# 2. RELEVANCE TO PUBLIC HEALTH

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

1,1,1-Trichloroethane is a synthetic chemical. In 2003, the estimated capacity of the commercial production of 1,1,1-trichloroethane in the United States was 510 million pounds. Under the Clean Air Act as amended in 1990, all production of 1,1,1-trichloroethane for domestic use was scheduled to cease as of January 1, 2002. It may be used for essential applications such as medical devices and aviation safety (for the testing of metal fatigue and corrosion of existing airplane engines and other parts susceptible to corrosion) until January 1, 2005 or for export to developing countries until January 1, 2012. 1,1,1-Trichloroethane was predominantly used as a chemical intermediate in the manufacture of hydrochlorofluorocarbons (HCFCs). It was also commonly used in vapor degreasing and cold cleaning, adhesives, coatings and inks, textiles, and electronics. Currently, 1,1,1-trichloroethane is almost entirely used as a precursor for hydrofluorocarbons.

1,1,1-Trichloroethane was released to the environment during the course of its manufacture, formulation, and use. It was frequently detected in the atmosphere and in water. In 2003, environmental releases of 1,1,1-trichloroethane reported under the EPA Toxics Release Inventory (TRI) program were about 114 thousand pounds in air emissions, 40 pounds in water discharges, and 16 hundred pounds in releases to land.

Monitoring studies of the ambient air levels of 1,1,1-trichloroethane in urban areas have reported concentrations in the range of 0.1–1 ppb, while the concentrations in rural areas have been reported to be <0.1 ppb (Table 6-3). Representative data taken from five geographic areas located throughout the United States report indoor concentrations of 0.3–4.4 ppb and outdoor concentrations of 0.11–0.92 ppb. A more recent EPA region V (Minnesota, Wisconsin, Michigan, Illinois, Indiana, and Ohio) National Human Exposure Assessment Survey (NHEXAS) detected a mean concentration of 1,1,1-trichloroethane to be 1.15 ppb in indoor air samples collected from residential areas from July 1995 to May 1997.

Levels of 1,1,1-trichloroethane detected in water ways near sources of emissions such as industrial waste water, hazardous waste sites, and spill locations are usually <1 ppb. Drinking water from surface or groundwater sources contained 1,1,1-trichloroethane concentrations of 0.01–3.5 ppb. Limited monitoring

data are available for the presence of 1,1,1-trichloroethane in soil. 1,1,1-Trichloroethane is expected to rapidly volatilize from soil and to leach through soil.

Environmental exposures of humans to 1,1,1-trichloroethane have been correlated with levels of parent compound and 1,1,1-trichloroethane metabolites (trichloroethanol and trichloroacetic acid) in expired air, blood, and urine. The appearance of trichloroacetic acid in urine is not unique to 1,1,1-trichloroethane, as it has also been identified as a urinary metabolite of trichloroethylene and tetrachloroethylene. If exposure is known to be solely to 1,1,1-trichloroethane, trichloroacetic acid levels in the urine may be a useful biomarker of exposure, because of the relatively long half-life of trichloroacetic acid. However, the length of time between 1,1,1-trichloroethane exposure and the measurement of breath, blood, or urine levels is critical to the accurate evaluation of the magnitude of exposure. Up to 90% of the 1,1,1-trichloroethane absorbed by any route is rapidly excreted unchanged in the expired air. Most of the remaining 10% is accounted for as the urinary metabolites trichloroethanol and trichloroacetic acid.

