Advisory Opinion for 1,1-Dichloroethylene (Vinylidene Chloride)

5013

Office of Drinking Water
U.S. Environmental Protection Agency
Washington, D.C. 20460

AN OFFICE OF DRINKING WATER HEALTH EFFECTS ADVISORY

The Office of Drinking Water provides advice on health effects upon request, concerning unregulated contaminants found in drinking water supplies. This information suggests the level of a contaminant in drinking water at which adverse health effects would not be anticipated. A margin of safety is factored in so as to protect the most sensitive members of the general population. The advisories are called Suggested No Adverse Response Levels (SNARLs). SNARLs have been calculated by EPA and by the National Academy of Sciences (NAS) for selected contaminants in drinking water. An EPA-SNARL and a NAS-SNARL may well differ due to the possible selection of different experimental studies for use as the basis for the calculations. Furthermore, NAS-SNARLs are calculated for adults while the EPA-SNARLs are established for a 10 kg body weight child. Normally EPA-SNARLs are provided for one-day, ten-day and longer-term exposure periods where available data exist. A SNARL does not condone the presence of a contaminant in drinking water, but rather provides useful information to assist in the setting of control priorities in cases where contamination occurs. EPA-SNARLs are provided on a case-by-case basis in emergency situations such as spills and accidents.

In the absence of a formal drinking water standard for an identified drinking water contaminant, the Office of Drinking Water develops EPA-SNARLs following the state-of-the-art concepts in toxicology for non-carcinogenic risk for short and longer term exposures. In cases where a substance has been identified as having carcinogenic potential, a range of estimates for carcinogenic risk based upon lifetime exposure as developed by the NAS (1977 or 1980) and/or EPA Carcinogen Assessment Group (EPA, 1980a) is presented. However, the EPA-SNARL calculations for all exposures ignore the possible carcinogenic risk that may result from these exposures. In addition, EPA-SNARLs usually do not consider the health risk resulting from possible synergistic effects of other chemicals in drinking water, food, and air.

EPA-SNARLs are not legally enforceable standards; they are not issued as an official regulation, and they may or may not lead ultimately to the issuance of national standards or Maximum Contaminant Levels (MCLs). The latter must take into account occurrence, relative source contribution factors, treatment technology, monitoring capability, and

costs, in addition to health effects. It is quite conceivable that the concentration set for EPA-SNARL purposes might differ from an eventual MCL. The EPA-SNARLs may also change as additional information becomes available. In short, EPA-SNARLs are offered as advice to assist those such as Regional and State environmental and health officials, local public officials, and water treatment facility personnel who are responsible for the protection of public health when dealing with specific contamination situations.

General Information and Properties

1,1-Dichloroethylene (1,1-DCE, vinylidene chloride) is used industrially as a chemical intermediate and in the manufacture of polyvinylidene copolymers (PVDCs). PVDCs are widely used in food wrappings in the manufacture of non-flammable synthetic fibers and as interior coatings for storage tanks and piping.

1,1-Dichloroethylene is a clear, colorless liquid with the molecular formula $C_2H_2Cl_2$ and a molecular weight of 96.95. It is slightly soluble in water (400 mg/l at 20°C), but readily soluble in organic solvents. In air, one (1) ppm is equivalent to 3.97 mg/m^3 and one (1) mg/l is equivalent to 252 ppm, when measured at 25°C and 760 mm Hg (Irish, 1963). It is extremely volatile, having a vapor pressure of 591 Torr (mm Hg) at 20°C and a boiling point of 31.5°C. It has a melting point of -122.1°C and a mild, sweet odor similar to that of chloroform. The liquid is heavier than water with a specific gravity of 1.3. Its vapor is over three times heavier than air and will, therefore, settle in low places in a still atmosphere. The monomer polymerizes to a plastic at temperatures above 0°C, especially in the presence of oxygen or other catalysts. The octanol/water partition coefficient for 1,1-dichloroethylene is 5.37 (Radding et al., 1977).

The present threshold limit value (TLV) for 1,1-dichloroethylene in the United States is 10 ppm (40 mg/m^3) (ACGIH, 1977).

Sources of Exposure

Pearson and McConnell (1975) indicated that degradation of a chlorinated hydrocarbon such as 1,1-dichloroethylene when dissolved in water is much slower than in the atmosphere. They estimated a tropospheric half-life of eight weeks. A rapid degradation in aqueous systems does occur in the presence of metallic iron (McConnell, et al., 1975).

1,1-Dichloroethylene has been detected in 2% of the finished drinking water samples from 103 cites tested (Coniglio et al., 1980). The mean concentration was 0.36 ug/l, with a range of 0.2-0.51 ug/l. None was detected in 105 raw water samples. Thirteen cities were sampled whose water came from ground water sources. Of the raw waters tested, 15.4% (2 cities) were positive, (mean = 0.5 ug/l). Of the finished waters tested, 7.7% (1 city) were positive (0.2 ug/l).

