TRICHLOROETHYLENE
CAS No. 79-01-6
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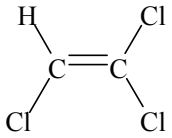

CARCINOGENICITY

Trichloroethylene (TCE) is *reasonably anticipated to be a human carcinogen* based on limited evidence of carcinogenicity from studies in humans, sufficient evidence of carcinogenicity from studies in experimental animals, which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors at multiple tissue sites in multiple species of experimental animals, , and information suggesting TCE acts through mechanisms that indicate it would likely cause cancer in humans.

Evidence for the carcinogenicity of TCE in humans comes from seven cohort studies with specific TCE exposures well characterized for individual study subjects. A meta-analysis of these cohort studies found that occupational exposure to TCE was associated with excess incidences of liver cancer, kidney cancer, non-Hodgkin's lymphoma, prostate cancer, and multiple myeloma, with the strongest evidence for the first three cancers (Wartenberg *et al.* 2000). Elevated risks of death from Hodgkin's disease, multiple myeloma, cervical cancer, and liver cancer also were observed (Wartenberg *et al.* 2000). Nevertheless, these studies are based on a relatively small number of exposed workers and were confounded by exposure to other solvents and other risk factors. Findings from other cohort studies, with less accurate assessment of TCE exposures, have more variable results. Exposure to TCE was assessed less accurately in case-control studies; in many studies, TCE exposure was estimated from exposures to solvents in general. These studies typically reported higher cancer rates for tumor sites similar to those observed in the cohort studies. Elevated risks were most consistently observed for kidney cancer, liver cancer, Hodgkin's disease, non-Hodgkin's lymphoma, and cervical cancer (Wartenberg *et al.* 2000).

The findings in humans are supported by evidence of carcinogenicity in experimental animals, in which tumors occurred at several of the sites as in humans. In mice, TCE induces benign and malignant tumors of the liver (NCI 1976, Maltoni *et al*. 1988, NTP 1990), lung (Maltoni *et al*. 1988), and blood (lymphoma) (Henschler *et al*. 1980). In rats, TCE induces kidney cancer (Maltoni *et al*. 1988, NTP 1988, 1990), interstitial-cell tumors of the testis (Maltoni *et al.* 1988, NTP 1988), and possibly leukemia (Maltoni *et al*. 1988).

ADDITIONAL INFORMATION RELEVANT TO CARCINOGENESIS OR POSSIBLE MECHANISMS OF CARCINOGENESIS

TCE is rapidly absorbed from the stomach, intestines, and lung. After absorption, TCE is distributed throughout the body and concentrates in fatty tissues, such as the liver, brain, and body fat. TCE is metabolized primarily through oxidation by cytochrome P-450 and conjugation with glutathione. TCE metabolism in mice, rats, and humans is qualitatively similar, producing the same primary metabolites, which include chloral hydrate, dichloroacetic acid, and

trichloroacetic acid. These primary toxic metabolites are produced by the P-450 pathway and are associated with liver and lung toxicity in rats and mice. Another by-product, dichlorovinylcysteine (DVC), also is a metabolite of the glutathione pathway and is associated with kidney toxicity.

Kidney tumors (renal-cell carcinomas) from workers occupationally exposed to high levels of TCE exhibited somatic mutations of the von Hippel-Landau (VHL) tumor suppressor gene, a gene that has been associated with renal-cell carcinoma (Brauch *et al.* 1999). Mutations in the VHL gene were found in 75% of renal-cell carcinomas from 44 TCE-exposed persons. DNA sequencing analysis showed that 39% of these tumors had a specific mutation, a C to T transition at nucleotide (nt) 454, resulting in a Pro to Ser amino acid change at codon 81. In four patients, the nt 454 mutation also was found in the nearby noncancerous kidney tissue. Moreover, this mutation was specific to TCE exposure, because it was not found in renal-cell carcinomas from patients not exposed to TCE, and it was related to the disease, because it was not found in germline DNA from either diseased or non-diseased individuals.