## 2.2 SUMMARY OF HEALTH EFFECTS

1,1,1-Trichloroethane is one of many solvents inhaled by some people to alter mood or consciousness. Available human and animal data indicate that the central nervous system is the most sensitive target for 1,1,1-trichloroethane toxicity. Clinical signs of toxicity associated with human exposure to large quantities of 1,1,1-trichloroethane include central nervous system depression, hypotension, cardiac arrhythmia, diarrhea and vomiting, mild hepatic effects, and dermal and ocular irritation. Deaths of persons exposed to high concentrations have been attributed to cardiac arrhythmia and respiratory failure secondary to central nervous system depression. Lower-level exposure to 1,1,1-trichloroethane may result in more subtle neurological effects such as impaired performance in tests designed to measure variables such as manual dexterity, eye-hand coordination, perceptual speed, and reaction time. Mild hepatotoxicity and decreased body weight gain have been demonstrated in some animals exposed to relatively large quantities of 1,1,1-trichloroethane. Mild developmental effects induced by high level exposure of animals have not been verified in humans. Available data are inadequate to determine the carcinogenicity of 1,1,1-trichloroethane. The EPA has classified 1,1,1-trichloroethane as group D, not classifiable as to human carcinogenicity, based on no reported human data and inadequate animal data. In general, route of exposure does not appear to be as important as circulating levels of 1,1,1-trichloroethane.

**Death.** The volatility of 1,1,1-trichloroethane, in addition to the rapid and extensive absorption and elimination of the inhaled compound, makes acute inhalation in product use situations the most likely lethal exposure scenario in humans. The acute lethal air concentration for humans is unknown; however, simulations of several lethal exposures suggest that it may be as low as 6,000 ppm. The results of animal studies indicate that the acute lethal exposure concentration decreases substantially with increasing exposure duration. Thus, the concentration required to cause animal death after a 6–7-hour exposure is 3–4 times less than that required after a 15-minute exposure.

Human deaths after inhalation exposure to 1,1,1-trichloroethane have been attributed to respiratory failure secondary to central nervous system depression and to cardiac arrhythmias. Animal studies reveal that arrhythmias may result from sensitization of the heart to epinephrine. Hypoxia may exacerbate the situation. Therefore, acute lethal exposure levels may be lower in individuals exposed during physical exertion. Physical exertion also may decrease the acute lethal exposure level by increasing the respiratory rate and lung perfusion rate, thereby increasing the systemic absorption of 1,1,1-trichloroethane.

Very little is known about the lethality of ingested 1,1,1-trichloroethane in humans. In one case of acute oral exposure, accidental ingestion of 600 mg/kg of 1,1,1-trichloroethane was not fatal. Animal studies suggest that even higher acute oral doses may not cause death.

**Neurological Effects.** Neurological effects are the preeminent signs of acute inhalation exposure to 1,1,1-trichloroethane in humans. The intoxicating effects of the inhaled chemical create a potential for its abuse. The severity of central nervous system depressant effects in humans during acute inhalation exposure increases as the exposure duration and level are increased. Impaired performance of psychophysiological function tests has been observed in individuals exposed to moderate concentrations (≥175 ppm). Dizziness, lightheadedness, and loss of coordination are caused by exposure to higher concentrations (>500 ppm). General anesthesia occurs at high levels (≥10,000 ppm). These effects subside rapidly after exposure. One report suggested that impaired memory and deficits in balance were persistent effects in a group of workers after chronic exposure to moderate to high levels of 1,1,1-trichloroethane.

Animals are useful models for examining the neurological effects of exposure to 1,1,1-trichloroethane. As in humans, central nervous system depression is the predominant effect of inhaled 1,1,1-trichloroethane. Signs include ataxia, unconsciousness, and death at increasing concentrations. No evidence of gross or histological damage was found in the brains of most exposed animals, although some evidence of

potential for cellular damage was indicated by reports of increased levels of glial fibrillary acid protein and decreased DNA content in the brain of gerbils after repeated exposure to low levels of the chemical. Alterations of brain metabolism also were observed in exposed animals. Behavioral changes, including impaired performance of neurobehavioral tests and increased motor activity, have been widely reported; however, the sites of action and biochemical mechanisms of neurotoxicity have not been identified. Neurophysiological changes also have been reported. These latter observations were made at a relatively high exposure level (4,000 ppm).