One might expect that the population most exposed to 1,1-dichloroethylene would be workers in industries manufacturing or using the chemical. For example, time weighted average (TWA) concentrations as high as 70 ppm were estimated during air sampling studies at a polyvinylidene chloride copolymer fiber production facility (Ott et al., 1976). 1,1-Dichloroethylene was also identified as a co-contaminant with vinyl chloride monomer in the working environment of polyvinyl chloride production plants, present at concentrations below 5 ppm, but typically at trace levels (Kramer and Mutchler, 1972).

Ambient levels of 1,1-dichloroethylene have been measured by Tenax sampling/gas chromatography-mass spectrometry analysis (Pellizzari, 1978). Maximum concentrations detected in various areas of the United States varied from a trace (260 ng/m^3) near Grand Canyon, Arizona, up to 2500 ng/m^3 at Front Royal, Virginia. The data may be low due to sample instability.

No data were found to indicate contamination of foodstuffs with 1,1-dichloroethylene residues.

Pharmacokinetics/Metabolism

1,1-Dichloroethylene, as a neutral, low molecular weight, lipid soluble material, should be readily absorbed following any route of administration. Pharmacokinetic studies in rats and mice based on urinary and biliary excretion data have shown that administration of a single oral dose of 1,1-dichloroethylene in the dose range 0.5-50 mg/kg results in rapid and complete absorption (McKenna et al., 1978b; Reichert et al., 1979; Jones and Hathway, 1978a). Rapid absorption and distribution of 1,1-DCE after intraperitoneal administration has also been demonstrated (Jones and Hathway, 1978a).

It is well established that the absorption of gases from the lung is highly dependent on the blood:gas partition coefficient. 1,1-Dichloroethylene has a high blood:gas partition coefficient (4.0), albeit less than trans-1,2-dichloroethylene (10.9) (Andersen et al., 1980). During inhalation exposure, steady-state conditions are reached in the whole animal within one hour (Filser and Bolt, 1979; Andersen et al., 1980).

Distribution of 1,1-DCE to the organs of rats following intragastric administration of an unspecified dose of [^{14}C]1,1-DCE in sequential autoradiograms of longitudinal sagittal sections through whole animals showed large ^{14}C concentrations in the kidneys and liver after 30 minutes and a more general distribution of ^{14}C throughout the soft organs of the body at 1 hour (Jones and Hathway, 1978a). The kidneys and liver retained ^{14}C for the longest time after dosing.

Subcellular distribution of [^{14}C] 30 minutes following inhalation of 2,000 ppm (8000 mg/m^3) of [^{14}C]1,1-DCE for 2 hours was determined in the microsomal, mitochondrial, and cytosolic compartments of the liver (Jaeger et al., 1977). More ^{14}C was found in liver fractions from fasted rats than from fed rats. There was no marked subcellular localization of ^{14}C since its concentration was about the same in mitochondria, cytoplasm and microsomes. The ^{14}C found in microsomes and mitochondria was largely covalently bound (TCA-insoluble). In contrast, the cytosol contained substantial amounts of TCA-soluble ^{14}C, suggesting the presence of metabolites. Significant amounts of the ^{14}C in microsomes and mitochondria was $CHCl_3$-soluble, suggesting that there is considerable binding of ^{14}C to lipids. The turnover rate of TCA-insoluble radioactivity derived from 1,1-DCE has a half-life of 2-3 hours.

Metabolic end products of chlorinated ethylenes are predominantly alcohols and carboxylic acids. Liebman and Ortiz (1977) have postulated the various metabolic pathways for 1,1-DCE. Chloroacetic acid has been identified as a product in perfused rat liver. Inhibition of epoxide hydrase resulted in a stimulation of chloroacetic acid formation from 1,1-DCE, leading to the conclusion that the glycol intermediate is relatively unimportant in the conversion of 1,1-DCE to chloroacetic acid (Leibman and Ortiz, 1977). Additionally, studies using competitive epoxide substrates have shown that epoxide hydrating pathways are of minimal significance in the metabolism of reactive intermediates of 1,1-DCE (Andersen et al., 1980). The essential feature of

the metabolic pathway for dichloroethylenes is that all of these compounds appear to be metabolized through epoxide intermediates which are reactive and may form covalent bonds with tissue macromolecules (Henschler, 1977; Henschler and Bonse, 1977).

In whole animals, it has been established that 1,1-DCE metabolites are conjugated with glutathione, presumably a detoxification process (McKenna et al., 1977, 1978a, 1978b; Jones and Hathway, 1978a; Reichert et al., 1978, 1979).

Reichert et al. (1979) identified three metabolites in rat urine, among these methylthioacetylaminoethanol. In addition, three unidentified materials were present in lesser concentrations. The identification of methylthioacetylaminoethanol suggests that, in addition to glutathione conjugation, a totally different reaction mechanism must exist which leads to the formation of ethanolamine derivatives. The ethanolamine is postulated to originate from membrane lipids which react with 1,1-DCE epoxide and/or its metabolites.

