (PFC) response in 3- and 8-week-old pups and increased delayed-type hypersensitivity in 8-week-old pups exposed to trichloroethylene throughout gestation until 3 or 8 weeks of age via the drinking water (Peden-Adams et al. 2006), and a candidate chronic RfD of 0.00051 mg/kg/day for fetal heart malformations in rats exposed to trichloroethylene via the maternal drinking water during gestation (Johnson et al. 2003). Selected details regarding EPA's methodology for derivation of the preferred chronic RfD using results from the three critical studies are presented below and summarized in Table A-2.

Study of Keil et al. (2009)

Reference: 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(5):443-453.

Experimental design: Groups of 9-week-old female B6C3F1 mice (9–10/group) were administered trichloroethylene in the drinking water at 0, 1,400, or 14,000 ppb (1.4 or 14 ppm) in 1% emulphor vehicle for 30 weeks. During the exposure period, serum levels of total IgG and autoantibodies (anti-ssDNA, -dsDNA, and -GA) were monitored. Body weights were recorded one day prior to the initiation of trichloroethylene TCE exposure and again at exposure termination. At sacrifice, spleen, thymus, liver, and kidney were weighed. Spleen and thymus were processed for assessment of cell counts and activity. Kidneys were processed for histopathologic evaluation; renal pathology was scored by grading glomerular inflammation, crescent formation, and necrosis in histopathology slides.

Effect noted in study and corresponding doses: Decreased thymus weight (30% lower than controls), increased serum levels of IgG and selected autoantibodies at 1.4 ppm trichloroethylene in the drinking water (EPA-estimated dose of 0.35 mg/kg/day).

Dose and end point used for MRL derivation: A PBPK model was used to calculate the idPOD (0.139 mg trichloroethylene metabolized/$kg^{3/4}$/day) from the applied dose LOAEL of 0.35 mg/kg/day. The mouse idPOD was converted to a HED_{99} of 0.048 mg/kg/day for lifetime continuous exposure derived from combined interspecies and intraspecies extrapolation using the PBPK model for trichloroethylene.

[ ] NOAEL [ ] LOAEL [X] HED_{99}

Uncertainty Factors used in MRL derivation:

[10] for use of a LOAEL
[3] because a PBPK model was used for interspecies extrapolation
[3] because a PBPK model was used to characterize human toxicokinetic variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? EPA estimated doses using the average of subchronic and chronic reference values for generic body weight and water consumption rates for female B6C3F1 mice.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Not applicable.

Study of Peden-Adams et al. (2006)

Reference: 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.

Experimental design: Groups of C3H/HeJ male and C57BL/6N female mice (5/sex/group) were administered trichloroethylene in the drinking water at 0, 1.4, or 14 ppm, beginning at pairing (1:1) and continued for 7 days of mating and throughout gestation (at least for the dams) and lactation. Pups (strain B6C3F1 is produced from the paired parental strains) were evaluated for body length (crown-rump), and timing of eye opening and ear unfolding. At weaning of the pups at 3 weeks of age, 5–7 pups/treatment group were weighed and sacrificed to assess kidney, liver, thymus, and spleen weights. Trichloroethylene-related effects on the immune system were assessed by measuring splenic lymphocyte proliferation, NK cell activity, sheep red blood cell (SRBC)-specific IgM production (PFC response), splenic B220+ cells, and thymic and splenic T-cell immunophenotypes. The remaining pups (4–5 pups/treatment group) were assessed at 8 weeks of age in a manner similar to those assessed at 3 weeks of age, with additional assessments of autoantibodies to dsDNA and delayed type hypersensitivity response (indicated by foot pad swelling following subcutaneous injection of SRBC).

Effect noted in study and corresponding doses: Decreased PFC response was observed in 3- and 8-week-old pups and increased delayed-type sensitivity was noted in 8-week-old pups at 1.4 and 14 ppm trichloroethylene in the drinking water (author-estimated maternal doses of 0.37 and 3.7 mg/kg/day).

Dose and end point used for MRL derivation: 0.37 mg/kg/day for decreased PFC response and increased delayed-type sensitivity.

[ ] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

[10] for use of a LOAEL
[10] for interspecies extrapolation
[10] for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Doses were estimated by the study authors.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Not applicable.

Study of Johnson et al. (2003)

Reference: Johnson PD, Goldberg SY, Mays MZ, et al. 2003. Threshold of trichloroethylene contamination in maternal drinking waters affecting fetal heart development in the rat. Environ Health Perspect 111(3):289-292.

Experimental design: Groups of pregnant Sprague-Dawley rats (9–13/exposure level) were administered trichloroethylene in the drinking water throughout gestation (GDs 1–22) at concentrations of 0, 0.0025, 0.25, 1.5, or 1,000 ppm. At termination on GD 22, dams and fetuses were examined for gross abnormalities and fetuses were weighed, measured for crown-rump length, and sexed. Fetal hearts and great vessels were examined for gross malformations and prepared for histopathologic evaluations.

Effect noted in study and corresponding doses: Increased incidences of fetuses with cardiac malformations at maternal exposure levels ≥0.25 ppm (estimated maternal doses ≥0.048 mg/kg/day).

