Advisory Opinion for 1,2-Dichloroethane
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

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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

Dichloroethane (1,2-) (1,2-DCE; ethylene dichloride) is a colorless liquid with a sweet taste and chloroform-like odor. Its solubility in water is 9 g/liter at 20°C, and it is completely miscible with ethanol, chloroform, ethyl ether, and octanol (Irish, 1963). 1,2-Dichloroethane has a molecular weight of 98.97, a specific gravity of 1.24 g/ml at 20°C, and a boiling point of 83.5°C. It is a moderately volatile compound with a vapor pressure of 87 torr at 25°C. A concentration of 1 part per million in air is equivalent to 4.05 mg/m^3. One milligram per liter of air is equivalent to 247 parts per million.

The present occupational standard for 1,2-dichloroethane is 50 ppm (200 mg/m^3) for an 8-hours/day exposure (U.S. DOL, 1972; ACGIH, 1977).

Sources of Exposure

Municipal water supplies were tested for 1,2-DCE as well as other organic compounds in two EPA surveys, the National Organics Reconnaissance Survey (NORS) in 1975 and the National Organic Monitoring Survey (NOMS) in 1976-77. NORS analyzed both raw and finished water samples by gas chromatography in 80 U.S. cities. At a detection limit of 0.1 ug/liter, 1,2-DCE was detected in 14% of the raw samples and 32.5% of the finished samples. The highest concentration reported in finished water was 6 ug/liter. However, of the 26 finished water samples in which 1,2-DCE was detected, 24 had concentrations of less than 1 ug/liter (Symons, et al. 1975).

The NOMS examined 113 community water supplies in three sampling and analysis phases (Mello, 1978). Dichloroethane was detected at concentrations of 0.9-4.3 ug/l in 10 of the 435 total samples gathered in all three phases of the survey.

1,2-DCE has been reported in 53 of 204 samples taken from surface waters near industrialized areas (Ewing, et al., 1977). The concentrations of 1,2-DCE ranged from 1-15 ppb, except for one sample from the Delaware River which was reported at 90 ppb.

The presence of 1,2-DCE in the environment appears to be caused by anthropogenic activities; no natural source of this chemical has been reported. Environmental releases of 1,2-DCE result primarily from the direct production and use of this chemical, and its presence in gasoline. Releases have also been suggested to occur from processes such as chlorination of organics in raw water during treatment, incineration of chlorinated products, or production of 1,2-DCE as a by-product of other chemical processes. Although these processes may release 1,2-DCE to land, water, and air, much of the land and water releases will vaporize into the atmosphere.

The concentration of 1,2-DCE in air distant from point sources has generally been below the detection limit of currently used analytical methods, about 0.1 ppb (0.5 ug/m^3). However, ambient levels near production and user facilities ranged as high as 200-500 ug/m^3 in a 10-day study at Lake Charles, Louisiana (PEDCo, 1979).

The potential exists for small quantities of 1,2-DCE to remain in agricultural products after fumigation. Lindgren et al. (1968) reported that wheat flour retained about 1,000 ppm 1,2-DCE one hour after termination of fumigation. Seven days after treatment, the levels had dropped to 22 ppm for surface samples and 46 ppm for center samples. No dichloroethane was found in bread baked from flour treated with 1,2-DCE seven days before use. In another study (Munsey et al., 1957), 1,2-DCE was added to flour at a concentration of 40 ppm. Bread prepared from the treated flour contained less than 2 ppm residual 1,2-DCE. However, quick-cooling rolled oats treated with 61 ppm 1,2-DCE retained 32-33 ppm of the substance through the cooking process (Munsey et al., 1957). In a third study (Storey et al., 1972), soybeans, fumigated for three days with a mixture of 75% 1,2-DCE and 25% carbon tetrachloride, aerated and stored overnight, were reported to contain 51 ppm 1,2-DCE residual. The dosage equivalent was 6 gal/1000 bushels of soybeans.

Human milk was reported to contain 1,2-DCE when nursing mothers were exposed to the chemical by inhalation (Urusova, 1953). Women, number not stated, were exposed to 63 mg/m^3 of 1,2-DCE for 1 hour. Milk samples taken 0.5-2.5 hours after exposure showed concentrations of 1,2-DCE of 5.4-6.4 mg/liter. In some cases, 1,2-DCE was detected at levels of 2-6 mg/liter 18 hours after exposure.

