Advisory Opinion for Trans-1,2-Dichloroethylene

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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

Trans-1,2-dichloroethylene is one of three isomers of dichloroethylene, all clear, colorless liquids with the molecular formula of $C_2H_2Cl_2$ and a molecular weight of 96.95 (Irish, 1963). It is moderately soluble in water (6300 mg/l), but soluble in most organic solvents (Irish, 1963). Trans-1,2-dichloroethylene is volatile, but less so than 1,1-dichloroethylene. The trans-isomer has a vapor pressure of 265 Torr (mm Hg) at 20°C and a boiling point of 47°C. Its vapor density is 3.34, over three times that of air, so that it will settle in low places in a still atmosphere. Its specific gravity is 1.27 at 25°C. Thus, it also would tend to sink in a still body of water.

Horsely (1947) lists a binary azeotrope with water (1.9% water by weight, boiling at 45.3°C) and a ternary azeotrope with water and ethanol (1.1% water, 94.5% trans-1,2-dichloroethylene and 4.4% ethanol by weight. This isomer also forms an azeotrope with ethanol alone.

In air, one (1) ppm is equivalent to 3.97 mg/m^3 and one (1) mg/l is equivalent to 252 ppm (Irish, 1963).

The present threshold limit value (TLV) for the dichloroethylenes in the United States is 200 ppm (794 mg/m^3) (ACGIH, 1977).

1,2-Dichloroethylene, as a mixture of the cis- and trans-isomers, is used as a solvent for such substances as fats, rubber, phenol and camphor and for retarding fermentation (Windholz et al., 1976). It is also used as a low temperature extraction solvent for heat sensitive substances and has been employed as a coolant in refrigeration plants (Hardie, 1964).

Sources of Exposure

Trans-1,2-dichloroethylene has been detected in a number of raw and finished drinking waters, principally from ground water sources. During the National Organics Reconnaissance Survey (NORS), this isomer was detected in Miami drinking water at 1.0 ug/l (U.S. EPA, 1975).

Trans-1,2-dichloroethylene was detected at 0.1 ug/l in one of 105 raw surface waters examined (Coniglio, et al, 1980). None was detected in 103 samples of finished water from these surface water supplies. Of ground water samples collected in 13 cities during one or more of several surveys (NORS, NOMS, or the recent SRI survey conducted for EPA), 15.4% of both raw and finished samples were positive for trans-1,2-dichloroethylene. Mean concentrations were 1.75 and 1.05 ug/l for raw and finished water, respectively (ranges = 0.2-3.3 and 0.2-1.9 ug/l, respectively).

Pellizzari (1978) found slightly higher levels of 1,2-dichloroethylene (cis- and trans- isomers not distinguished) than 1,1-dichloroethylene during his air sampling survey. The greatest amount of 1,1-dichloroethylene measured was 2500 ng/m^3 at Front Royal, Virginia. Maximum concentrations of 1,2-dichloroethylene detected in various areas of the United States varied from a trace (detection limit = 260 ng/m^3) near Magna, Utah, South Charleston, West Virginia, and Grand Canyon, Arizona, to 5263 ng/m^3 at the Kin-Buc Disposal Site in Edison, New Jersey.

No data are available on the presence of either isomer of 1,2-dichloroethylene in foodstuffs.

Pharmacokinetics

Trans-1,2-dichloroethylene, as a neutral, low molecular weight, lipid soluble material, should be systemically absorbed following any route of administration.

No pharmacokinetic data appear to exist which define the absorption rate of trans-1,2-dichloroethylene after oral exposure. However, pharmacokinetic studies based on urinary and biliary excretion data show that administration of a single oral dose of 1,1-dichloroethylene (1.0 or 50 mg/kg) results in rapid and complete absorption in rats and mice (McKenna, et al, 1978b). Rapid absorption and distribution of 1,1-dichloroethylene after intraperitoneal administration to rats also occurs (Jones and Hathway, 1978). For purposes of SNARL development, then, we will assume that trans-1,2-dichloroethylene is absorbed rapidly and completely after oral exposure.