Data show that the metabolism of 1,1-DCE is readily saturable (Reichert et al., 1979; Jones and Hathway, 1978a; Jaeger et al., 1977; McKenna et al., 1977, 1978a, 1978b). Thus, as the dosage is increased a larger absolute amount of metabolite is formed, but a lesser percentage of the administered dose is metabolized. This has been observed after various routes of administration. As the dose is increased and metabolism reaches saturation, more parent compound is excreted into the air.

Studies comparing the relative ability of mice and rats to metabolize 1,1-DCE have been conducted. Data on disposition of ^{14}C from inhaled [^{14}C]1,1-DCE in mice and rats (McKenna et al., 1977) show that the mouse develops a higher body burden of 1,1-DCE than the rat at 10 ppm (5.3 meq 1,1-DCE/kg vs. 2.89 meq/kg). The disposition of 1,1-DCE appears quite similar in the two species. However, as a result of the overall greater rate of metabolism, covalently bound 1,1-DCE metabolites are more than four times higher in the mouse liver than in the rat liver, and more than 6 times higher in mouse kidney than in the rat. The substantial difference in distribution may be responsible for the different sensitivity of the two species to the carcinogenic effects of 1,1-DCE (Hathway, 1977).

Considerable work on the excretion of 1,1-DCE and its metabolites has been done using [^{14}C]1,1-DCE (Jaeger et al., 1977; McKenna et al., 1977, 1978a, 1978b; Jones and Hathway, 1978a; Reichert and Werner, 1978; Reichert et al., 1979). The data show that both unmetabolized 1,1-DCE and CO_2, formed by metabolism of 1,1-DCE are excreted via the lung, whereas the other metabolites are eliminated via renal and biliary excretion. However, the pattern of excretion depends upon the concentration of 1,1-DCE in the blood, which is affected by the amount of chemical administered and to a certain extent, by the route of administration. At low dose levels, where metabolism is effective and the concentration of 1,1-DCE in the blood is low, most of the ^{14}C is eliminated as metabolites via renal and biliary excretion. It has been shown that a portion of the material excreted in the urine was actually of biliary origin and entered the urine by means of enterohepatic circulation (Jones and Hathway, 1978a). At higher dose levels ($\sim$200 ppm) where the concentration of 1,1-DCE in blood is much higher, metabolism approaches saturation and becomes less effective in removing the xenobiotic from the blood as it passes through the liver (Andersen et al., 1979). As a result, increasing amounts of unmetabolized 1,1-DCE are eliminated through the lung.

For 1,1-DCE the rate of elimination is relatively rapid, since most of the total absorbed dose is eliminated in the first 24-72 hours after administration. Disappearance of covalently bound metabolites of 1,1-DCE, measured as TCA-insoluble fractions, also appears to be fairly rapid with a reported half-life of 2-3 hours (Jaeger et al., 1977).

It is interesting to note that, based on the analysis of pharmacokinetic data from gas uptake studies, it has been suggested that the rate limiting step in metabolism of DCEs at low concentration is blood flow to the liver (Andersen et al., 1980). The rate at which an inhaled chemical is presented to the liver is related to pulmonary absorption. Since the weight-adjusted breathing volume decreases as body weight increases, the concentration of DCEs in the blood and presented to the liver would be expected to be reduced to a similar degree. For a rat, the resting breathing volume is estimated to be 32 liters/kg hr. For a moderately active 70 kg man, the 8-hr. work shift breathing volume is usually taken to be 10m^3, i.e., 18 liters/kg hr. Therefore, it is expected that at lower exposure concentrations, a lesser amount of DCEs would be presented to the liver in man relative to the rat. It has therefore been suggested that at low atmospheric concentrations, DCE metabolism would be slower in man than rats. This would shift the K_m (ppm in atmosphere) to even higher concentrations for man (Andersen et al., 1980).

Health Effects

1,1-Dichloroethylene, like other chlorinated hydrocarbons, causes depression of the central nervous system after acute exposures to high levels of the substance. Exposure to high concentrations can cause narcosis and presumably could lead to death due to depression of the respiratory system. In addition, 1,1-dichloroethylene causes liver and kidney damage in animals; similar damage could be expected to occur in humans following prolonged exposures to high concentrations. Inhalation exposure to this compound also has been shown to sensitize the myocardium of rats to catecholamines (Siletchnik and Carlson, 1974).

Jenkins, et al. (1972) tested the effects of single 100, 300 or 500 mg/kg oral doses of 1,1-dichloroethylene in corn oil administered to adult male Holtzman rats. Activities of five liver or plasma enzymes were determined. Twenty-two to 46 hours after dosing with 100 mg/kg, liver glucose-6-phosphatase (G-6-P) was reduced to 80% of control and liver alkaline phosphatase (AP) was doubled ($P < 0.05$). At 300 mg/kg, after 22-46 hours, liver G-6-P was further reduced to 53% of control, liver AP nearly quintupled, liver tyrosine transaminase quadrupled, and plasma alkaline transaminase was elevated 150% ($P < 0.05$). At 500 mg/kg, all four enzymes were further affected; in addition, plasma alkaline phosphatase was elevated over 400% above control ($P < 0.05$).