Little information was located regarding neurological effects in humans or animals after oral or dermal exposure to 1,1,1-trichloroethane. Existing data indicate that a single oral exposure to a dose of approximately 600 mg/kg did not produce overt signs of neurotoxicity. It is assumed, however, that sufficiently high doses of 1,1,1-trichloroethane administered orally or dermally will result in neurological effects. Oral exposure to 1,1,1-trichloroethane produced neurophysiological changes in rats given moderate doses (700 mg/kg/day) and gross neurobehavioral changes (hyperexcitability and narcosis) in rats given high doses (≥2,500 mg/kg/day). No neurological effects were observed in the offspring of rats treated by gavage during gestation and lactation with up to 750 mg 1,1,1-trichloroethane/kg/day (see Developmental Effects). No clinical signs of neurotoxicity were seen in rats and mice receiving 1,1,1-trichloroethane in the diet at concentrations as high as 80,000 ppm (doses as high as 4,800 and 5,000 mg/kg/day in males and females, respectively) for 13 weeks.

**Cardiovascular Effects.** 1,1,1-Trichloroethane can lower blood pressure (mildly to severely) in humans and can induce transient myocardial injury. Such effects, however, are likely only after exposure to very high concentrations of 1,1,1-trichloroethane vapor. Chronic exposure of workers to levels ≤250 ppm did not affect blood pressure, heart rate, or electrocardiogram results in humans. Reduced blood pressure accompanies exposure to anesthetic concentrations of 1,1,1-trichloroethane vapor (10,000–26,000 ppm). The effects are not permanent and subside shortly after exposure. The hypotensive mechanism has been studied in animals and appears to involve cardiac depression and peripheral vasodilation.

Human deaths following 1,1,1-trichloroethane inhalation are often attributed to cardiac arrhythmias. Such conclusions are based on animal studies in which arrhythmias have been produced during or immediately following acute inhalation exposure to 1,1,1-trichloroethane. The mechanism for the arrhythmias apparently involves sensitization of the heart to endogenous epinephrine. The exposure level at which cardiac sensitization occurs in humans is not known, but in animals, concentrations as low as

5,000 ppm are effective after only 10 minutes of inhalation. Physical exertion, stress, or any other stimulus of epinephrine release from the adrenal medulla may render an individual more vulnerable to 1,1,1-trichloroethane. Hypoxia may further increase a subject's susceptibility.

**Hepatic Effects.** 1,1,1-Trichloroethane may be a mild hepatotoxin in humans, although the evidence is not conclusive. Increased levels of serum bilirubin, lactate dehydrogenase (LDH), alkaline phosphatase, and serum glutamic oxaloacetic transaminase (SGOT), all suggestive of liver injury, have been reported in humans exposed to high levels of 1,1,1-trichloroethane by inhalation or ingestion. Elevated serum LDH, gamma-glutamyl transpeptidase (GGT), SGOT, and glutamic pyruvic transaminase (SGPT), and pathologic signs of progressive liver disease were noted in a patient who was occupationally exposed to 1,1,1-trichloroethane for several years. Removal of the patient from exposure resulted in improvement of the impaired liver function. Mild hepatic changes have also been noted in liver biopsies of exposed individuals and at autopsy in individuals who died after acute inhalation exposure to high concentrations of 1,1,1-trichloroethane. Animal studies indicate that exposure to relatively high 1,1,1-trichloroethane concentrations in air (≥1,000 ppm) or high oral doses (≥1,334 mg/kg) are required to produce liver injury. Effects observed in animals include necrosis, fatty change, increased liver weight, and changes in liver and serum enzyme levels. These effects are reversible and subside after termination of exposure (in the case of necrosis, hepatocytes in the proximity of the killed cells proliferate and replace them).

**Body Weight Effects.** Although 1,1,1-trichloroethane-induced body weight effects have not been observed in humans, reduced body weight gain has been reported in animals exposed to relatively high concentrations of 1,1,1-trichloroethane in air or diet. For example, dose-related reduced body weight gains (ranging from 12 to 33% lower than controls) were observed in male mice receiving 1,1,1-trichloroethane in the diet for 13 weeks at concentrations ranging from 5,000 to 80,000 ppm. Dose-related reduced body weight gain was also noted in similarly-treated female mice and male rats. Although most of the animal studies did not provide information regarding food consumption during exposure to 1,1,1-trichloroethane, the body weight effects observed in the NTP study occurred in the absence of apparent reductions in food consumption.