The absorption of gases from the lung is highly dependent upon the blood:gas partition coefficient. Sato and Nakajima (1979) showed that trans-1,2-dichloroethylene has a blood:gas partition coefficient of 5.8 in the rat. While it has a high blood solubility, this chemical in air reaches a steady-state within the whole rat in about 1.5 hours (Filser and Bolt, 1979).

Using relatively new pharmacokinetic procedures, a mixed partition coefficient(S) of 10.9 was determined for the trans-isomer (Andersen et al., 1980). A mixed partition coefficient is defined as the concentration of a chemical in the richly perfused tissues divided by its concentration in the gas phase. This was over 2.5 times higher than that determined for 1,1-dichloroethylene. Thus, a rat exposed to trans-1,2-dichloroethylene would contain more chemical at equilibrium than would a rat exposed to the same concentration of 1,1-dichloroethylene.

Distribution data on trans-1,2-dichloroethylene are not available. However, if this isomer follows the same distribution pattern as that observed for 1,1-dichloroethylene, the highest concentration would be found in the liver and kidney (McKenna, et al, 1978a). These studies were performed in rats, exposed by inhalation to concentrations varying from 10-2000 ppm (40-8000 mg/m^3) for 2 or 6 hours.

Bonse, et al. (1975) observed that metabolism of trans-1,2-dichloroethylene in perfused rat liver produced detectable amounts of dichloroethanol and dichloroacetic acid, possibly indicating the initial formation of dichloroacetaldehyde. Liebman and Ortiz (1977) have postulated the metabolic pathways for trans-1,2-dichloroethylene. One proposed pathway would be conversion to a reactive epoxide intermediate, then to monochloroacetyl chloride and monochloroacetic acid. The authors also suggested that the production of dichloroacetaldehyde may occur by rearrangement of the glycol or the epoxide with migration of a chloride ion. Their attempts to identify a chromatographic peak as dichloroacetaldehyde were inconclusive.

An essential feature of the metabolic pathway is that the compound appears to be metabolized to an epoxide intermediate which is reactive and which may form covalent bonds with tissue macromolecules (Henschler, 1977; Henschler and Bonse, 1977). These authors have synthesized the epoxides for both isomers of 1,2-dichloroethylene; they believe that these epoxides are formed <u>in vivo</u> during the metabolic process. Each was inactive when tested for mutagenic potential in a

modified Ames system (Greim, et al, 1975). However, these results only added support to the hypothesis of Henschler and co-workers that the epoxides with symmetrical chlorines are more stable and less likely to be mutagenic. This does not exclude the possibility that these symmetrical epoxides may still interact with other tissue macromolecules, a process which may result in some form of damage other than mutagenic or carcinogenic.

There are apparently no published studies which test the interaction of the isomers of 1,2-dichloroethylene with DNA; nor are there any which evaluate the interaction of these two isomers with other tissue macromolecules.

No data concerning the excretion of trans-1,2-dichloroethylene are available. The rate of elimination of 1,1-dichloroethylene is relatively rapid, with most of a dose being eliminated in the first 24-72 hours after cessation of exposure. One might assume that trans-1,2-dichloroethylene would be eliminated at a similar rate.

Health Effects

There are no published reports available to us at this time which describe non-fatal accidental, occupational or controlled exposures to trans-1,2-dichloroethylene in humans by any route or for any duration of exposure. Only through secondary references do we know that at high concentrations (> 9500 ppm or 38,000 mg/m^3) central nervous system effects have been observed in humans as reported in the German scientific literature (Villinger, 1907; Albrecht, 1927; Lehmann and Flury, 1938). It would appear that the trans-isomer was about twice as potent as the cis-isomer in depressing the central nervous system.

