

# HEALTH EFFECTS OF TRICHLOROETHYLENE

## Human Exposure

Trichloroethylene is a common environmental contaminant at Superfund sites, Department of Defense facilities, and certain manufacturing operations (e.g., aircraft, spacecraft). It has been found at approximately 852 of the 1,416 sites proposed for inclusion on the U.S. Environmental Protection Agency (EPA) National Priorities List. On the basis of data reported to the EPA Toxic Release Inventory, it was estimated that approximately 42 million pounds of trichloroethylene were released into the environment in 1994 (#Scott and Cogliano, 2000).

People can be exposed to trichloroethylene from contaminated air (outdoor and indoor), water, and soil. Data from 2004 on ambient air concentrations of trichloroethylene indicate an average of 0.37  $\mu\text{g}/\text{m}^3$  (range, 0-6.32  $\mu\text{g}/\text{m}^3$ ), a concentration that has remained fairly consistent since 1996 (#National Research Council, 2006). Mean concentrations at various land-use sites include 1.84  $\mu\text{g}/\text{m}^3$  in commercial areas, 1.54  $\mu\text{g}/\text{m}^3$  in industrial areas, 1.08  $\mu\text{g}/\text{m}^3$  in agricultural areas, and 0.89  $\mu\text{g}/\text{m}^3$  in residential areas. Indoor air can become contaminated by certain consumer products (e.g., adhesives, tapes) and by volatilization from contaminated water supplies. Vapor intrusion through walls and floors can also be a source of indoor exposure when buildings are near contaminated groundwater.

Trichloroethylene is the most frequently reported organic contaminant in groundwater. The Agency for Toxic Substances and Disease Registry (ATSDR 1997a) estimates that between 9% and 34% of drinking water supply sources tested in the United States contain some trichloroethylene. This has led the EPA to set standards for the amount of TCE that is allowed in the water samples. The goal standard is zero parts per billion, because this is the only level the EPA can prove to have no effects on the population. The realistic standard is 5 parts per billion, because that is as low as scientists feel is possible at present (#EPA, 2006). The release of TCE into the environment continues to rise. The states having the highest levels of the contaminant are Pennsylvania and Illinois. When levels were measured from 1987 to 1993, Pennsylvania showed the highest amount of TCE in drinking water with 33,450 pounds. West Virginia had the highest amount of TCE going directly into the water sources. TCE is a major

contaminant found in almost one half of all Superfund Sites (#NIEHS, 2007). Those most at risk of exposure to TCE are people who work in factories that produce TCE or live near a TCE factory, an industrial waste site, or a military base (#EPA, 2007).

### **Metabolites and Exposure**

Trichloroethylene toxicity comes primarily from its metabolites, but people may be exposed to the metabolites from sources other than trichloroethylene. For example, chlorination of drinking water produces the by-products chloral, chloral hydrate, monochloroacetic acid, dichloroacetic acid, and trichloroacetic acid. Chloral is used in the production of polyurethanes and as a chemical intermediate for the herbicide trichloroacetic acid. Chloral hydrate is a pharmaceutical used as a hypnotic and sedative. The metabolite monochloroacetic acid is used in pharmaceuticals, as an herbicide, and as a chemical intermediate in the production of indigoid dyes. Trichloroacetic acid is also used as a chemical intermediate and in the production of herbicides (#Simon, 2005).

Other chemical compounds have some of the same metabolites as trichloroethylene, including tetrachloroethylene, 1,1,1-trichloroethane, 1,2-dichloroethylene (cis-, trans-, and mixed isomers), 1,1,1,2-tetrachloroethane, and 1,1-dichloroethane.

Tetrachloroethylene is used in textile dry cleaning, as part of the processing and finishing in cleaning and degreasing metals, and as a chemical intermediate in the synthesis of some fluorocarbons. 1,1,1-Trichloroethane is used as a solvent and in pesticides, textile processing, cutting oil formulations, and printing inks. 1,2-Dichloroethylene, 1,1,1,2-tetrachloroethane, and 1,1-dichloroethane are used primarily as solvents in cleaning, degreasing, and extracting processes (#Simon, 2005).

### **Cancer**

Trichloroethylene has shown reasonable evidence that it may increase risk of certain types of cancers in humans. Studies on experimental animals have shown that overexposure to TCE has caused a greater occurrence of renal and liver cell carcinomas, other studies may suggest an increased occurrence of testicular and lung cancers as well. Renal cell carcinoma studies provided adequate data suggesting that TCE acts on VHL, a tumor suppressing gene. Genotoxic effects were seen after an overexposure of TCE and damage to the VHL gene led to a higher occurrence of RCC (renal cell carcinoma). When the trichloroethylene is absorbed into the liver, it produces metabolites such as trichloroacetic acid and Dichloroacetic Acid. These have been shown responsible for the tumors in laboratory animals tested. The animal studies show

that Trichloroethylene and its metabolites is a complete carcinogen, meaning it acts on both tumor initiation and progression. These findings suggest that high levels of exposure may lead to cancer in experimental animals and therefore the International Agency for Research on Cancer (IARC) has determined that trichloroethylene is probably carcinogenic to humans. Studies involving humans with long-term exposure of high levels of trichloroethylene in drinking water or in workplace air have increased incidences of cancer. Since most of these studies have strictly used experimental animals (mice and rats), it is not possible to predict whether humans are more susceptible to the carcinogenic effects or not.

