Section 2: Toxicological Profile for Trichloroethylene (TCE)

Jennifer Smith

Introduction

Trichloroethylene (TCE) is a legal organic chemical commonly used commercially and in industry. It can be used as a solvent to clean grease from metal, a paint stripper, an ingredient in paints and varnishes, an adhesive solvent and a chemical to manufacture other organic chemicals. Consumer products that contain TCE include typewriter correction fluids, paint removers/strippers, adhesives, spot removers, and rug cleaning fluids (ATSDR 1997). Some common uses of TCE prior to an FDA ban in 1977 were as an anesthetic, grain fumigant, wound disinfectant, and pet food additive (ATSDR 1997). There were only two manufacturers of TCE in the United States as of 1986, with a combined production of 320 million pounds annually (ATSDR 1997). In 1993, 16.3 million pounds of TCE was imported into the US and 72.6 million pounds of TCE was exported (Fisher et al. 1998). In New York State there were 55 facilities that used TCE for on-site use/processing in 1993 as a reactant, for repackaging, as a chemical processing aid, as a manufacturing aid, or for other uses (ATSDR 1997).

The current limit for TCE in air for New York State according to the New York State Department of Health (NYSDOH) is 1 ppbv (1 ppbv is one part per billion by volume, e.g., 1 volume of gaseous TCE per billion volumes of air). OSHA allows an 8-hour time weighted average exposure limit of 100,000 ppbv; the 15-minute time weighted average limit for exposure is 300,000 ppbv (OSHA 1993). The threshold limit value for occupational exposure is 50,000 ppbv (American Conference of Governmental Industrial Hygienists 1997). The threshold limit value is the maximum value that most

adult workers are expected to be able to tolerate without adverse effects. Time weighted average means that the value has been averaged over an 8-hour day/forty hour workweek. For reference, TCE can be smelled at levels of 120,000 to 500,000 ppbv.

The National Institute for Occupational Safety and Health set a 60-minute ceiling occupational exposure limit of 2,000 ppbv. Though these limits are higher than the NYSDOH standard for indoor air (1 ppbv), a complicating factor in assessing the risk of TCE exposure is that other contaminants are also generally present in environmental cases that can act synergistically to increase risk. Additionally, sensitive individuals such as children, pregnant mothers, the elderly, those who drink and those who smoke may require a significantly lower level to ensure minimal risk.

Environmental Fate

TCE is the most commonly reported organic groundwater contaminant (Bourg et al. 1992). In addition, between 9 and 34% of drinking water in the United States has TCE contamination (ATSDR 1997). TCE is classified as a dense non-aqueous phase liquid (DNAPL), since the specific gravity (ratio of chemical density to that of water) is 1.46 (US EPA 2005). TCE also has low solubility in water. This can potentially make assessments of transport difficult, since migration into the vapor phase is dependent on water concentrations, water table depth and fluctuations, and temperature. Migration in the liquid phase can occur at increased rates compared to groundwater, due to the fact that liquid TCE has a higher density than water. The organic carbon-partitioning coefficient (Koc) for TCE has also been experimentally derived, with values from 106-460 (Garbarini and Lion 1986). Koc is a measure of a chemical's affinity for organic matter in soils, where higher values correspond with higher retention in organic matter

(values greater than 1000). This indicates TCE will not sorb readily to organic matter in saturated soils. TCE dissolved in groundwater is expected to move with groundwater rather than sticking to organic matter. However, TCE may be physically trapped as puddles of liquid TCE inside geological formations (discussed in geology and transport sections).

Volatilization of TCE into a vapor phase in air occurs rapidly. The volatilization half-life of 1 mg/L TCE was experimentally investigated as 21 minutes at 25^{o}C (Diling et al. 1975). Volatilization from the aqueous phase occurs at a much higher rate than the volatilized TCE is degraded by photolysis or hydrolysis (Jensen and Rosenburg 1975). Moreover, chemical hydrolysis only occurs at very high temperatures and pH - not under normal conditions encountered in a natural environment (ATSDR 1997). Photolysis is the degradation of a compound due to exposure to light, where photons break chemical bonds. Hydrolysis occurs when chemical bonds are split by water. This indicates that if liquid TCE or TCE dissolved in water is exposed to air, it will rapidly evaporate into the vapor phase and increase the amount of TCE in air that may intrude into nearby buildings. The amount of TCE that can be introduced into air by water containing TCE or by liquid pools of TCE is very large compared to the health standards. The Henry's Law constant for TCE dissolved in water is 0.3 $\left[\frac{\text{mg TCE / liter air}}{\text{mg TCE / liter water}}\right]$. The vapor pressure of liquid TCE is 73 mm Hg. This means that air in contact with water saturated with TCE (1100 mg TCE per liter of water) will contain 330,000 mg TCE per m^3 air (or >60,000,000 ppbv TCE). Air in equilibrium with a puddle of liquid TCE will contain 96,000,000 ppbv of TCE.

