Advisory Opinion for Cis-I,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

Cis-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 (3.5 g/l at 25°C), but soluble in most organic solvents. The cis-isomer has a vapor pressure of 208 Torr (mm Hg) at 25°C and a boiling point of 60°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 (3.35% water by weight, boiling at 55.3°C) and a ternary azeotrope with water and ethanol (2.85% water, 90.5% cis-1,2-dichloroethylene and 6.65% ethanol by weight, boiling at 53.8° C). This isomer also forms an azeotrope with ethanol or methanol 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 existing 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 also is 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

Cis-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 16.0 ug/l (U.S. EPA, 1975). Concentrations of 0.1 ug/l were observed in samples from Cincinnati and Philadelphia; none was detected in drinking waters from the other cities.

Cis-1,2-dichloroethylene was detected at an average concentration of 0.17 ug/l in three of 105 raw surface waters examined (2.9%) in a number of surveys (Coniglio, et al, 1980). An average of 0.66 ug/l was detected in five of 103 samples (4.9%) of finished water from these surface water supplies. Of 13 ground water samples collected in 13 cities during one or more of several surveys (NORS, NOMS, or the recent SRI survey conducted for EPA), four (30.8%) of the samples were positive for cis-1,2-dichloroethylene. Three samples contained less than 1 ug/l; one sample contained 37 ug/l.

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 maximum amount of 1,1-dichloroethylene measured was 2500 ng/m^3 at Front Royal, Virginia. Maximum concentrations of 1,2-dichloroethylenes detected in various areas of the United States varied from a trace (detection limit = 260 ng/m^3 or higher) 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 (an industrial site near an urban area).

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

Pharmacokinetics

Cis-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 cis-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 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 cis-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 cis-1,2-dichloroethylene has a blood:gas partition coefficient of 9.2 in the rat. While it has a high blood solubility, this chemical in air reaches a steady-state within the whole rat in about 2 hours (Filser and Bolt, 1979).

Distribution data on cis-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 ($\sim$40-8000 mg/m^3) for 2 or 6 hours.

Bonse, et al. (1975) observed that metabolism of cis-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 cis-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 chemically the epoxides for both isomers of 1,2-dichloroethylene; they believe that these epoxides are formed in vivo 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 tissue macromolecules other than DNA, a process which may result in some form of damage other than mutagenesis or carcinogenesis.

There apparently are 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 cis-1,2-dichloroethylene are available. The rate of elimination of 1,1-dichloroethylene is relatively rapid, with most of a dose being excreted in the first 24-72 hours after cessation of exposure. One might assume that cis-1,2-dichloroethylene would be eliminated at a similar rate.

Health Effects

There are no published studies available to us at this time which describe accidental, occupational or controlled exposures to cis-1,2-dichloroethylene in humans by any route or for any duration of exposure. At high concentrations (4000 ppm) central nervous system effects have been described from unpublished data (Irish, 1963). This concentration was estimated to be sufficient to rapidly produce a state resembling drunkenness and was judged likely to result in unconsciousness if exposure were continued.

Data on the toxicity of cis-1,2-dichloroethylene in animals are severely limited. No LD_{50} values for the cis- isomer alone have been published. The lowest lethal oral dose for the mixture in the human (70 kg) is estimated to be 500 mg/kg (McBirney, 1954).

Jenkins, et al. (1972) tested the effects of single 400 or 1500 mg/kg oral doses of each isomer of dichloroethylene in corn oil given to adult female Holtzman rats weighing 200-470 g. Liver and plasma enzyme activities were determined 20 hours after dosing. The cis- isomer appeared to exert a more potent effect than did the trans- isomer at the higher dose. No significant difference between the two isomers was seen at the lower dose. Each was less potent than 1,1-dichloroethylene. At 400 mg/kg, cis-1,2-dichloroethylene significantly increased liver alkaline phosphatase to a level 10% above control ($P < 0.05$). At 1500 mg/kg, this isomer significantly decreased the level of liver glucose-6-phosphatase to about 88% of control ($P < 0.05$). Liver tyrosine transaminase was decreased to 80% of control, and plasma alanine transaminase to 14% of control ($P < 0.05$). Plasma alkaline phosphatase was not altered.

In an animal study reporting on the central nervous system effect of the cis- isomer, the chemical did not anesthetize rats in 4 hours at 8000 ppm (~32,000 mg/m^3), but at 16,000 ppm (~64,000 mg/m^3), they were anesthetized in 8 minutes and killed within 4 hours (Irish, 1963).

Freundt and Macholz (1978) showed that single 8-hour inhalation exposures to cis-1,2-dichloroethylene at 200, 600 or 1000 ppm (~800, 2400 or 4000 mg/m^3, respectively) concentrations resulted in a dose-dependent and significant increase in hexobarbital sleeping time, zoxazolamine paralysis time and the metabolic formation of 4-aminoantipyrine (AAP) from aminopyrine in adult female Wistar rats. The effects induced by the cis- isomer were more severe than those induced by the trans- isomer. The authors attributed this difference to the higher uptake of the cis- isomer by liver tissue. The investigators concluded that the inhibition of hepatic drug metabolism, as reflected in the change in AAP levels, was caused by a competitive, reversible interaction of the chemical with the mixed function oxidase system.