Trichloroethylene is metabolized in the body by two major pathways: the oxidative pathway and the glutathione-conjugation pathway. The metabolites these pathways generate are thought to be responsible for the toxicity and carcinogenicity observed in different organ systems. Key scientific issues for characterizing these hazards include identifying the metabolites responsible for the effects, elucidating the mode of action, and understanding the relevance of animal data for humans (#National Research Council, 2006).

### **Kidney Toxicity and Cancer**

Trichloroethylene and some of its metabolites in the glutathione-conjugation pathway have been shown to be nephrotoxic and nephrocarcinogenic. There is concordance between animal and human studies. In bioassays, rats developed tubular toxicity before they developed tumors. Investigations of nephrotoxicity in human populations show that highly exposed workers exhibit evidence of damage to the proximal tubule. The magnitude of exposure needed to produce kidney damage is not clear (#National Research Council, 2006).

Trichloroethylene nephrotoxicity is associated with a multistep metabolic pathway. It is generally accepted that the metabolite S-(1,2-dichlorovinyl)-L-cysteine is the penultimate nephrotoxicant. The metabolite can undergo bioactivation by conjugation to reactive species that are genotoxic and cytotoxic and by sulfoxidation. Sulfoxides are more potent nephrotoxicants than their parent S-conjugates. Both S-(1,2-dichlorovinyl)-L-cysteine and S-(1,2-dichlorovinyl)-L-cysteine sulfoxide appear to play a role in renal tubular cell toxicity (#National Research Council, 2006).

Evidence from experimental, mechanistic, and epidemiologic studies supports the conclusion that trichloroethylene is a potential kidney carcinogen. In animal studies, the

nephrocarcinogenic effects of trichloroethylene were more pronounced in male rats than in female rats and were absent in male and female mice. Studies on trichloroethylene metabolism in rodents and in humans indicate a bioactivation role in the development of nephrocarcinogenicity. This has been linked with the formation of S-(1,2-dichlorovinyl)-L-cysteine; however, there are no studies of the carcinogenic potential of this metabolite (#National Research Council, 2006).

Animal studies show that trichloroethylene acts as a complete carcinogen (at the stages of both tumor initiation and promotion and progression) in a dose-dependent manner, with nephrotoxicity as the promoter for cells initiated by a trichloroethylene metabolite. It is not possible to predict whether humans are more or less susceptible to the carcinogenic effects than other animals, because species differences in the extent of formation of S-(1,2-dichlorovinyl)-L-cysteine have not been fully characterized. Furthermore, the cytochrome P-450 enzyme isoforms that metabolize trichloroethylene have polymorphisms within national populations, resulting in considerable interindividual differences in enzyme expression. The committee ruled out the accumulation of  $\alpha_2\mu$ -globulin, peroxisome-proliferator activated receptor  $\alpha$  (PPAR $\alpha$ ) agonism, and formic acid production as modes of action for the production of renal tumors in rodents (#National Research Council, 2006).

Renal clear cell carcinoma, the carcinoma most often induced by trichloroethylene, was shown to link with the homozygous inactivation of the von Hippel-Lindau (VHL) tumor suppressor gene. The evidence indicates a strong association between trichloroethylene and VHL mutation, especially in protein expression, and kidney cancer in humans. Some studies have reported increased occurrence of mutations in renal cancer cells of patients exposed to high concentrations of trichloroethylene. The genotoxic effect of trichloroethylene metabolites likely results from bioactivation pathways in the kidney leading to renal VHL gene damage and renal cell carcinomas. However, there remains a lack of direct evidence that alterations in the VHL gene initiate renal tumors, but the alterations, especially in protein expression, might contribute to tumor progression. In the absence of information on the temporal relationship between VHL mutations and renal tumor initiation, it is prudent to assume that trichloroethylene-induced VHL mutations are initiating events. Direct evidence of alterations in the VHL gene in association with tumor progression remains to be determined (#National Research Council, 2006).

## Liver Toxicity and Cancer

Animal data on trichloroethylene indicate that relatively high doses are needed to induce liver toxicity and cancer, even in susceptible strains of mice. The three major oxidative metabolites of trichloroethylene-trichloroacetic acid, dichloroacetic acid, and chloral hydrate-can contribute to liver toxicity and cancer in rodents. Trichloroethylene produces hepatotoxicity in experimental animals and humans that depends on generation of reactive intermediates by the enzyme cytochrome P-450 in the liver. Studies with laboratory animals indicate that trichloroethylene and its metabolites also produce liver effects independent of hepatotoxicity, including elevation in plasma bile acid concentration and accumulation of liver glycogen. The relevance and significance of these effects to humans remain to be elucidated (#National Research Council, 2006).