It is reasonable from a biological perspective that the kidney tumors observed in humans are related to TCE exposure because (1) the site and histopathological characteristics of the tumors in humans and experimental animals are similar (Vamvakas *et al.* 1993), (2) a portion of the molecular mechanism of this type of cancer (nephrocarcinogenicity) has been discovered (Dekant *et al.* 1986, cited in Bernauer *et al.* 1996), (3) the metabolites derived from TCE (the likely ultimate electrophilic intermediates of its bioactivation) are identical in humans and experimental animals (Birner *et al*. 1993, cited in Clewell *et al*. 1995), and (4) taking the key urinary metabolites (mercapturic acids) as an indicator of the bioactivation of TCE (Birner *et al.* 1993, cited in Clewell *et al.* 1995), humans seem to be more sensitive than rats in developing the primary biochemical lesion that precedes kidney cancer.

In general, TCE and most of its major metabolites (chloral hydrate, dichloroacetic acid, and trichloroacetic acid) are not potent genotoxicants in a broad range of bacterial, lower eukaryotic, and *in vitro* and *in vivo* mammalian test systems. In mammalian cell-culture studies, TCE did not induce chromosomal aberrations in Chinese hamster ovary (CHO) cells, unscheduled DNA synthesis in rat hepatocytes, or gene mutations in human lymphoblastoid cells, but it did induce sister chromatid exchange in CHO cells, gene mutations in mouse lymphoma cells, and morphological transformation of rat embryo cells. In rodent *in vivo* studies, TCE did not induce unscheduled DNA synthesis, sister chromatid exchange, dominant lethal mutations, or chromosomal aberrations. TCE gave mixed results for DNA single-strand breaks or alkali-labile sites in mouse liver and positive results for micronucleus formation in mice. Studies of chromosomal aberrations, aneuploidy, and sister chromatid exchange in peripheral lymphocytes of workers exposed to TCE were inconclusive. The DVC metabolite appears to be a more potent mutagen than TCE. DVC is mutagenic in *Salmonella typhimurium* and may induce primary DNA damage in mammalian cells *in vitro* and *in vivo*.

PROPERTIES

TCE is a colorless liquid with a sweet, chloroform-like odor. Upon combustion, TCE produces irritants and toxic gases, which may include hydrogen chloride. In the presence of moisture and light, it breaks down into hydrochloric acid (HSDB 2002).

USE

TCE is used mainly as a degreaser for metal parts (CMR 1983, cited in Gist and Burg 1995). Five main industrial groups use TCE in vapor or cold degreasing operations: furniture and fixtures, fabricated metal products, electrical and electronic equipment, transport equipment, and miscellaneous manufacturing industries (IARC 1995). TCE can be used as an extraction solvent and a chemical intermediate and as a component in adhesives, lubricants, paints, varnishes, paint strippers, pesticides, and cold metal cleaners (ATSDR 1997).

PRODUCTION

The International Agency for Research on Cancer (IARC) 1995) reported that two companies in the United States produced TCE in 1992, with a combined annual capacity of 160,000 tons (145,000 metric tons). The *Directory of Chemical Producers in the United States* listed only one producer (SRI 1996).

EXPOSURE

Because TCE is pervasive in the environment, most people are likely to be exposed to TCE by simply eating, drinking, and breathing. The third National Health and Nutrition Examination Survey (NHANES III) suggested that approximately 10% of the population had detectable levels of TCE in their blood. NHANES III examined TCE concentrations in 677 people who were exposed to TCE, but not at their workplace, from 1988 to 1994, who represented a range of ages, races, genders, and regions of residence. TCE levels in whole blood were below the detection limit (0.01 μg/L) in approximately 90% of the people sampled. Assuming that TCE levels below the detection limit averaged half of the detection limit, the mean concentration was 0.015 μg/L (Wu and Schaum 2000). The Agency for Toxic Substances and Disease Registry (ATSDR) is developing information on potential public exposure to TCE and possible long-term health consequences in a subregistry to the National Exposure Registry specifically for hazardous waste sites. The TCE subregistry currently includes three sites in Michigan, four sites in Indiana, six sites in Illinois, and one site each in Pennsylvania and Arizona. Environmental and tissue data will serve as the basis for estimating exposure (Gist *et al.* 1994).