Teratogenicity

No reports on the teratogenic potential of cis-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 medium concentration of the cis-isomer was 2.9 mM, that of t-1,2-DCE was 2.3 mM, and that of 1,1-DCE was 2.5 mM.

Both 1,1-dichloroethylene and cis-1,2-dichloroethylene were mutagenic in the host-mediated assay using Salmonella tester strains in mice (Gerna and Kypenova, 1977). Of the three isomeric dichloroethylenes, only cis-1,2-dichloroethylene produced chromosomal aberrations in bone marrow cells of mice following repeated intraperitoneal injections (daily injections at 1/2 LD_{50} for five or ten days).

Carcinogenicity

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

SNARL Development

One-day SNARL

There are few animal studies available which provide dose-response data on the toxicity of cis-1,2-dichloroethylene (Irish, 1963; Jenkins et al, 1972; Freundt and Macholz, 1978). Only the study by Jenkins and co-workers provides information on what might be identified as a minimal effect level. In measuring levels of three liver enzymes and two plasma enzymes, indicators of liver function, these authors showed that a single 400 mg/kg oral dose to the rat produced a significant change only in liver alkaline phosphatase, while the other enzyme levels were not significantly affected. This slight degree of liver involvement is felt not to be life-threatening; evidence developed for 1,1-dichloroethylene points to the fact that this degree of liver effect appears to be quite rapidly and completely reversible once exposure has ceased.

The Jenkins et al. results may be used to develop a one-day SNARL. It would be derived thusly:

$$\frac{400 \text{ mg/kg} \times 10 \text{ kg} \times 100\%}{1000 \times 1} = 4 \text{ mg/l}$$

Where: 400 mg/kg = minimal effect dose

10 kg = weight of protected individual (child)

100% = percentage of dose absorbed

1000 = safety factor

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

Ten-day SNARL

A ten-day SNARL can be derived from the one-day SNARL which will adequately protect the sensitive individual from adverse health effects over that duration of exposure. As stated above, any slight alteration in liver function is felt to be quickly and readily reversible after cessation of exposure.

A ten-day SNARL would be derived simply by dividing the one-day SNARL by 10 to get 0.4 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-1,2-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

The best options for community systems to remove cis-1,2-dichloroethylene appear to be granular activated carbon (GAC), diffused or packed tower aeration, and synthetic resins. The preferred treatment needs to be evaluated on a case-by-case basis. Pilot scale testing is essential to estimate cost effectiveness since the quality of water may greatly affect performance for each of the treatments. Pilot scale data indicate that this compound is not as easily removed by aeration (GAC or synthetic resins) as is trichloroethylene or tetrachloroethylene.

Counter current diffused aeration, in a 30" diameter 10' deep column, operating with a 10 minute contact time and an air to water ratio of 30:1, removed 85% of cis-1,2-dichloroethylene (present in groundwater at concentrations of 18-118 ug/l). At an air to water ratio of 5:1, and the same operating conditions, 58% cis-1,2-dichloroethylene was removed from the same water. Counter current diffused aeration with 1.5 in. diameter columns, a 10 minute contact time and an air to water ratio of 4:1 removed 80% of the chemical in a different groundwater sample containing 0.5 ug/l of the chemical. The performance of diffused aeration will be affected by the design of the diffusers and matrix effects (e.g., TOC and dissolved solids content). The extent to which each of these effects performance has not yet been evaluated.

Packed column aeration may be a more economical treatment alternative than diffused aeration. However, no empirical data are yet available to compare costs.

GAC with a bed depth of 2.5 ft and an Empty Bed Contact Time (EBCT) of 6 minutes was used to treat a groundwater containing 25 ug/l cis-1,2-dichloroethylene and 10 mg/l TOC. Breakthrough of the chemical (when concentrations in the effluent exceeded .1 ug/l) occurred after 18 days of service or 4,300 bed volumes of throughput. The loading of cis-1,2-dichloroethylene on the carbon at breakthrough was 0.3 mg/gm. Amberlite XE-340, a synthetic resin, with the same bed depth and EBCT, did not have breakthrough until after 60 days of service or 14,400 bed volumes of throughput; the loading of the chemical on the resin at breakthrough was 0.7 mg/gm. The extent that service life of the adsorbent will be affected by other organic substances competing for adsorption sites is not yet known.

In emergency situations, or where funding is not available for community treatment, boiling can be effectively used to reduce cis-1,2-dichloroethylene concentrations to acceptable levels. Ten minutes of boiling at a water depth of 8 cm. should reduce concentrations of 150 ug/l to 5 ug/l or less.

Conclusions and Recommendations

One-day and ten-day SNARLs of 4 mg/l and 0.4 mg/l, respectively, have been developed for cis-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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