In deep subsurface regions, degradation (biotic or abiotic) is minimal. Rates of biodegradation will be influenced by nutrient availability, temperature and weather TCE-consuming organisms are present. Biodegradation of TCE can occur completely if present in aerobic (oxygen present) conditions. Biodegradation may also occur under anaerobic (oxygen absent) conditions, via reductive dehalogenation. This process occurs when hydrogen replaces chlorine (the halogen) in a chlorinated compound sequentially. However, the last chlorine in this process is very difficult to remove and therefore takes a long time to completely degrade or mineralize to ethene (a benign degradation compound). The second to last product is vinyl chloride, a known carcinogen. Vinyl chloride can be mineralized biotically if aerobic conditions are then present. In nature, conditions are commonly aerobic above the ground water table or in areas of rapid inflow of surface water. In areas of relatively stagnant water below the water table, conditions are generally anaerobic.

Bioconcentration refers to increased concentrations of a chemical in organism tissues relative to environmental conditions. Biomagnification occurs when there is a cumulative increase in the concentration of a chemical in organisms at successively higher levels of the food chain. Bioconcentration and biomagnification of TCE are virtually negligible. A study by Saisho et al. (1994) found bioconcentration factors of 4.52 and 2.71 for blue mussel and killifish, respectively. Biomagnification was investigated in the aquatic food chain, where concentrations were less than 100-fold in fish liver, sea bird eggs and sea seal blubber, suggesting some biomagnification (Pearson and McConnell 1975). Laboratory studies of fruits and vegetables have found uptake of TCE in the foliage of carrot and radish plants; bioconcentration factors were between 4.4

and 63.9 (Schroll et al. 1994). Bioconcentration factors that are less than 200 are considered to be negligible in magnitude.

Exposure

The primary exposure pathways are: ingestion of contaminated drinking water or inhalation (Wu and Schaum 2000). Inhalation is the primary route of exposure on the South Hill. TCE is present in ambient air across the nation. In 1993 alone, 30.2 million pounds of TCE was emitted into the atmosphere (ATSDR 1997). Ambient air concentrations of TCE found in the United States ranged from 0.04-0.72 ppb, 0.39 ppb, 0.21-0.59 ppb in Oregon, Pennsylvania, and New Jersey, respectively, during 1983-84 (Ligocki et al. 1985, Sullivan et al. 1985, Harkov et al. 1984). Air concentrations in these studies were found to vary between the fall/winter and spring/summer seasons. Wallace et al. (1985) found indoor air to contribute more overall TCE exposure than outdoor air, where the ratio of indoor to outdoor concentrations was about 5:1 in North Carolina. Indoor air concentrations have been measured as 5 ppb in a North Carolina office building, 0.14 ppb in a Washington, DC school and 0.15 ppb in an elderly home in Washington, DC (Hartwell et al. 1985). The average inhalation uptake in the United States can be estimated as 11-33 mg/day, and uptake due to oral exposure is approximately 2-20 mg/day (Wu and Schaum 2000). Upon inhalation exposure to TCE, about half will be absorbed into the bloodstream and the other half exhaled. Once in the bloodstream, TCE will either be exhaled or modified in the liver and kidneys for urinary excretion.

Other exposures to TCE can occur through food: dairy products such as milk, cheese and butter (0.3-10 ppb), oils and fats (0-19 ppb), beverages such as canned fruit

drink, ale, instant coffee, tea and wine (0.02-60 ppb), fruits and vegetables (0-5 ppb) and bread (7 ppb) (McConnell et al. 1975). Breast milk has also been shown to contain TCE in 8 of 8 mothers sampled who resided in urban areas (Pellizzari et al. 1982). Though these routes are generally not the primary mechanism of exposure, it is important to consider the cumulative effects of these background levels with any additional sources.

Toxicological Endpoints

This is not a complete list of all toxicological endpoints of TCE, but a compilation of the most studied effects found in the literature. The International Agency for Research on Cancer has classified TCE as a probable human carcinogen, because there is sufficient evidence in experimental animals but limited evidence in humans (Iavicoli 2005). TCE toxicity in humans has been fairly well studied at higher concentrations, especially with regards to occupationally exposed adults: over 80 published articles on TCE's carcinogenicity to humans, more than 20 reports on occupationally exposed groups, 40 case-control studies and more than a dozen community-based studies (Watenberg et al. 2000). The most common effects from TCE inhalation exposure include neurotoxicity, heptatoxicity and nephrotoxicity. Reproductive and developmental toxicity have been extensively studied, with largely negative results (Barton et al. 1996). Chemically induced genetic mutation inducing tumors in humans does not appear to be caused by TCE or its metabolites. This is because very high levels of TCE are required to cause genotoxicity (Moore and Harrington-Brock 2000). Liver and lung tumors and lymphomas have been reported in mice inhalation studies (Watenberg 2000).