Data on the acute toxicity of trans-1,2-dichloroethylene in animals are limited. Freundt, et al. (1977) determined the oral LD_{50} in the 200 g rat to be 1300 mg/kg. When given intraperitoneally, the LD_{50} increased six-fold to 7800 mg/kg. The LD_{50} after intraperitoneal administration to the mouse was 4160 mg/kg.

Jenkins, et al. (1972) tested the effects of single 400 or 1500 mg/kg oral doses of each isomer of 1,2-dichloroethylene in corn oil given to adult female Holtzman rats weighing 200-470 g. Liver and plasma enzyme activities were determined. The trans- isomer appeared to exert a less potent effect at the higher dose than did the cis- isomer. The trans- isomer caused changes in the level of only one

enzyme, whereas the cis- isomer caused significant changes in the levels of three enzymes. No difference was observed at the lower dose. Each was less potent than 1,1-dichloroethylene at any dose level.

At 400 mg/kg, trans-1,2-dichloroethylene significantly increased glucose-6-phosphate to a level 11% above control ($P < 0.05$). At 1500 mg/kg, this isomer significantly decreased the level of liver tyrosine transaminase to about 80% of control (Jenkins, et al, 1972) ($P < 0.05$). Liver alkaline phosphatase, plasma alkaline phosphatase and alanine transaminase were not significantly affected at either dose.

Freundt, et al (1977) reported on the effects of trans-1,2-dichloroethylene after inhalation in mature female Wistar rats (180-200 g) at 200 ppm ($\sim$800 mg/m^3) (the currently-established TLV/MAC in a number of countries) and at 1000 and 3000 ppm ($\sim$ 4,000 and 12,000 mg/m^3, respectively). A brief (8-hour) or prolonged exposure (8 hours/day, 5 days/week for 1, 2, 8 or 16 weeks) at 200 ppm ($\sim$800 mg/m^3) yielded an increased incidence of slight to severe fatty degeneration of the hepatic lobule and lipid accumulation by the Kupffer cells. Changes were observed in one of six rats exposed once. Two of six rats showed slight changes after one week of exposure; three of six rats exhibited slight changes during the two week exposure. Damage became more noticeable in a higher percentage of the animals as the length of exposure increased to 8 or 16 weeks. At all exposure levels, the appearance of pulmonary capillary hyperemia and distention ofthe alveolar septum was increased over that observed in controls. At 8 and 16 weeks of exposure, severe pneumonic infiltration was observed in three of the six treated rats; none occurred in the controls.

At higher levels of exposure (1000 (4000 mg/m^3) or 3000 (12,000 mg/m^3) ppm for 8 hours), liver and pulmonary effects similar to those observed at 200 ppm were seen in two of six treated rats. At these higher levels, fibrous swelling and hyperemia of cardiac muscle also occurred in four of six rats treated at each exposure level. This effect persisted until at least 14 hours post-exposure, although the liver effects appeared to be reversing somewhat at that time.

At all doses and durations of exposure, there was no evidence of histopathology involving the kidneys, spleen, brain, striated muscle (quadriceps) or peripheral nerve (sciatic). In addition, there were no signs of central nervous system depression (pre-narcotic signs or narcosis).

A number of biochemical and hematological parameters in rat blood were also tested in the Freundt, et al (1977) study. No changes in serum cholesterol, albumin, uric acid, urea nitrogen, glucose, alkaline phosphatase, SGOT or SGPT were observed after 8 hours' exposure at 200 ppm (800 mg/m^3). Exposure at 1000 ppm (4000 mg/m^3) for 8 hours resulted in significant reductions in serum albumin, urea nitrogen and alkaline phosphatase ($0.01 < P < 0.05$). Eight hour exposures to both 200 and 1000 ppm concentrations caused a significant decrease in the number of leukocytes; 1000 ppm also significantly decreased the number of erythrocytes ($0.01 < P < 0.05$). Clinico-chemical parameters were not studied at the 3000 ppm exposure level.