**Developmental Effects.** Developmental effects in humans exposed to 1,1,1-trichloroethane have not been observed. Epidemiology studies found no relationship between adverse pregnancy outcomes and maternal exposure to 1,1,1-trichloroethane. Minor embryotoxic effects were observed in rats and rabbits after inhalation exposure to high concentrations of 1,1,1-trichloroethane. Effects included decreased fetal

weights, increased minor soft tissue and skeletal anomalies, and delayed ossification. Exposure of pregnant mice to 1,1,1-trichloroethane at a concentration of 2,000 ppm for 17 hours/day on gestation days 12–17 resulted in significantly reduced postnatal pup weights, overt developmental delays (pinnae detachment, incisor eruption, eye opening), and impaired performance in behavioral tests (righting reflex, forelimb grip strength, negative geotaxis, inverted screen climbing). In a similar study of pregnant rats that were exposed to 7,000 ppm of 1,1,1-trichloroethane 3 times/day for 60 minutes on gestation days 13–19, two of nine litters were completely resorbed and significant increases in gestation length were noted. Developmental effects included increased mortality at birth, decreased litter weight, and significant deficits in coordination, muscle strength, and spontaneous motor activity. The developmental defects reported in three of these studies may have been associated with significant maternal toxicity. Neither an inhalation study using a lower, although still high, concentration nor drinking water studies revealed any developmental effects. Furthermore, a comprehensive study in which pregnant rats were gavaged with 1,1,1-trichloroethane during gestation and lactation found no neurobehavioral alterations in the pups tested up to 2 months of age. Overall, 1,1,1-trichloroethane does not appear to be a significant developmental toxicant in animals; effects appear to occur at high levels (>2,000 ppm). However, in view of the known neurological effects of 1,1,1-trichloroethane in humans and animals, additional developmental studies that examine neurological end points would be an important component of a complete investigation of 1,1,1-trichloroethane's potential developmental toxicity in humans.

**Cancer.** A relationship between exposure to 1,1,1-trichloroethane and cancer in humans has not been established. Among animals, no effects were found in a well-designed inhalation study at exposure levels ≤1,500 ppm. The results of an oral study indicate that 1,1,1-trichloroethane may have increased the occurrence of immunoblastic lymphosarcoma in rats; however, the biological and statistical significance of these results are questionable because of the study design limitations. The results of another oral (gavage) cancer bioassay were negative, but high early mortality in treated animals in this study made these results questionable.

Information is also limited on the role of 1,1,1-trichloroethane metabolites in the parent compound's toxicity. Reactive metabolites are important in the carcinogenicity of other chloroethanes (i.e., 1,1,2,2-tetrachloroethane). Binding to DNA, which is correlated with carcinogenicity in chlorinated ethanes, was weak in an *in vivo* test. Even weak binding, however, indicates the potential to interact with DNA. Cell biotransformation tests were positive for this chemical. The results of these assays may have been confounded by the presence of stabilizing agents, however. Two of the common stabilizing additives in commercial formulations of 1,1,1-trichloroethane are 1,2-epoxybutane (butylene oxide) and

1,4-dioxane (diethylene dioxide). Both stabilizers have been identified as animal carcinogens. At this time, it does not appear that 1,1,1-trichloroethane exposure poses a clear cancer risk in animals; however, as discussed above, the limitations of the available studies prevent a definitive assessment of the risk of cancer in humans exposed to the compound. Related to potential exposures near NPL hazardous waste sites, the risk appears to be of little significance.

## 2.3 MINIMAL RISK LEVELS (MRLs)

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made for 1,1,1-trichloroethane. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

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

### *Inhalation MRLs*

- An MRL of 2 ppm has been derived for acute-duration inhalation exposure (14 days or less) to 1,1,1-trichloroethane.