Humans occupationally exposed to TCE have increased incidence of liver, kidney, and cervical cancers, as well as non-Hodgkin's Lymphoma, Hodgkin's disease

and multiple myeloma (Wartenberg et al. 2000), though these concentrations are many orders of magnitude higher than air in homes measured on the South Hill. A study by Axelson et al. (1994), found no evidence that trichloroethylene was a human carcinogen for an average occupational inhalation exposure level of 20,000 ppbv when studying inhalation effects in 1,424 men and 249 women from 1955 until 1987. This is because average cancer rates were lower than expected. Some other effects of TCE inhalation exposure are neurological, liver and kidney effects (Barton and Clewell III 2000). Ertle et al. (1972) reported "psycho-organic syndrome", characterized as unrest, generalized fatigue, disturbed vision and neurological aberrations, to be caused by exposure to TCE. Headaches, sleepiness, fatigue and/or drowsiness have occurred at approximately 100,000 ppbv and are characteristic of neurological toxicity (Barton and Clewell III 2000, Barton and Das 1996). Headache (27,000 ppbv) and drowsiness (81,000 ppbv) occurred in human volunteers exposed to TCE for 1-4 hours (Nomiyama and Nomiyama 1977). One study on low level occupational exposure (average 6,000 ppbv) found that TCE had negative effects on the immune system (Iavicoli 2005).

Information on toxicological effects on the order of magnitude of those on the South Hill of Ithaca (i.e. at the ppb range) was difficult to obtain for inhalation exposures. There is still a significant gap in the scientific knowledge on what the long term consequences could be. However, information on the toxicological effects from oral exposure (due to contaminated drinking water wells) was available at lower doses. Residents in Wobum, Massachusetts had increased adverse effects on the immune system causing increased risk to respiratory infections (asthma, bronchitis, and pneumonia) and increased cases of leukemia in children orally exposed to 267 ppb of TCE between 1971

and 1979 (Byers et al. 1988). Three hundred sixty two individuals exposed to 6 to 500 ppb of TCE and other chemicals through drinking water wells in Tuscon, Arizona found increased frequencies of 10 systemic lupus erythematosus symptoms, arthritis, Raynaud's phenomenon, malar rash, skin lesions related to sun exposure, seizure or convulsions, and mood disorders, as well as decreased blink reflex, eye closure, choice reaction time, and intelligence test scores (Kilbum and Warshaw 1992, 1993). A study of 80,938 births and 594 fetal deaths in New Jersey linked with contaminated drinking water (>10ppb TCE) found an association with oral clefts, central nervous system defects, neural tube defects, and major cardiac defects (Bove et al. 1995).

TCE Metabolism

TCE inhaled will either be exhaled before being absorbed into the bloodstream by tissues, or metabolized and excreted through the urinary tract (Dobrev et al. 2002). Toxicological effects of TCE are largely due to the metabolites, including trichloroacetaldehyde, chloral hydrate, dichloroacetate, trichloroacetate, trichloroethanol and trichloroethanol-glucuronide (Barton et al. 1996). Other parent compounds that produce the same metabolites are tetrachloroethylene (PERC), methyl chloroform (MC), 1,1,1,2-tetrachloroethane, *cis*-1,2-dichloroethylene, *trans*-1,2-dichloroethylene, 1,2-dichloroethylene and 1,1-dichloroethane (Wu and Schaum 2000). Exposures to TCE, PERC and MC simultaneously at their respective time-weighted average threshold limit values, has been shown to result in elevated (22% increase) TCE blood levels compared with individual chemical exposures (Dobrev et al. 2001). The reason kidney and liver cancer are the most common cancers associated with TCE exposure is because of metabolites. There are two major pathways of TCE metabolism in the body, one

involving oxidation with cytochrome P450s and the other is conjugation with glutathione (Lash et al. 2000). Cytochrome P450s are very versatile enzymes, found in high concentrations in the liver (86% of the body's P450s), which can perform a host of reactions. However, in the case of TCE degradation, the metabolites produced in the liver are carcinogenic. These metabolites include chloral hydrate, trichloroacetate, and dichloroacetate (Lash et al. 2000). The second major pathway of TCE metabolism is glutathione conjugation, in which glutathione, a peptide of amino acids, is attached to TCE. This primes it for urinary excretion. However, metabolites that occur in the kidneys from this conjugation have been associated with kidney cancer. The P450 pathway has higher activity and affinity than glutathione conjugation (Lash et al. 2000).

Behaviors that can increase the risks of cancer from TCE exposure include alcohol consumption and smoking. Alcohol can interfere with TCE excretion and metabolism, increasing the formation of trichloroethanol, a metabolite also associated with cancer. Individuals who consume alcohol may be in a particularly sensitive population (Barton et al. 1996). Smoking may also increase the risk of genotoxic effects from TCE exposure (Seiji et al. 1990). Mothers who are breast-feeding should also be aware that TCE could accumulate in breast milk (noted earlier). With regards to TCE toxicity, it is most important to note that there are significant gaps in the scientific knowledge of long-term low-level exposures. This is largely due to the difficulty in finding a human population not exposed to low levels of TCE against which exposed groups can be compared.