A single long-term study has been conducted with 1,1-DCE administered in the drinking water of rats (Humiston et al., 1978). Groups of 96 Sprague-Dawley rats (48 males and 48 females) were exposed for 2 years at nominal concentrations of 60 ppm, 100 ppm, and 200 ppm. These dose levels corresponded to approximate daily intakes in the range of 7 mg/kg, 11 mg/kg, and 22 mg/kg at the 60, 100, and 200 ppm concentrations, respectively. In comparison to control animals, treated rats displayed no significant or consistent differences in general appearance, body weight, food consumption, water consumption, hematologic values, urinalysis, clinical chemistry values, or organ weights. Gross and histopathologic examination of tissues from treated rats, however, revealed a number of statistically significant lesions. The authors considered the most important lesions to be the hepatocellular fatty change and periportal hepatocellular hypertrophy which occurred in male rats at the 200 ppm dose level and in females at all dose levels. The authors did not observe any hepatocellular necrosis that was considered treatment-related.

Teratogenicity

The teratogenic potential of inhaled or ingested 1,1-DCE has been evaluated in rats and rabbits (Murray et al., 1979). Inhalation exposure for both species was 7 hours/day at 20 (rats only), 80, and 160 ppm. In the ingestion study, rats were given drinking water with 200 ppm 1,1-DCE or approximately 40 mg/kg/day. Administration to rats was on days 6 to 15 of gestation and on days 6 to 18 for rabbits. In rats, inhalation of 80 to 160 ppm of DCE produced significant maternal effects including decreased weight gain, decreased food consumption, increased water consumption and increased liver weight (160 ppm only). In the offspring, there was a significantly increased incidence of skeletal alterations at 80 and 160 ppm; these alterations included delayed ossification of various bones and wavy ribs. In rabbits, 160 ppm caused a significant increase in resorptions in the dams and a significant change in several minor skeletal variations in the offspring. In both rats and rabbits exposed to 1,1-DCE by inhalation, the authors noted that concentrations which caused little evidence of maternal toxicity (20 ppm in rats and 80 ppm in rabbits) caused no adverse effect on embryonal or fetal development. In rats receiving 1,1-DCE by ingestion, the only significant effect noted was an increase in mean fetal crown rump length. The authors concluded that 1,1-DCE was not teratogenic at this exposure level.

Mutagenicity

1,1-DCE was mutagenic in Salmonella typhimurium strains TA 1530, TA 100 (Bartsch et al., 1975; Simmon et al., 1977; Simmon and Tardiff, 1978) and TA 1535 (Jones and Hathway, 1978b) and in E. coli K12 (Greim et al., 1975). In both bacterial systems, mutagenic activity required microsomal activation. It also was mutagenic in the host-mediated assay using Salmonella tester strains in mice (Cerna and Kypenova, 1977). 1,1-Dichloroethylene did not produce any chromosomal aberrations in bone marrow cells following repeated intraperitoneal injections (Cerna and Kypenova, 1977).

The finding of increased mutation rates in bacterial systems has not been confirmed in mammalian systems. 1,1-DCE was non-mutagenic in V79 Chinese hamster cells in the presence of 15,000 g liver supernatant from phenobarbital-pretreated rats and mice (Drevon and Kuroki, 1979). CD-1 male mice

exposed to 10, 30, or 50 ppm of 1,1-DCE for 6 hours/day for 5 days failed to produce dominant lethal mutations (Andersen and Jenkins, 1977). Similarly, adult CD male rats exposed to 55 ppm 1,1-DCE for 6 hours/day, 5 days/week for 11 weeks failed to produce dominant lethal mutations (Short et al., 1977c).

Carcinogenicity

The carcinogenicity of 1,1-DCE is currently being evaluated in studies with mice and rats sponsored by the National Toxicology Program. These studies have been completed but the reports were not yet available at the time this SNARL package was drafted.

Studies of the potential carcinogenicity of 1,1-DCE have been conducted with mice, rats and hamsters using either oral administration or inhalation exposure. Preliminary results, after a total of 98 weeks observation in the inhalation study and 93 weeks in the gavage study have been reported (Maltoni 1977, Maltoni et al., 1977). In the inhalation study, Swiss mice were exposed to 10 or 25 ppm of 1,1-DCE for 4 hours/day, 4 to 5 days/week for 52 weeks and then observed for the remainder of the study. Exposure to 10 ppm of 1,1-DCE caused no statistically significant increase in incidence of any tumor in Swiss mice. At 25 ppm, 17% of the mice (25/300) exposed to 1,1-DCE had developed kidney adenocarcinomas compared to none in the control group (190 males, 190 females). The majority of tumors were observed in male mice (24 males, 1 female). In contrast, no kidney adenocarcinomas were observed in Sprague-Dawley rats under the same exposure regimen at exposures up to 200 ppm. Data from this study also showed a significant increase in mammary adenocarcinomas in female Swiss mice inhaling 25 ppm and in female Sprague-Dawley rats inhaling 100 and 150 ppm of 1,1-DCE. At 10, 25 or 50 ppm of 1,1-DCE there was no increase in tumor incidence in Sprague-Dawley rats of either sex. Oral administration of 20 mg/kg of 1,1-DCE 4 to 5 days/week for 52 weeks to female Sprague-Dawley rats resulted in a 42% incidence of mammary tumors in 21 of 30 animals, whereas control animals had a 34% incidence (34/100). Hamsters exposed for 52 weeks by inhalation to 25 ppm of 1,1-DCE did not exhibit an increased tumor incidence after 74 weeks.