Trichloroethylene, chloral hydrate, and trichloroacetic acid induce liver cancer in mice when blood concentrations achieve millimolar concentrations. In contrast, dichloroacetic acid is active in rats as well and requires a much lower concentration to produce liver tumors. Trichloroethylene and its metabolites promote liver cancer. The mode of action for trichloroacetic acid in liver is principally as a liver peroxisome proliferator and agonist of PPAR $\alpha$  rather than as a genotoxicant. A significant lack of concordance in the sensitivity of human and rodent hepatocytes to peroxisome proliferators and early events associated with liver tumor promotion has been noted, with humans being much less sensitive. In addition, there is no supporting epidemiologic evidence of enhanced occurrence of liver tumors in humans administered potent rodent peroxisome proliferators. The weak carcinogenic activity in the liver of chloral hydrate in male B6C3F1 mice combined with lower rates of oxidation and higher rates of conjugation in humans compared with mice indicate that the mode of action for mice is not relevant to humans.

Species differences in susceptibility and phenotypic differences in tumors derived from trichloroethylene and its metabolites suggest that there are mechanistic differences in the way these chemicals cause tumors that cannot be fully explained by peroxisome proliferation. In rodents, the promotional activity of dichloroacetic acid includes a significant effect on cellular metabolism and cellular proliferation that encompasses a mitogenic mode of action. Assuming a mitogenic mode of action for dichloroacetic acid as a rodent liver carcinogen, genotypic species differences between mice and humans suggest that humans would be much less susceptible to liver carcinogenesis.

## **Respiratory Toxicity and Cancer**

Trichloroethylene has been shown to induce lung tumors in rodents. It is well documented that the mode of action for this effect is localization of cytochrome P-450 metabolites of trichloroethylene in the Clara cells of the lungs and that pulmonary metabolism of trichloroethylene is species dependent. The proximate toxicant for the Clara cell, whether chloral, dichloroacetyl chloride, or another metabolite, is still under study. The collective evidence indicates that rodents and humans are significantly different in their capacity to metabolize trichloroethylene in the lungs, with humans having less capacity. Results of most epidemiologic studies of occupational exposure to trichloroethylene do not show a strong association between trichloroethylene exposure and increased incidence of lung tumors. Thus, pulmonary cancer does not appear to be a critical end point in assessing human health risks to trichloroethylene.

## **Non-cancer Endpoints**

The chlorinated hydrocarbon trichloroethylene (TCE) is used extensively in industry as an anesthetic and solvent, thus, this chemical has caused various harmful effects in human beings. When inhaled, trichloroethylene can cause headaches, dizziness, poor coordination, and potentially unconsciousness (similar effects as intoxication). Inhalation can also cause lung damage as well as heart, nerve, kidney and liver damage, followed by death. Consumption of this chemical also causes similar effects as inhalation along with nausea, a weakened immune system and a damaged fetal development in pregnant woman. TCE has also been shown to increase speech impairments for children under 10 years of age (#ATSDR NER, 1999). Skin contact with this chlorinated hydrocarbon causes a rash to form (#ATSDR Tox FAQs, 2007). Epidemiologically, trichloroethylene has also been seen to cause heart defects in children who have consumed water with high amounts of this chemical, which corresponds to the effects seen in laboratory animals (#ATSDR Public Health Statement, 2007).

Multiple animal studies have found decreased fetal growth after maternal exposure to trichloroethylene. Impaired fetal growth was also a consistent finding in different community studies of mothers exposed to drinking water contaminated with trichloroethylene or tetrachloroethylene, a compound that has some of the same metabolites as trichloroethylene. However, a mechanistic basis for this effect remains to be elucidated (#National Research Council, 2006).

Epidemiologic investigations of communities exposed to trichloroethylene have also

reported mixed results. A 2- to 3-fold increase in risk of congenital heart defects was found in multiple studies, and the most frequently found defects were the same in animal and human studies (defects of the interventricular septae and the valves). In addition, mechanistic support is provided by studies in animals demonstrating altered proliferation in the endocardial cushions at low dose or alterations in endothelial cell activation and decreased expression of two markers of epithelial mesenchymal cell transformation, a key process in valve and septum formation. Evidence that trichloroacetic acid and Dichloroacetic Acid are as potent as trichloroethylene suggests that CYP2E1 metabolic activation, as well as the fractional formation of trichloroacetic acid from chloral, is important in trichloroethylene cardiac teratogenesis (#National Research Council, 2006).

Source : <http://www.toxipedia.org/display/toxipedia/Trichloroethylene>