A later study by Freundt and Macholz (1978) showed that a single 8-hour inhalation exposure to trans-1,2-dichloroethylene at 200 ppm (800 mg/m^3) resulted in significant increases in hexobarbital sleeping time, the zoxazolamine paralysis time and the metabolic formation of 4-aminoantipyrine from aminopyrine in adult female Wistar rats. The effects were less severe after trans-1,2-dichloroethylene than after cis-isomer. In addition, trans-1,2-dichloroethylene competitively inhibited the oxidative N-demethylation of aminopyrine, and the O-methylation of p-nitroanisole in rat liver microsomes. The investigators concluded that the inhibition of hepatic drug metabolism was caused by a competitive, reversible interaction of the chemical with the mixed function oxidase system.

Teratogenicity

No reports on the teratogenic potential of trans-1,2-dichloroethylene are available at the present time.

Mutagenicity

Both cis- and trans-1,2-dichloroethylene were non-mutagenic when assayed with E. coli K12 at similar concentrations used for 1,1-dichloroethylene at which the latter was found to be mutagenic (Greim, et al, 1975). The median concentration of the trans-isomer was 2.3 mM, that of cis-1,2-dichloroethylene 2.9 mM, and that of 1,1-dichloroethylene 2.5 mM.

Trans-1,2-dichloroethylene was found to be non-mutagenic in the host-mediated assay using Salmonella tester strains in mice (Cerna and Kypenova, 1977). In contrast, both cis-1,2- and 1,1-dichloroethylene were mutagenic in this system. In addition, trans-1,2-dichloroethylene did not produce chromosomal aberrations in bone marrow cells following repeated intraperitoneal injections in mice.

Carcinogenicity

No studies have been completed which test the carcinogenic potential of trans-1,2-dichloroethylene. It is currently under consideration for testing by the National Toxicology Program.

SNARL Development

One-day SNARL

Although there are no published animal studies on trans-1,2-dichloroethylene which define a no-effect level, there are two studies which describe a minimal effect level as well as a dose response (Jenkins, et al, 1972; Freundt, et al, 1977). The results of the Freundt et al. study appear to be the best to use since more parameters were measured, a significant number of which showed no change from control after a single 8-hour exposure to 200 ppm. Also, this study better describes the dose-response relationship over several durations and concentrations.

The study by Freundt, et al. (1977) identified a minimal effect level of 200 ppm inhaled over a single 8-hour exposure period. This exposure resulted in slight liver effects in one of six animals, as observed histologically. In addition, no changes were observed in any of several serum biochemical parameters.

A one-day SNARL developed from the Freundt, et al study would be derived thusly:

Step 1:

$$\frac{(200 \times 3.97)\ mg/m^3 \times 8 \times 1 \times 0.3}{70} = 27.2\ mg/kg\ (total\ dose)$$

Where: (200 x 3.97) mg/m^3 = dose converted from ppm to mg/m^3

8 = duration of exposure in hours

1 = ratio of lung/body weight ratios between adult man and rat, as per Olsen and Gehring (1976)

0.3 = assumed ratio of dose taken up/dose exposed to

70 = weight in kg of adult exposed to 200 ppm dose

Step 2:

$$\frac{27.2\ \text{mg/kg} \times 10\ \text{kg}}{100 \times 1\ 1} = 2.72\ \text{mg/l}$$

Where: 27.4 = total dose in mg/kg

10 kg = weight of child

100 = safety factor

1 1 = volume of drinking water imbibed/day by 10 kg child

Ten-day SNARL

A ten-day SNARL can be derived from the one-day SNARL which should adequately protect the sensitive individual from adverse health effects over that duration of exposure.

A ten-day SNARL would be derived simply by dividing the one-day SNARL by 10 to get 0.27 mg/l.