In another inhalation study, (Lee et al., 1978) CD-1 mice and CD rats were exposed to 55 ppm of 1,1-DCE for 6 hours/day, 5 days/week for 7 to 12 months. Hepatic hemangiosarcomas were observed in the mice exposed to 1,1-DCE: 2/35 for males and 1/35 for females in the treated group compared to 0/26 for males and 0/36 for females in the control group. The significance of these hepatomas was judged to be questionable because such tumors have been reported to occur spontaneously in small numbers at this age (Percy and Jonas, 1971; Shen, 1974). However, two rats developed hemangiosarcomas in the mesenteric lymph node or subcutaneous tissue which were judged probably to be caused by 1,1-DCE. Although kidney pathology was observed, there was no report of adenocarcinoma.

An inhalation study using both Wistar rats and Sprague-Dawley rats has been reported (Viola and Caputo, 1977). Exposures were to 1,1-DCE concentrations from 75 to 200 ppm for 4 hours/day, 5 days/week for 12 months. Data from this study were interpreted as showing no grossly observable interrelation between tumor production and 1,1-DCE inhalation.

Additionally, male and female Sprague-Dawley rats were exposed to 1,1-DCE either by inhalation (25 or 75 ppm for 6 hours/day, 5 days/week for 18 months) or by ingestion in drinking water (60, 100 or 200 ppm for two years). In the interim report of this study (Rampy et al., 1977), there was no evidence of increased tumor incidence in animals treated with 1,1-DCE.

The effect of weekly oral administration of 50 mg/kg of 1,1-DCE following in utero exposure (150 mg/kg on day 17 of gestation) was studied in BDIV rats (Ponomarkov and Tomatis, 1980). The oral administration was continued throughout the lifetime of the animals until the study was terminated after 120 weeks. There was no statistically significant increase in the total number of tumor bearing animals. However, an increased incidence of tumors at certain sites was observed: liver tumors in females and menangiomas in males. Additionally, hyperplastic nodules of the liver were observed in both male and female rats; these were not seen in control animals. The authors concluded that the results provided limited evidence of carcinogenicity of 1,1-DCE.

The carcinogenic effects of 1,1-DCE were also investigated in Ha:ICR Swiss mice by several routes of administration (Van Duuren et al., 1979). 1,1-DCE was inactive as a whole mouse skin carcinogen and inactive by subcutaneous injection. In the two stage carcinogenesis assay using phorbal myristate acetate as a promoter, 1,1-DCE was shown to be active as a skin tumor initiator.

There are no published studies with adequately good data to permit an evaluation of the carcinogenic risk of vinylidene chloride to humans (Bahlman et al., 1979). One study reported no excessive cancer risk among 138 workers occupationally exposed to 1,1-DCE, but methodological limitations of this study (Ott et al., 1976) do not permit an adequate evaluation of the carcinogenic risk, since the number of individuals lost to follow-up in this study was high and the period of observation was relatively short. In a second study, mortality was examined among 629 workers occupationally exposed in a vinylidene chloride (1,1-DCE) production and polymerization plant where there was also exposure to vinyl chloride and acrylonitrile. It was reported that 7 of the 35 deaths that occurred were from malignant tumors. This was not greater than the expected number. Two bronchial carcinomas occurred in persons aged 35-39, whereas 0.8 were expected. However, no information was given on smoking habits (Theiss et al., 1977).

The Office of Water Regulations and Standards (U.S. EPA, 1980a) in setting ambient water quality criteria for 1,1-DCE, based its development of these criteria upon the finding of Maltoni (1977) that this chemical caused a significant increase in the number of renal adenocarcinomas observed in Swiss mice exposed to 25 ppm, 4 hours/day, 4-5 days/week for 52 weeks. The Office established a range of criteria based upon levels estimated to increase the lifetime risk of cancer 1 in 100,000, 1 in 1,000,000, or 1 in 10,000,000. The criteria ranged from 3.3-0.033 ug/l, respectively, for an adult consuming 2 liters of that contaminated ambient water per day and ingesting 6.5 g/day of contaminated aquatic organisms. If total exposure were solely from drinking the water, the resulting criteria would range from 3.4-0.034 ug/l, representing a 10^{-5}-10^{-7} risk, respectively.