Metabolism/Pharmacokinetics

1,2-Dichloroethane is absorbed by humans and laboratory animals through the lungs (Spencer, et al., 1951, Urusova, 1953) gastrointestinal tract (Alumot, et al., 1976) and skin (Urusova, 1953).

The proportion of a dose of 1,2-DCE absorbed through the skin is unknown. The nature of its chemical and physical properties would suggest that significant amounts of this substance would be absorbed when ingested; in fact, Reitz, et al. (1980) accounted for 96% of the radioactivity of a single oral dose of labeled 1,2-DCE in the excreta or exhaled air. Therefore, in the development of a SNARL for 1,2-dichloroethane, it will be assumed that 100% of any dose ingested will be absorbed by the exposed individual.

Action on halogenated ethanes by the cytochrome P-450 dependent mixed function oxidases (MFOs) would be expected to yield 2-haloacetaldehyde initially (Hill, et al., 1978). Thus, 2-chloroacetaldehyde could result from the metabolism of 1,2-dichloroethane. Dehydration to 2-chloroacetic acid may occur (Yllner, 1971) or further reaction with glutathione may form s-carboxymethylglutathione, which may be further metabolized to s-carboxymethylcysteine and thiodiacetic acid (Yllner, 1971; Anders and Livesey, 1980). It is suggested that at least two reactive metabolites are formed during the metabolism of 1,2-DCE.

The distribution of the chemical in various tissues was measured after a single oral dose of 150 mg/kg of 1,2-DCE in corn oil given to rats (Reitz, et al., 1980). The liver and kidneys were reported to have the highest concentration 48 hours after dosing, followed by the forestomach, stomach, and spleen. Organ distribution of 1,2-DCE followed the same pattern when rats inhaled a dose of 150 ppm (608 mg/m^3) for six hours. It would seem, then, that the target organs for dichloroethane do not vary with different routes of exposure. However, it can be shown that the amount of 1,2-DCE reaching any one target organ may differ as a function of dose and route of exposure. Maximum blood levels of 8-9 ug/ml were measured during the six-hour inhalation exposure at 150 ppm, the steady-state peak being reached in 2-3 hours (Reitz et al., 1980). On the other hand, Spreafico et al. (1980) showed that blood levels of nearly 70 ug/ml were attained within 45 minutes after ingestion of 150 mg/kg DCE by rats. Maximum blood levels were reached more quickly at lower doses of 25 or 50 mg/kg, as could be expected. Also, the peak reached was not as high as after ingesting 150 mg/kg (13 ug/ml after 25 mg/kg; 32 ug/ml after 50 mg/kg). Similar proportional increases occur in tissue levels as measured in adipose tissue, liver and lung after each of the three doses.

1,2-Dichloroethane has been shown to be metabolized rapidly and excreted. Mice injected intraperitoneally with 0.05-0.17 g/kg 1,2-DCE were reported to exhale 10-42% of the initial dose unchanged within 24 hours (Yllner, 1971). By 24 hours after dosing, 93-96% of labeled 1,2-DCE was excreted either unchanged

or as metabolites. Reitz, et al. (1980) reported that 96% of the radioactivity from a single 150 mg/kg oral or a 150 ppm six hour inhalation exposure of rats to labeled 1,2-DCE was eliminated from the body within 48 hours. The results of these studies indicate that it is unlikely that substantial bioaccumulation of 1,2-DCE occurs after a single exposure.

Health Effects

The toxic effects of 1,2-DCE from both acute and chronic exposure include liver and kidney dysfunction accompanied by circulatory damage. These effects have been documented in humans and animals (Plaa and Larson, 1965; Yodaiken and Babcock, 1973). The compound is also reported to cause conjunctival irritation in humans exposed by inhalation (Irish, 1963) and corneal clouding in dogs exposed by subcutaneous injection (Kuwabara, et al., 1968). Exposure to 1,2-DCE is also reported to cause headache, dizziness and nausea and vomiting in humans (Irish, 1963). If exposure is continued, death may result from respiratory or circulatory failure (Yodaiken and Babcock, 1973).