Dose and end point used for MRL derivation: EPA (2011e) calculated a rat $BMDL_{01}$ of 0.0207 mg/kg/day from the fetal heart malformation incidence data using a BMR of 1% extra risk that was preferred due to accounting for intralitter effects using a nested model and pups being the unit of measure. The highest-dose group (1,000-fold higher than next highest) was dropped to improve model fit. The rat $BMDL_{01}$ was 0.0207 mg/kg/day. A PBPK model was used to calculate the idPOD of 0.0142 mg trichloroethylene metabolized by oxidation/kg body weight$^{3/4}$/day. The rat idPOD was converted to a HED_{99} of 0.0051 mg/kg/day for continuous lifetime exposure derived from combined interspecies and intraspecies extrapolation using the PBPK model (EPA 2011e).

[ ] NOAEL [ ] LOAEL [X] HED_{99}

Uncertainty Factors used in MRL derivation:

[X] 3 because a PBPK model was used for interspecies extrapolation
[X] 3 because a PBPK model was used to characterize human toxicokinetic extrapolation

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Doses were calculated by the study authors.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? Not applicable.

Other additional studies or pertinent information that lend support to this MRL: EPA determined potential PODs for candidate chronic RfD and RfC values for numerous studies by utilizing the LOAEL/NOAEL approach, BMD analysis, and/or PBPK modeling of human and animal data considered

suitable for dose-response assessment. EPA employed a PBPK model to calculate an idPOD for plausible internal dose-metrics based on present understanding of the role 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 HED_{99} or HEC_{99} values for candidate critical effects.

Among the lowest candidate RfDs (0.0003–0.0005 mg/kg/day) EPA selected three to serve as 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 PFC 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 from the three critical studies 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 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 (Woolhiser et al. 2006).

Table A-2. Derivation of Candidate RfDs from Critical Effects that Support the Preferred RfD for Trichloroethylene

Keil et al. (2009)—Decreased thymus weight in female B6C3F1 mice exposed for 30 weeks by drinking water.

- idPOD = 0.139 mg trichloroethylene metabolized/kg$^{3/4}$/day, which is the PBPK model-predicted internal dose at the applied dose LOAEL of 0.35 mg/kg/day (continuous) (no BMD modeling due to inadequate model fit caused by supralinear dose-response shape).
- HED_{99} = 0.048 mg/kg/day (lifetime continuous exposure)[a] derived from combined interspecies and intraspecies extrapolation using PBPK model.
- UF_{loael} = 10 because POD is a LOAEL for an adverse effect.
- UF_{is} = 3.16 because the PBPK model was used for interspecies extrapolation.
- UF_h = 3.16 because the PBPK model was used to characterize human toxicokinetic variability.
- PBPK model-based candidate RfD = 0.048/100 = 0.00048 mg/kg/day.

Peden-Adams et al. (2006)—Decreased PFC response (at 3 and 8 weeks of age), increased delayed-type hypersensitivity (at 8 weeks of age) in pups exposed from GD 0 until 3 or 8 weeks of age through drinking water (placental and lactational transfer, and pup ingestion).

- POD = 0.37 mg/kg/day is the applied dose LOAEL (estimated daily dam dose) (no BMD modeling due to inadequate model fit caused by supralinear dose-response shape). No PBPK modeling was attempted due to lack of appropriate models/parameters to account for complicated fetal/pup exposure pattern.
- UF_{loael} = 10 because POD is a LOAEL for multiple adverse effects.
- UF_{is} = 10 for interspecies extrapolation because PBPK model was not used.
- UF_h = 10 for human variability because PBPK model was not used.
- Candidate RfD = 0.37/1000 = 0.00037 mg/kg/day.

Johnson et al. (2003)—Fetal heart malformations in Sprague-Dawley rats exposed from GDs 1 to 22 by drinking water

- idPOD = 0.0142 mg trichloroethylene metabolized by oxidation/kg$^{3/4}$/day, which is the BMDL from BMD modeling using PBPK model-predicted internal doses, with highest-dose group (1,000-fold higher than next highest-dose group) dropped, pup as unit of analysis, BMR = 1% (due to severity of defects, some of which could have been fatal), and a nested Log-logistic model to account for intralitter correlation.
- HED_{99} = 0.0051 mg/kg/day (lifetime continuous exposure)[a] derived from combined interspecies and intraspecies extrapolation using PBPK model.
- UF_{is} = 3.16 because the PBPK model was used for interspecies extrapolation.
- UF_h = 3.16 because the PBPK model was used to characterize human toxicokinetic variability.
- PBPK model-based candidate RfD = 0.0051/10 = 0.00051 mg/kg/day.

[a]Dose-metrics were converted to daily or weekly averages based on simulations lasting 10 weeks for rats and mice and 100 weeks for humans. Additional simulation length (i.e., simulations longer than 100 weeks for humans) did not add substantially to the average (i.e., less than a few percent change with a doubling of simulation time); therefore, the simulation of 100 weeks for humans was considered representative of continuous lifetime exposure to humans.

BMD = benchmark dose; BMDL = lower 95% confidence limit on the BMD; BMR = benchmark response; GD = gestation day; HED_{99} = 99th percentile estimate of human equivalent dose; idPOD = internal dose POD; LOAEL = lowest-observed-adverse-effect level; PBPK = physiologically-based pharmacokinetic; PFC = plaque-forming cell; POD = point of departure; RfC = reference concentration; UF = uncertainty factor; UF_{is} = interspecies UF; UF_h = human variability UF; UF_{loael} = LOAEL-to-NOAEL UF

Source: EPA 2011e

Agency Contact (Chemical Manager): G. Daniel Todd, Ph.D.

LSE ATTACHMENT

The information in the LSE Attachment includes levels of significant exposure to trichloroethylene that were identified in the 1997 Toxicological Profile for Trichloroethylene as well as update information reported in this Addendum for Trichloroethylene.