SNARL Development

One-day SNARL

There are very limited ingestion data upon which to base a one-day SNARL. The results of the Jenkins et al. study (1972) in which the authors measured the level of activity of five liver or plasma enzymes after single oral doses of 100, 300 or 500 mg/kg 1,1-dichloroethylene in corn oil may be used. The SNARL would be derived thusly:

$$\frac{100 \text{ mg/kg} \times 10 \text{ kg} \times 100\%}{1000 \times 1 \text{ liter}} = 1.0 \text{ mg/l}$$

Where:

100 mg/kg = minimal effect dose

10 kg = weight of protected individual (child)

100% = percentage of dose absorbed

1000 = safety factor

1 liter = volume in liters of drinking water imbibed per day by 10 kg child

Longer-term SNARL

A longer-term SNARL can be calculated from a two-year study in which 1,1-dichloroethylene was administered to rats at 60, 100 or 200 ppm in drinking water for 18 months (Rampy et al., 1977; Humiston et al., 1978). Interim results indicated that no adverse effects occurred as determined by clinical chemistry, hematology, mortality or histology (Rampy et al., 1977). However, when the study was completed, it was shown that minimal liver changes had occurred in females at all dose levels (Humiston et al., 1978). The 60 ppm dose level could be considered a minimal-effect level. A longer-term SNARL could be calculated thusly:

$$\frac{7 \text{ mg/kg/day} \times 10 \text{ kg} \times 1.0}{1000 \times 1 \text{ liter}} = 0.07 \text{ mg/l}$$

Where:

7 mg/kg = daily consumption by rat at 60 ppm dose level

10 kg = weight of child

1.0 = measure of absorption from GI tract

1000 = safety factor employed with minimal effect dose

1 liter = volume of drinking water consumed daily by 10 kg child

Analysis

1,1-DCE can be analyzed by a purge-and-trap gas chromatographic procedure used for the determination of volatile organohalides in drinking water (U.S. EPA, 1980b). Volatile chemicals are extracted by an inert gas which is bubbled through the aqueous sample. The compounds, now in the gaseous phase, are swept from the purging device and are trapped in a short column containing an adsorbent material. After a predetermined period of time, the trapped components are thermally desorbed and backflushed onto the head of a gas chromatographic column where separation takes place.

The suggested chromatographic parameters are given below:

Primary column: eight feet long x 0.1 inch ID stainless steel or glass tubing, packed with 1% SP-1000 on Carbopack-B (60-80) mesh.

Carrier gas: helium at 40 ml/min.

Temperature: 45°C for 3 minutes, then program at 8°C/minute to 220°C.

Detector: Hall model electrolytic conductivity or other halogen specific detector.

Sample size: 5 ml.

This procedure is applicable to the measurement of 1,1-DCE over a concentration range of 0.4 to 1500 ug/liter. The retention time for this compound in the recommended primary column is 476 seconds. Allyl chloride may interfere with the analysis of 1,1-DCE under the chromatographic conditions

specified above. However, this chemical does not appear to occur at detectable levels in most drinking waters. Nevertheless, confirmatory analysis by a GC-MS or by a secondary analytical column is highly recommended.

Treatment

(Forthcoming from STB)

Conclusions and Recommendations

EPA-SNARLs for 1,1-DCE have been developed for durations of exposures of one-day and longer-term. The potential for carcinogenicity of this substance has not been considered in the development of these SNARLs, although evidence does exist to suggest that the chemical does interact with tissue macromolecules and appears to be a carcinogen in Swiss mice and perhaps in CD rats.

To summarize, the one-day SNARL is 1.0 mg/l;
the longer-term SNARL is 0.07 mg/l

In order to be able to develop a ten-day SNARL based upon ingestion data, it can be recommended that subchronic studies in animals receiving 1,1-DCE in their drinking water be conducted to better define the toxicity of this compound in water. In fact, funding under the EPA Competitive Grants program has been made to an investigator to carry out these experiments in rats exposed to this substance by ingestion and inhalation. No-effect levels will be identified. When these data become available, they will be reviewed for acceptability in their application in the development of SNARLs. If they can be used, this presently proposed series of SNARLs will be evaluated and perhaps changed on the basis of the new information.

REFERENCES

American Council of Governmental Industrial Hygienists (ACGIH). 1977. TLVs. Threshold limit values for chemical substances and physical agents in the workroom environment. p. 30.

Andersen, M.E., M.L. Gargas, R.A. Jones and L.J. Jenkins, Jr. 1979. The use of inhalation techniques to assess the kinetic constants of 1,1-dichloroethylene metabolism. Toxicol. Appl. Pharmacol. 47:395-409.

Andersen, M.E., M.L. Gargas, R.A. Jones and L.J. Jenkins, Jr. 1980. Determination of the kinetic constants for metabolism of inhaled toxicants in vivo using gas uptake measurements. Toxicol. Appl. Pharmacol. 54:100-116.

Andersen, M.E. and L.J. Jenkins, Jr. 1977. Oral toxicity of 1,1-dichloroethylene in the rat: Effects of sex, age and fasting. Environ. Health Perspec. 21:157-163.