U.S. Environmental Protection Agency's (EPA's) Toxic Chemical Release Inventory for 1995 (TRI 1997) contains reports of environmental releases of TCE from 717 U.S. facilities. Of these, 591 reported releases to the atmosphere of more than 2,000 lb (0.9072 metric tons), with releases ranging from 2,000 to more than 200,000 lb. The total amount of TCE released in 1995 by the 717 facilities was 25,484,235 lb (11,559 metric tons), and the 17 greatest emitters together released 6.1 million lb (2,770.4 metric tons). The largest releases generally were from metalworking facilities, with three sites each reporting under Standard Industrial Classification (SIC) codes 3317 (steel pipe and tubes) and 3714 (motor vehicle parts and accessories). Other facilities (one each) reported under SICs 3089 (plastics and plastic products, not elsewhere classified), 3671 (electron tubes), and 3721 (aircraft).

Inhalation is the main route of potential environmental exposure to TCE. Mean TCE background levels in air range from 0.03 ppb (0.16 $\mu g/m^3$) in rural areas to 0.46 ppb (2.5 $\mu g/m^3$) in urban and suburban areas. Areas near emission sources have TCE in the air at concentrations of up to 1.2 ppb (6.4 $\mu g/m^3$) (ATSDR 1997).

TCE is one of the volatile organic compounds measured in the EPA's large-scale Total Exposure Assessment Methodology studies (Wallace *et al.* 1996). Studies in Maryland, New Jersey, and California, conducted from 1981 through 1987, measured TCE exposure with personal air monitors, which were carried by 750 persons for 24 hours. The median personal air concentrations of TCE were 0.3 to 3.0 μg/m^3. Breath samples taken in the evenings after several hours at home (from 50 to 350 persons in two New Jersey cities in 1981 to 1983 and 75 persons in two California towns in 1984) contained TCE at concentrations of 0.1 to 0.9 μg/m^3 (median personal air concentrations of 1.7 to 3.0 μg/m^3). However, TCE was not detected in the breath of 140 persons in Los Angeles (with TCE personal air levels of 0.3 to 1.2 μg/m^3, in 1984 or 1987) or in the breath of 75 persons in Baltimore (with TCE personal air levels of 1.1 μg/m^3, in 1987).

EPA's Aerometric Information Retrieval System obtained ambient air measurements of TCE from various state and local environmental agencies (from 1985 to 1998, 1,200 measurements from 25 states). The 1998 air levels were measured by 115 monitors in 14 states (range 0.01 to 3.9 μg/m^3, average = 0.88 μg/m^3). Using this average (and a daily inhalation rate of 20 m^3 of air), the estimated daily inhalation exposure to TCE was 18 μg (Wu and Schaum 2000).

Industrial wastewater is the primary source of release of TCE into water systems. EPA's Toxic Chemical Release Inventory for 1995 (TRI 1997) includes data from 28 facilities that each released more than 10 lb (4.5 kg) of TCE to water. Five facilities each released 250 to 280 lb (114 to 127 kg). The total release of TCE to water was 1,477 lb (0.670 metric tons). Four of the five facilities were metalworking plants, and one facility was a plant that produced TCE as a by-product and for on-site use and processing. The total releases of TCE to land and underground injection wells in 1995 were 3,577 lb (1.622 metric tons) and 550 lb (0.249 metric tons), respectively (TRI 1997). TCE background levels in large bodies of water range from 0.001 to 0.007 ppb (μg/L), and values reported for rainwater and snow are 0.0008 to 0.039 ppb (μg/L) (Gist and Burg 1995).

