Fact Sheet Date: March 12, 1998

NEW YORK STATE
- HUMAN HEALTH FACT SHEET -

Ambient Water Quality Value for Protection of Sources of Potable Water

SUBSTANCE: 1,1,1,2-Tetrachloroethane **CAS REGISTRY NUMBER:** 630-20-6

AMBIENT WATER QUALITY VALUE: 5 ug/L

BASIS: Surface Water: Principal Organic Contaminant Classes

Groundwater: Former Reference to 10 NYCRR Subpart 5-1 Principal Organic Contaminant (POC) General Maximum Contaminant Level (MCL)

SUMMARY OF INFORMATION

1,1,1,2-Tetrachloroethane ($ClCH_2CCl_3$) is used as a feedstock for the synthesis of solvents such as trichloroethylene and tetrachloroethylene.

Pharmacokinetics

Truhaut (1972) identified 2,2,2-trichloroethanol and trichloroglucuronic acid in the urine of rats, guinea pigs and rabbits after oral administration of 1,1,1,2-tetrachloroethane (1,1,1,2-TCE). Trichloroethanol was oxidized in rats to trichloroacetic acid, found in the urine after inhalation or intraperitoneal injection of 1,1,1,2-TCE. Ikeda and Ohtsuji (1972) found trichloroethanol and trichloroacetic acid as major urinary metabolites. After subcutaneous administration Yllner (1971) found 43% of the administered dose in female mice expired after 3 days. The principal urinary and fecal metabolites after 3 days were trichloroethanol (31%) and trichloroacetic acid (4%) of the dose administered. About 78% of the dose was excreted within 3 days.

Acute/Subchronic Effects

Little is known about the effects of acute exposure in humans to 1,1,1,2-TCE.

Men with prolonged exposure to tetrachloroethane fumes (isomer not specified) suffered weakness, nausea and acute hepatic damage (Norman et al., 1981).

Oral LD_{50} values of 1500, 670 and 780 mg/kg for 1,1,1,2-TCE were found in male Swiss-Webster mice, male Wistar rats and female Wistar rats, respectively, by Truhaut et al. (1974). The acute effects of administration of 1,1,1,2-TCE range from death at 5,000 mg/kg in mice and rats and at 1000 mg/kg in rats (NTP, 1983), to severe centrilobular necrosis of the liver at 1000 mg/kg in mice and granular liver with centrilobular cytoplasmic swelling in male rats receiving 1000 mg/kg. Female rats given 800 mg/kg, of 1,1,1,2-TCE had severe microvacuolar steatosis of the liver, congested lungs and spleens with hemosiderin deposits and macrophages (Truhaut et al., 1974).

Female Wistar rats given 300 mg/kg 1,1,1,2-TCE by gavage in olive oil 5 days/week for two weeks developed fatty degeneration of the liver, accumulation of triglycerides, decreases in lactate dehydrogenase, malate dehydrogenase and glutamic pyruvic transaminase compared to controls. Male rats' livers were not affected (Truhaut, et al. 1975).

In rabbits given 500 mg/kg 1,1,1,2-TCE by gavage, Truhaut et al. (1973) noted elevations in several liver enzymes indicative of liver injury and aberrant electrocardiographic Q waves. Blood cholesterol and total lipids were increased at 96 hr after dosing. Guinea pigs and rabbits given 500 mg/kg in one dose developed severe centrilobular necrosis of the liver after 1 day and 3 days, respectively. Heart tissue was characterized by edematous dissociation of myocardial fibrils.

Chronic Effects

Toxicity to humans has not been observed in long-term exposure where 1,1,1,2-TCE was the only solvent exposure (USEPA, 1989; Norman et al., 1981).

NTP (1983) exposed rats to 0, 125 or 250 mg/kg 1,1,1,2-TCE in corn oil by gavage, 5 days/week for 103 weeks. There were no differences in body weights due to treatment. High dose rats were uncoordinated and their survival rate was significantly less than controls, partly due to accidental killing (NTP, 1983).

Mineralization of the kidney occurred in 12/48 (25%) of the control males, 19/50 (38%) of the low-dose males and 26/48 (54%) of the high-dose males. The lesion was characterized by multifocal deposits of basophilic material (probably calcium) and crystals in the tubules of the papilla considered related to intake of 1,1,1,2-TCE. Hepatic clear cell change in females was dose related. The LOAEL from this study is 125 mg/kg.

Genotoxicity

1,1,1,2-Tetrachloroethane shows limited evidence of non-mutagenicity in vivo and in vitro (Ashby and Tennant, 1993). The compound has been tested in a variety of bacterial and mammalian genotoxicity tests for genetic mutations and for chromosome damage and abberations, with conflicting but predominantly negative results. Positive results in 3 strains of the S. typhimurium reverse mutation (Ames) test were reported by Strobel and Grummt, 1987 (RTECS, 1993). However, negative results for the same Salmonella strains were reported by Jackson and Stack (1993) and Simmon et al. (1977) in addition to negative results with S. typhimurium 1535 (Milman et al., 1988), 1538 and 1537. In other strains, BA13 and BAL13, 1,1,1,2-TCE was genetically inactive (Roldan - Arjona and Garcia-Pedrajas, 1991) in the L-arabinose resistance test.