Bartsch, H., C. Malaveille, R. Montesano and L. Tomatis. 1975. Tissue-mediated mutagenicity of vinylidene chloride and 2-chlorobutadiene in Salmonella typhimurium. Nature. 255:641-643.

Cerna, M. and H. Kypenova. 1977. Mutagenic activity of chloroethylenes analyzed by screening system tests. Mutat. Res. 46:214.

Coniglio, W., K. Miller and D. MacKeever. 1980. The occurrence of volatile organics in drinking water. Briefing prepared for DAA for Drinking Water. U.S. EPA. 48 pp.

Drevon, C. and Kuroki. 1979. Mutagenicity of vinyl chloride, vinylidene chloride and chloroprene in V79 Chinese hamster cells. Mutat. Res. 67:173-182.

Filser, J.G. and H.M. Bolt. 1979. Pharmacokinetics of halogenated ethylenes in rats. Arch. Toxicol. 42:123-136.

Greim, H., G. Bonse, Z. Radwan, D. Reichert, D. Henschler. 1975. Mutagenicity in vitro and potential carcinogenicity of chlorinated ethylenes as a function of metabolic oxirane formation. Biochem. Pharmacol. 24:2013-2017.

Hathway, D.E. 1977. Comparative mammalian metabolism of vinyl chloride and vinylidene chloride in relation to oncogenic potential. Environ. Health Perspec. 21:55-59.

Henschler, D. 1977. Metabolism and mutagenicity of halogenated olefins - a comparison of structure and activity. Environ. Health Perspec. 21:61-64.

Henschler, D. and G. Bonse. 1977. Metabolic activation of chlorinated ethylenes; Dependence of mutagenic effect on electrophilic reactivity of the metabolically formed epoxides. Arch. Toxicol. 26:62-65.

Humiston, C.G., J.F. Quast, C.E. Wade, J. Ballard, J.E. Beyer and R.W. Lisowe. 1978. Results of a two-year toxicity and oncogenicity study with vinylidene chloride incorporated in the drinking water of rats. Report MCA No.: VCD 1.3-Tox-Orl-Dow. Toxicology Research Laboratory Health and Environmental Research, Dow Chemical U.S.A., Midland, Michigan.

Irish, D.D. 1963. Vinylidene chloride. In: Industrial Hygiene and Toxicology, 2nd ed. F.A. Patty, ed. Vol. II. John Wiley and Sons, Inc., New York. pp. 1305-1309.

Jaeger, J.J., L.G. Shoner and L. Coffman. 1977. 1,1-Dichloroethylene hepatotoxicity: Proposed mechanism of action of distribution and binding of ^{14}C radioactivity following inhalation exposure in rats. Environ. Health Perspec. 21:113-119.

Jenkins, L.J., Jr., M.J. Trabulus and S.D. Murphy. 1972. Biochemical effects of 1,1-dichloroethylene in rats: Comparison with carbon tetrachloride and 1,2-dichloroethylene. Toxicol. Appl. Pharmacol. 23:501-510.

Jones, B.K. and D.E. Hathway. 1978a. The biological fate of vinylidene chloride. Chem. Biol. Interactions. 20:27-41.

Jones, B.K. and D.E. Hathway. 1978b. Tissue-mediated mutagenicity of vinylidene chloride in Salmonella typhimurium TA 1535. Cancer Lett. 5:1-6.

Kramer, C. and J. Mutchler. 1972. The correlation of clinical and environmental measurements for workers exposed to vinyl chloride. Am. Ind. Hyg. Assoc. J. 33: 19-30.

Lee, C.C., J.C. Bhandari, J.M. Winston and W.B. House. 1978. Carcinogenicity of vinyl chloride and vinylidene chloride. J. Toxicol. Environ. Health. 4:15-30.

Liebman, K.C. and E. Ortiz. 1977. Metabolism of halogenated ethylenes. Environ. Health Perspec. 21:91-97.

Maltoni, C. 1977. Recent findings on the carcinogenicity of chlorinated olefins. Environ. Health Perspec. 21:1-5.

Maltoni, C., G. Cotti, L. Morisi and P. Chieco. 1977. Carcinogenicity bioassays of vinylidene chloride. Research plan and early results. Med. Lav. 68:241-262.

McConnell, G., D.M. Ferguson and C.R. Pearson. 1975. Chlorinated hydrocarbons and the environment. Endeavour 34:13-18.

McKenna, M.J., P.G. Watanabe and P.J. Gehring. 1977. Pharmacokinetics of vinylidene chloride in the rat. Environ. Health Perspec. 21:99-105.

McKenna, M.J., J.A. Zempel, E.O. Madrid, and P.J. Gehring. 1978a. The pharmacokinetics of (^{14}C) vinylidene chloride in rats following inhalation exposure. Toxicol. Appl. Pharmacol. 45:599-610.

McKenna, M.J., J.A. Zempel, E.O. Madrid, W.H. Braun and P.J. Gehring. 1978b. Metabolism and pharmacokinetic profile of vinylidene chloride in rats following oral administration. Toxicol. Appl. Pharmacol. 45:821-835.