In EPA's Contract Laboratory Program Statistical Database, TCE is reported to occur in about 3% of surface-water samples, at an average level (geometric mean concentration) of 40.2 ppb (individual sample values ranged from 0.0001 to 120 ppb) and in 19% of groundwater samples at a geometric mean concentration of 27.3 ppb (individual sample values ranged from less than 0.1 to at least 27,300 ppb) (EPA 1989, cited in IARC 1995). A California survey of large water utilities in 1984 found a median TCE concentration of 3.0 μg/L. Based on this median and average daily water consumption of 2 L, estimated daily TCE exposure through drinking water is 6 μg (Wu and Schaum 2000). This estimate is consistent with ATSDR's (1997) estimate of 2 to 20 μg/day for the general population.

TCE is present in typewriter correction fluids, paint removers, strippers, adhesives, spot removers, and rug-cleaning fluids (Gist and Burg 1995). TCE is no longer used as an extraction solvent for cosmetics and drug products or as a dry-cleaning agent (IARC 1995).

TCE has been found in a variety of foods, with the highest levels in meats, at 12 to 16 ppb (0.09 to 0.12 μmol/kg), and U.S. margarine, at 440 to 3,600 ppb (3.35 to 27.4 μmol/kg) (ATSDR 1997). TCE was used as a solvent for extraction of natural fats and oils, spices, hops, and caffeine (from coffee), but the U.S. Food and Drug Administration (FDA) banned these uses in 1977 (IARC 1995).

According to the National Occupational Exposure Survey for 1981 to 1983 (NIOSH, 1990), 401,373 employees in 23,225 facilities in the U.S. potentially were exposed to TCE.

REGULATIONS

EPA regulates TCE under the Clean Air Act (as a hazardous air pollutant), the Safe Drinking Water Act (SDWA), the Superfund Amendments and Reauthorization Act (SARA), the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), and the Clean Water Act (CWA). Under the SWDA, the maximum contaminant level for TCE in drinking water is 0.005 mg/L. TCE is regulated under the Resource Conservation and Recovery Act as a halogenated organic compound (HOC) and under the land disposal restrictions. Under the latter, hazardous wastes that contain total concentrations of HOCs of at least 1,000 mg/L (liquids) or 1,000 mg/kg (nonliquids) are prohibited from land disposal. Priority data needs under SARA include exposure levels for humans living near hazardous waste sites and for other populations and epidemiological studies on health effects, including carcinogenicity. TCE is on the CERCLA List of Hazardous Substances, with a reportable quantity of 100 lb (45.4 kg). TCE is regulated under the CWA as a priority pollutant in final discharges resulting from steam electric power generation. It is designated a hazardous substance if discharged to navigable waters.

FDA regulations govern the presence of TCE in color additives, bottled water, and food as extraction solvent residues, and as an indirect additive as a migrant from adhesives or other materials used in food packaging.

The American Conference of Governmental Industrial Hygienists recommends a threshold limit value of 50 ppm (269 mg/m^3) and a short-term exposure limit or ceiling of 100 ppm (537 mg/m^3). The National Institute for Occupational Safety and Health (NIOSH) considers TCE to be a potential occupational carcinogen. NIOSH's recommended exposure limits are 2 ppm (11 mg/m^3) during use of TCE as an anesthetic and 25 ppm (130 mg/m^3) as a 10-hour time-weighted average (TWA) during all other exposures. The Occupational Safety and Health Administration's (OSHA's) permissible exposure limit for TCE in workroom air is 100 ppm (537 mg/m^3) as an 8-hour TWA, with a ceiling value of 200 ppm (1,070 mg/m^3). OSHA also regulates TCE under the Hazard Communication Standard and as a chemical hazard in laboratories. Regulations are summarized in Volume II, Table 180.

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