The acute-duration inhalation MRL is based on a lowest-observed-adverse-effect level (LOAEL) of 175 ppm for reduced performance of psychomotor tests in a human study by Mackay et al. (1987). Individuals exposed to 175 or 350 ppm of 1,1,1-trichloroethane for 3.5 hours demonstrated impaired performance of psychomotor tests. The derivation of this MRL is supported by results of other human

studies. Gamberale and Hultengren (1973) found psychophysiological test performance deficits in exposed individuals, although at a higher concentration than the LOAEL of 175 ppm identified by Mackay et al. (1987). Muttray et al. (1999, 2000) found EEG changes consistent with increased drowsiness and slight irritant nasal responses in volunteers exposed to 200 ppm. Numerous studies described behavioral and neurophysiological effects in animals.

Although the LOAEL of 175 ppm in the critical study of Mackay et al. (1987) was associated with only a 3.5-hour exposure period, the acute-duration inhalation MRL is intended to be protective of a continuous acute-duration exposure. Data reported by Nolan et al. (1984) and Mackay et al. (1987) indicate that blood levels of 1,1,1-trichloroethane approach steady state during 2 hours of continuous inhalation exposure in humans. Neurobehavioral performance was correlated with 1,1,1-trichloroethane blood levels and there was little additional change in most measures of neurobehavioral performance as exposure duration increased from 2 to 3 hours (Mackay et al. 1987). Therefore, the LOAEL of 175 ppm was not adjusted for exposure duration.

- An MRL of 0.7 ppm has been derived for intermediate-duration inhalation exposure (15–364 days) to 1,1,1-trichloroethane.

The intermediate-duration inhalation MRL is based on a no-observed-adverse-effect level (NOAEL) of 70 ppm derived from the study by Rosengren et al. (1985), which found evidence of astrogliosis (increased glial fibrillary acid protein levels) in the brains of gerbils exposed to 210 or 1,000 ppm, but not 70 ppm, of 1,1,1-trichloroethane continuously for 3 months. Choice of a neurological end point for derivation of the MRL is supported by numerous studies in humans and animals showing neurological effects to be the critical end point for 1,1,1-trichloroethane.

A chronic-duration inhalation MRL was not derived because suitable studies including tests for subtle neurological effects were not available.

***Oral MRLs***

An acute-duration oral MRL was not derived for 1,1,1-trichloroethane due to the lack of adequate information. Acute-duration oral exposure in humans is limited to a single account of an accidental exposure. Comprehensive acute-duration oral toxicity studies in animals were not located and available studies did not clearly establish sensitive targets and dose-response relationships.

- An MRL of 20 mg/kg/day has been derived for intermediate-duration oral exposure (15−364 days) to 1,1,1-trichloroethane.

The intermediate-duration oral MRL is based on treatment-related body weight effects in mice (NTP 2000). Groups of male and female B6C3F1 mice (10 per group) were fed diets containing 0 (untreated feed); 0 (microcapsule vehicle in feed); 5,000, 10,000, 20,000, 40,000, or 80,000 ppm of micro-encapsulated 1,1,1-trichloroethane (99% pure) 7 days/week for 13 weeks. Average daily doses calculated by the researchers were 850, 1,750, 3,500, 7,370, and 15,000 mg/kg in male mice; and 1,340, 2,820, 5,600, 11,125, and 23,000 mg/kg in female mice. Clinical signs and body weights were recorded weekly. Food consumption was determined every 3–4 days. Water consumption was not reported. Vaginal cytology and sperm motility evaluations were performed on all mice in the vehicle control and the three highest dose groups of mice. At necropsy, all mice were subjected to gross pathological examinations, and the heart, lungs, thymus, liver, right kidney, and right testis were weighed. Mice in untreated and vehicle control and high-dose groups were subjected to complete histopathologic examinations.