Short-term Exposure

Human ingestion of 1,2-DCE has been documented in various case reports (Yodaiken and Babcock, 1973; Hueper and Smith, 1935; Lockhead and Close, 1951). The chemical has been ingested under different circumstances (e.g., recreational use, suicide attempts) by persons of diverse occupations and ages. Adverse effects also have been reported to result from occupational exposure by inhalation or dermal absorption.

Yodaiken and Babcock (1973) reported on the lethal exposure to 1,2-DCE of a 14-year old male who drank 15 ml (340 mg/kg) of the liquid to "get high". Despite supportive treatment, the patient died on the sixth day after ingestion of the chemical. During treatment, serum enzyme levels increased, blood glucose decreased, serum calcium levels increased, and blood clotting time increased. Autopsy findings included extensive necrosis of the liver and epithelial cell damage in the entire corticotubular structure of the kidneys accompanied by degeneration in the proximal tubules.

Non-fatal cases of poisoning by ingestion have been reported in the literature, but all as described in NIOSH, 1976, are in foreign language journals and are unavailable for evaluation at this time (Ienistea and Mezincesco, 1943; Bloch, 1946; Stuhlert, 1947; plus others).

The effects of acute oral exposure to 1,2-DCE in rats were reported by Johnson (1965). Four female rats, strain unspecified, were dosed by gavage with 1,2-DCE (400 mg/kg) dissolved in

arachis oil, glycerol formal or normal saline and killed 2 hours after dosing. The concentration of glutathione in liver decreased to 53, 81, 40, and 34% of control levels in the four animals. The dose of 400 mg/kg was roughly one-half the LD_{50}.

Longer-term Exposure

Alumot, et al. (1976) reported the effects of subchronic and chronic exposure of rats to feed fumigated with 1,2-DCE. In the subchronic experiment, groups of six rats were fed a diet containing 300 or 600 mg of 1,2-DCE/kg of feed for 5 weeks or 1,600 mg of 1,2-DCE/kg of feed for 7 weeks. The fumigated feed was stored in airtight containers; 1,2-DCE loss during the storage period of 7-10 days was determined to be 5%. The animals were allowed access to the feed only at set time intervals so that loss of 1,2-DCE by volatilization would be minimal. However, the authors did not calculate a conversion of dosages from mg/kg of feed to mg/kg of body weight using average body weight, amount of food consumed, and the volatilization of the substance from the feed. Therefore, one can not establish the actual dosage of 1,2-DCE administered. At the end of the experiment the animals were killed. The animals fed the highest dosage, 1600 mg/kg of feed, showed a 15% increase in liver fat. No effects were seen at the two lower doses.

In the chronic exposure (Alumot, et al., 1976), groups of 36 rats (18 male and 18 female littermates) were fed mash containing 1,2-DCE at 0, 250, and 500 mg/kg of feed. After 2 years, the surviving animals were killed. Serum values for glucose, protein, albumin, urea, uric acid, cholesterol, glutamic-oxaloacetic transaminase, and glutamic-pyruvic transaminase in the treated animals did not differ from those in controls. No fatty livers were detected in the treated animals. Thus, in the tests used, the authors found no biochemical or histopathological abnormalities attributable to 1,2-DCE exposure. However, interpretation of the results was complicated by the widespread incidence of chronic respiratory disease in the animals and low survival rates (12 and 17%, respectively, for dosed males, 56 and 67%, respectively, for dosed females). Although the authors report no adverse effects at either dose, this conclusion can be questioned because of the poor survival and chronic infection of the experimental animals.

Additionally, lack of detailed data (as discussed previously) prevented conversion to mg/kg of body weight dosage units. Thus a dose-reponse relationship is difficult to establish. The authors propose an acceptable daily intake for 1,2-DCE of 25 mg/kg, but offer no detailed rationale for this amount.

Carcinogenicity

1,2-DCE has been shown to be carcinogenic in rats and mice when administered orally (NCI, 1978) but non-carcinogenic when administered by inhalation (Maltoni, et al., 1980).

1,2-DCE at doses of 47 or 95 mg/kg/day was administered in corn oil by gavage five times weekly to 50 Osborne-Mendel rats of each sex for 78 weeks followed by an observation period of 23 weeks for males and 15 weeks for females. A statistically significant increase in the incidence of squamous cell carcinoma of the forestomach and hemangiosarcoma of the circulatory system was observed in male but not female rats ($P < 0.04$). The female rats had a significantly increased incidence of adenocarcinoma of the mammary glands ($P < 0.002$) (NCI, 1978).