Tests of mammalian cell mutation gave conflicting results. The forward mutation assay in L5178Y mouse lymphoma cells was positive in one lab (Myr and Caspary, 1991), negative in another (McGregor et al., 1988) for mutagenic activity. In the hepatocyte DNA repair test, 1,1,1,2-tetrachloroethane showed no activity in two separate assays (Williams et al., 1989; Milman et al., 1988).

Two assays of the ability of 1,1,1,2-tetrachloroethane to induce cell transformation in the BALB/3T3 mouse (Williams et al., 1989; Milman et al., 1988) were negative. In two promotion-inhibition assays to induce enzyme-altered foci in rat liver, 1,1,1,2-TCE showed no activity (Story et al., 1986; Milman et al., 1988).

Clearly positive results were found in the DNA binding assay in the Wistar rat and BALB mice (Colacci et al., 1989; Paolini et al., 1990) and in the gene mutation conversion test in S. cerevisiae (Paolini et al., 1990).

Differing points of view have been developed by authors examining structure- activity predictions of the mutagenic or carcinogenic potential of 1,1,1,2-TCE. Rosenkranz and Klopman (1990) identified a mouse specific biophore in the molecule (Cl-C-Cl) they view as predicting carcinogenicity. Using a system of structural fragments (structural alert) that correlate with mutagenic and genotoxic carcinogens, Ashby and Tennant (1991) classed 1,1,1,2-TCE as a nongentoxic putative carcinogen. They group it with carcinogens affecting a single species at a single site.

Carcinogenicity

The NTP (1983) exposed male and female B6C3F_1 mice to 0, 250 or 500 mg/kg 1,1,1,2-tetrachloroethane in corn oil gavage 5 times a week for 103 weeks and male and female rats to 0, 125 or 250 mg/kg. There were increases in the incidence in combined hepatic neoplastic modules/carcinomas in male rats and increased mammary fibroadenoma in low-

dose female rats, but not in high-dose females. In both male and female mice apparently increased incidences of hepatocellular adenomas and carcinomas occurred.

Virtually the only evidence about the carcinogenicity of this chemical is this flawed 1983

NTP bioassay. It was agreed by reviewers of the bioassay results that the data in rats are inadequate due to the premature deaths of 42 rats, which affected the statistical power. The design of the mouse study was flawed because the high dose exceeded the maximum tolerated dose in the high-dose group and none of these mice lived past 65 weeks. Two of the reviewers (Vesselonovitch and Swenberg) maintained that the toxicity at the high dose precluded the use of the high-dose endpoint for assessing carcinogenicity. "Clear evidence of an increased incidence of hepatocellar carcinoma in male mice was not found" (NTP, 1983). Therefore, the bioassay shows evidence of carcinogenicity in only one species (mouse) and one sex (female) and the high-dose toxicity in females may make use of the data questionable. One reviewer (Swenberg) maintained the deaths in mice were not caused by tumors, which negated the study altogether.

There appears to be increased incidence of mouse liver tumors (one species, one sex) in a flawed study with little supporting data that would constitute insufficient evidence to regulate 1,1,1,2-TCE as a carcinogen.

DERIVATION OF VALUES

Since there is inadequate evidence of carcinogenicity of 1,1,1,2-TCE, the development of a value on chronic endpoints could be considered. Based on the NTP (1983) data on kidney mineralization in rats an ADI can be calculated using the LOAEL of 125 mg/kg corrected to a time-weighted average (125 mg/kg x 5/7 d/wk) of 89 mg/kg/day, an uncertainty factor of 100 for inter- and intra-species variation, 10 for LOAEL-to-NOAEL conversion and 3 for lack of adequate supporting studies. The ADI is 0.03 mg/kg/d. Based on a 70 kg adult, 2L water consumption, and 20% relative source contribution, a water quality value of 210 ug/L can be calculated (6 NYCRR 702.5).

Surface Water

Regulations [6 NYCRR 702.2(b)] require that the value be the most stringent of the values derived using the procedures found in sections 702.3 through 702.7. The principal organic contaminant class value of 5 ug/L (702.3(b)) represents the most stringent value that can be derived for 1,1,1,2-TCE. Therefore, the ambient surface water quality value for 1,1,1,2-TCE is 5 ug/L.

Groundwater

The principal organic contaminant (POC) groundwater standard of 5 ug/L (6 NYCRR 703.5) applies to 1,1,1,2-TCE. This standard became effective on January 9, 1989 by inclusion by reference to 10 NYCRR Subpart 5-1 standards. The basis and derivation of the POC standard are described in a separate fact sheet.

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SEARCH STRATEGY

IRIS - 9/93
RTECS - 9/93
CCRIS - 9/93
Database search on TOXLINE and BIOSIS - September 1993.

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