Analysis

Cis-1,2-dichloroethylene and trans-1,2-dichloroethylene can be analyzed by the purge-and-trap gas chromatographic procedure used for the determination of volatile organohalides in drinking waters (U.S. EPA, 1980b; Bellar and Lichtenberg, 1979). In this procedure, volatile components are extracted by an inert gas which is bubbled through the aqueous sample. The compounds are swept from the purging device into a short sorbent trap. 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 recommended primary columns for organohalide analysis do not adequately resolve the cis- and trans-1,2-dichloroethylene isomers. Therefore, it is suggested that the column recommended for confirmatory analysis be used when these two chemicals are being determined. The recommended chromatographic conditions for the analysis are given below:

Column: Six feet long x 0.1 inch ID stainless steel or glass.

Packing: n - octane on Porisil - C (100/120 mesh).

Temperature: 50°C isothermal for 3 minutes, then program at 6°/minute to 170°C.

Carrier gas: Helium at 40 ml/minute.

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

Sample volume: 5 ml.

The retention time for the cis- isomer is 726 seconds and for the trans- isomer is 563 seconds under the conditions specified above. Confirmatory analysis of each isomer by a second column or by GC-MS techniques is recommended. Although the MS itself will not distinguish between cis- and trans- dichloroethylene, the difference in GC retention times will allow for proper identification.

The purge-and-trap procedure is applicable to the measurement of most organohalides over a concentration range of 0.1 to 1500 ug/l when the Hall model electrolytic conductivity detector is used. Other halogen-specific detectors are generally limited to measurements of 1.0 ug/l or above.

Treatment

Very few data are available concerning the removal of trans-1,2-dichloroethylene from drinking water. Available data suggest that both aeration and adsorption by granular activated carbon will be somewhat effective in reducing the levels of this chemical.

Dobbs and Cohen (1980) developed adsorption isotherms for a number of organic chemicals, including trans-1,2-dichloroethylene. Their data show that, at an equilibrium concentration of 100 ug/l, the activated carbon had an adsorptive capacity of 0.9 mg of trans-1,2-dichloroethylene per gram of carbon. Their data further show that this chemical should be adsorbed with greater efficiency than methylene chloride, but with far less efficiency than either tetrachloroethylene or chlorobenzene.

Theoretical considerations indicate that aeration may have some effectiveness in reducing the levels of trans-1,2-dichloroethylene. Love and Eilers (1981) found that the Henry's Law constant for a substance is a good predictive tool for forecasting the relative amenability of that substance to aeration. Love (1981) further reported the

Henry's Law constant for trans-1,2-dichloroethylene as 0.27. This suggests that this chemical will be somewhat amenable to air stripping, being somewhat more easily removed than chlorobenzene (a chemical known to be relatively poorly removed by aeration with a Henry's Law constant of 0.19), but much less easily removed than tetrachloroethylene (a chemical known to be amenable to aeration with a Henry's Law constant of 1.2).

In summary, the levels of trans-1,2-dichloroethylene in drinking water can be reduced by either aeration or adsorption onto activated carbon. However, no full-scale field data are currently available to support this conclusion. All approaches should be considered since the preferred approach will undoubtedly be determined on a case-by-case basis. In addition, once a possible long-term treatment technique has been identified, pilot-scale studies should be conducted, not only to verify initial conclusions, but also to estimate technical and economic considerations which such a system will entail.

Conclusions and Recommendations

One-day and ten-day SNARLs of 2.7 mg/l and 0.27 mg/l, respectively, have been developed for trans-1,2-dichloroethylene. At this time, no satisfactory dose-response no-effect level data exist from which a longer-term SNARL can be derived. In addition, it would be preferable to have dose-response, no-effect data for the one-day and ten-day SNARLs as well. A grant has been awarded under the EPA Competitive Grants program to study the toxicity of all three dichloroethylenes and compare the percentage absorption via ingestion and inhalation. Data from this study, which will include no-effect, dose-response data, should be available in 1982. At that time, the data will be reviewed and, if found suitable, will form the basis for the revision of the existent SNARLs. If the data are found lacking, further research will be requested.

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DISCLAIMER

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