In a complementary gavage study, 50 hybrid B6C3F1 mice of each sex were dosed five times weekly for 78 weeks with 195 or 97 mg/kg/day in corn oil for male mice and 299 or 149 mg/kg/day in corn oil for female mice. The mice were observed for 12-13 weeks following cessation of the treatment. A statistically significant increase in the incidence of mammary adenocarcinoma ($P < .04$) and endometrial stromal polyps or sarcomas ($P < .016$) was seen in the female mice; the incidence of alveolar/bronchiolar adenomas was increased in both sexes ($P < 0.028$) (NCI, 1978).

In an inhalation study, Swiss mice or Sprague-Dawley rats of each sex were exposed to 607.5, 202.5, 40.5, or 20.3 mg/m^3 of 1,2-DCE for 7 hours daily, 5 days per week for 78 weeks. At the end of the exposure period, the animals were allowed to live out their natural lives. In no case did the incidence of a particular type of tumor appear to be dose-related (Maltoni, et al., 1980). The authors concluded that 1,2-DCE was not carcinogenic under the conditions of their experiment.

Mutagenicity

Brem et al. (1974) found 1,2-DCE to be weakly mutagenic in Salmonella typhimurium (Strain TA 1530, TA 1535 and TA 1538) and in DNA polymerase deficient Escherichia coli. A more recent study (Rannug and Beije, 1979) extends these results. 1,2-DCE was added to the perfusion fluid for isolated, perfused rat liver. Bile samples taken 15-30 minutes after addition of the chemical to the perfusion system were highly mutagenic when incubated with S. typhimurium strains TA1530 and TA1535. Samples of the perfusion fluid containing 1,2-DCE were only weakly mutagenic. The authors concluded that the highly mutagenic substance excreted in the bile was a glutathione conjugate of 1,2-DCE.

As a result of the glutathione dependent metabolic process, the episulfonium ion would be formed which would be highly reactive and could play a role in the compound's mutagenic activity (Rannug, et al., 1978; Rannug and Beije, 1979; Rannug, 1980). In addition, 2-chloroacetaldehyde, when formed during oxidative metabolism by the P-450 MFOs, would also be reactive. It has been suggested that this substance is involved in the covalent binding to tissue macromolecules (Hill, et al., 1978). Furthermore, this compound has been shown to be mutagenic (McCann, et al., 1975).

In addition, 1,2-DCE has been shown to induce sex-linked recessive lethals in Drosophila melanogaster larve and adults (Rapoport, 1960; Shakarnis, 1969; 1970).

Teratogenicity

Alumot et al. (1976) found no teratogenic or reproductive effects, as measured by the percentage of female bearing litters, litter size, mortality of young, or body weight of young, in rats fed diets containing 250 or 500 ppm 1,2-DCE for two years. As mentioned earlier, incomplete documentation of the study prevents one from stating with certainty exactly how much chemical the animals actually ingested.

SNARL Development

The toxicity of 1,2-DCE appears to be manifested principally as liver and kidney dysfunction, and, especially after acute exposure, organ hemorrhaging apparently due to interference with the blood clotting mechanism. Carcinogenicity bioassay results are equivocal, the oral studies suggesting that the substance is an animal carcinogen, the inhalation studies having negative results.

No satisfactory dose response, no-effect level data are available from which a SNARL can be written for any duration of exposure. None of the accounts of occupational exposure include adequate information concerning dose or duration of exposure. Most of the non-occupational ingestion case reports describe fatal consequences or are in foreign language journals that are inaccessible at this time. The Subcommittee on Toxicology of the Safe Drinking Water Committee (NAS, 1980) declined to recommend a 24-hour, 7-day SNARL, concluding that there is insufficient information available to do so.

As mentioned above, the subchronic and chronic ingestion studies of Alumot et al. (1976) in rats are seriously flawed. The authors did not monitor volatilization of the compound from the feed as it was being presented to the experimental animals, only

during the storage period; nor, is the amount of feed consumed by the animals documented. Therefore, no accurate determination of the amount of compound ingested per unit of body weight of the animals can be made. For these reasons, the Alumot study cannot be used as the basis for the setting of a longer-term SNARL. The National Academy of Sciences (1980) reached much the same conclusion, stating that "since the number of recent reports suggest that DCE may be a mutagen and/or a carcinogen," further studies must be carried out before a longer-term SNARL can be derived.