Murray, F.J., K.D. Nitschke, L.W. Rampy and B.A. Schwetz. 1979. Embryotoxicity and fetotoxicity of inhaled or ingested vinylidene chloride in rats and rabbits. Toxicol. Appl. Pharmacol. 49:189-202.

National Academy of Sciences. 1977. Drinking Water and Health, Volume 1. Safe Drinking Water Committee, Washington, D.C.

National Academy of Sciences. 1980. Toxicity of selected drinking water contaminants. In: Drinking Water and Health, Volume 3. Safe Drinking Water Committee, Washington, D.C.

Ott, M.G., W.A. Fishbeck, J.C. Townsend and E.J. Schneider. 1976. A health study of employees exposed to vinylidene chloride. J. Occup. Med. 18:735-738.

Pearson, C.R. and G. McConnell. 1975. Chlorinated C1 and C2 hydrocarbons in the marine environment. Proc. R. Soc. London B. 189:305-332.

Pellizzari, E.D. 1978. Quantification of chlorinated hydrocarbons in previously collected air samples. U.S. EPA, Research Triangle Park, NC. EPA-450/3-78-112.

Percy, D.H. and A.M. Jonas. 1971. Incidence of spontaneous tumors in CD-1 HaM/ICR mice. J. Natl. Cancer Inst. 46: 1045-1065.

Ponomarkov, V. and I. Tomatis. 1980. Long-term testing of vinylidene chloride and chloropropene for carcinogenicity in rats. Oncology 37:136-141.

Radding, S.B., D.H. Liu, H.L. Johnson and T. Mill. 1977. Review of environmental fate of selected chemicals. U.S. EPA, Contract No. 68-01-2681.

Rampy, L.W., J.F. Quast, C.G. Humiston, M.F. Blamer and B.A. Schwetz. 1977. Interim results of two-year toxicological studies in rats of vinylidene chloride incorporated in the drinking water or administered by repeated inhalation. Environ. Health Perspec. 21:33-43.

Reichert, D., H.W. Werner and D. Henschler. 1978. Role of liver glutathione in 1,1-dichloroethylene metabolism and hepatotoxicity in intact rats and isolated perfused rat liver. Arch. Toxicol. 41:169-178.

Reichert, D., H.W. Werner, M. Metzler and D. Henschler. 1979. Molecular mechanism of 1,1-dichloroethylene toxicity: excreted metabolites reveal different pathways of reactive intermediates. Arch. Toxicol. 42:159-169.

Reichert, D. and H.W. Werner. 1978. Disposition and metabolism of (^{14}C) 1,1-dichloroethylene after single oral administration in rats. (Abstract) Naunyn-Schmiedeberg's Arch. Pharmacol. (Suppl.) R-22.

Shen, P. 1974. Tumors in control mice: Literature tabulation. Toxicol. Appl. Pharmacol. 30:337-359.

Short, R.D., J.L. Minor, J.M. Winston and C.C. Lee. 1977 . A dominant lethal study in male rats after repeated exposures to vinyl chloride or vinylidene chloride. J. Toxicol. Environ. Health 3:965-968.

Siletchnik, L.M. and G.P. Carlson. 1974. Cardiac sensitizing effects of 1,1-dichloroethylene: Enhancement by phenobarbital pretreatment. Arch. Int. Pharmacodyn. 210:359-364.

Simmon, V.F., K. Kauhanen and R.G. Tardiff. 1977. Mutagenic activity of chemicals identified in drinking water. Dev. Toxicol. Environ. Sci. 2:249-258.

Simmon, V.F. and R.G. Tardiff. 1978. The mutagenic activity of halogenated compounds found in chlorinated drinking water. Water Chlorination: Environ. Impact Health Effects Proc. Conf. 2:417-431.

Theiss, A.M. 1977. Mortality study of vinylidene chloride exposed persons in BASF. Proceedings of 5th Medichem. Congr. San Francisco, 1977. Reported by Ponomarkov and Tomatis. 1980. Oncology. 37:136-141.

U.S. EPA. 1980a. Water Quality Criteria Documents; Availability. Federal Register 45(231):79318-79379.

U.S. EPA. 1980b. The determination of halogenated chemical indicators of industrial contamination in water by the purge and trap method, Method 502.1. Environmental Monitoring and Support Laboratory, Cincinnati, Ohio 45268. September.

Van Duuren, B.L., B.M. Goldschmidt, G. Loewengart, A.C. Smith, S. Melchionne, I. Seldman and D. Roth. 1979. Carcinogenicity of halogenated olefinic and aliphatic hydrocarbons in mice. J. Natl. Cancer Inst. 63:1433-1439.

Viola, P.L. and A. Caputo. 1977. Carcinogenicity studies on vinylidene chloride. Environ. Health Perspec. 21:45-47.

DISCLAIMER

This health advisory is a preliminary draft. It has not been released formally by the Office of Drinking Water, U.S. Environmental Protection Agency, and should not at this stage be construed to represent the position of the Office of Drinking Water. It is being circulated for comments on its technical merit.