There were no exposure-related deaths and no indications of treatment-related clinical or histo-pathological effects. Food consumption was slightly increased in 1,1,1-trichloroethane-treated groups, relative to untreated and vehicle controls. As shown in Table A-1 of Appendix A, the final mean body weights in the 5,000, 10,000, 20,000, 40,000, and 80,000 ppm male groups were 91, 91, 88, 90, and 85% of the vehicle control mean. In the female mice, the respective final mean body weights were 97, 93, 89, 88, and 84% of the vehicle control mean. The effects on mean final body weight and mean body weight gain reached the level of statistical significance in all treated groups of male mice and in the 20,000 and 10,000 ppm groups, respectively, of female mice. NTP (2000) estimated the dose of 10,000 ppm (1,750 and 2,820 mg/kg/day in male and female mice, respectively) to represent a NOAEL. According to ATSDR policy, a treatment-related change in body weight of 10% or more (relative to controls) may be considered to represent an adverse effect. Therefore, the 20,000 ppm (3,500 and 5,600 mg/kg/day in males and females, respectively) level is considered to represent a LOAEL for decreased mean terminal body weight (≥10% lower than control values).

All continuous data models in the EPA Benchmark Dose Software (version 1.3.2) were fit to the terminal body weight data for male and female mice in the NTP (2000) study. A 10% change in mean terminal body weight relative to the control mean was selected as the benchmark response (BMR) level. A 10% change in body weight is the minimal level of change generally considered to be biologically significant, according to EPA benchmark dose guidance (EPA 2000).

Based on the goodness-of-fit statistic, male mouse data were not adequately fit by any of the continuous data models. An adequate fit was obtained for the female mouse data using the Hill model (p=0.68; EPA benchmark dose guidance recommends a p-value ≥0.1), which yielded BMD and $BMDL_{10}$ values of 5,064 and 2,185 mg/kg/day, respectively (see Figure A-1 of Appendix A for a plot of the predicted and observed means).

The $BMDL_{10}$ of 2,185 mg/kg/day was used as the point of departure for deriving the intermediate-duration oral MRL for 1,1,1-trichloroethane. A total uncertainty factor (UF) of 100 (10 for extrapolation from animals to humans and 10 for human variability) was applied to the $BMDL_{10}$ as follows:

Intermediate-duration oral MRL = 2,185 mg/kg/day ($BMDL_{10}$) ÷ 100 (UF) = 20 mg/kg/day

The choice of 1,1,1-trichloroethane-induced body weight changes as the critical effect is supported by results of other subchronic- and chronic-duration oral and inhalation animal studies in which body weight effects were reported, either in the absence of other signs of toxicity (Adams et al. 1950; Bruckner et al. 2001; Prendergast et al. 1967) or at doses causing minimal liver lesions (Calhoun et al. 1981; Quast et al. 1978, 1988). Bruckner et al. (2001) reported a frank effect level (FEL) of 2,500 mg/kg (1,786 mg/kg/day when adjusted for exposure 5 days/week) for gross central nervous system depression and death in rats exposed by gavage. Investigation of systemic end points was limited to the liver; only mild hepatic changes were found and only at lethal doses. Sensitive neurological endpoints were not monitored. NTP (2000) observed no gross central nervous system effects or deaths at doses up to about 5,000 mg/kg/day in rats or 23,000 mg/kg/day in mice. The differences in the findings of the Bruckner et al. (2001) and NTP (2000) studies can be attributed to the bolus dosing employed by Bruckner et al. (2001). In comparison to relatively steady intake throughout the day in the diet, bolus dosing will produce much higher peak blood levels as the entire daily dose is rapidly absorbed. The gross central nervous system effects and mortality observed by Bruckner et al. (2001) are likely a reflection of the high peak blood levels by this mode of administration. Such bolus oral exposure is not considered relevant to longer-term or chronic exposure scenarios in humans. Therefore, the results of Bruckner et al. (2001) were not used as the basis for derivation of an intermediate-duration oral MRL for 1,1,1-trichloroethane.

A chronic-duration oral MRL was not derived for 1,1,1-trichloroethane. No relevant human data were located. Chronic-duration oral animal studies were designed as cancer bioassays and included only limited investigation of noncancer endpoints (Maltoni et al. 1986; NCI 1977).