The National Academy of Sciences (NAS) and EPA's Carcinogen Assessment Group (CAG) have calculated projected incremental excess cancer risks associated with the consumption of a specific chemical via drinking water alone by mathematical extrapolation from high dose animal studies. Using the risk estimates generated by the NAS (1980) where the multi-stage model was utilized, a range of 1,2-DCE concentrations can be computed that would normally increase the risk of one excess cancer per million (10^6), per hundred thousand (10^5) or per ten thousand (10^4) people over a 70-year lifetime, assuming daily consumption at the stated exposure level. The range of concentrations estimated to represent the range of risks is shown in the table below.

Drinking Water Concentrations and Associated Cancer Risks

Excess Lifetime Cancer Risk	Range of Concentrations (ug/l*)		
	CAG (95% CL**)	NAS (95% CL)	NAS (point estimate)
10^{-4}	95	70	140
10^{-5}	9.5	7.0	14
10^{-6}	0.95	0.7	1.4

* Assumes the consumption of two liters of water per day.
** Confidence Limit

A series of short-term and longer-term experiments with 1,2-DCE on several end-points of toxicity have been carried by a group of investigators over the past several years. Results from these experiments should be available in July 1981.

Experiments will soon be underway to investigate the effects of 1,2-DCE on clotting mechanisms. This study should provide no-effect levels for this particular end-point of toxicity. Aspects of cardiovascular toxicity may be addressed in the future through a request for initiation of EPA-sponsored research.

No SNARLs will be developed at this time. The Health Effects Branch concludes that there are no satisfactory data available at

this time for the derivation and subsequent scientific support of a 1-day, 10-day or longer-term SNARL. This decision will be reconsidered when, and if, the long-awaited experimental data become available, as promised, in July 1981.

Analysis

1,2-Dichloroethane can be analyzed by the purge and trap method used for the determination of volatile organohalides in drinking waters (Bellar and Lichtenberg, 1979; U.S. EPA, 1980b). The 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 and separated under programmed conditions.

The recommended primary columns for organohalide analysis do not adequately resolve 1,2-DCE and chloroform when the concentration difference between these compounds is larger than a factor of ten. The column recommended for confirmatory analysis provides unique separation of 1,2-DCE from other organohalides, including chloroform, under these conditions. Therefore, it is suggested that this column be used for the analysis of 1,2-DCE in finished drinking waters. The recommended parameters for the analysis of this compound are detailed 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.

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

Sample volume: 5 ml

The retention time for 1,2-DCE under the conditions specified above is 921 seconds.

The purge and trap procedure is applicable to the measurement of most organohalides over the 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. Confirmatory analysis by GC-MS or by a different analytical column is highly recommended.

Treatment

The information available on the removal of 1,2-DCE from drinking water is limited (U.S. EPA, 1980c). 1,2-DCE is not easily removed from water by aeration: for example, an air-to-water ratio of 4:1 removed only 40 percent of the 1,2-DCE from contaminated well water. Absorption of 1,2-DCE on filters containing granular activated carbon and resins has been shown to be a more effective means of its removal from drinking water. Filtration through Witcarb R 950 granular activated carbon resulted in an effluent concentration of 1,2-DCE below 0.10 ug/liter for 31 weeks as compared to an average influent concentration of 1.4 ug/liter. Conventional coagulation and filtration were not effective in removing 1,2-DCE at average concentrations of 8 ug/liter from drinking water, but the use of a full scale adsorber containing 76 cm of Westvaco WV-G granular activated carbon was successful in reducing the 1,2-DCE concentration to less than 0.1 ug/liter.

Conclusions and Recommendations

As stated above in the SNARL Development section, no satisfactory no-effect level data are available from which to derive SNARLs for 1,2-DCE at any duration of exposure. Therefore, the Health Effects Branch has concluded that, at this time, no SNARL for any duration will be developed.

Research is needed to identify no-effect levels for the most sensitive end-points of toxicity, so that SNARLs can be developed. A series of short-term and longer-term experiments with 1,2-DCE on several end-points of toxicity have been carried out by a group of investigators over the past several years. Results from these experiments should be available in July 1981. Once the data from this study become available, they will be evaluated for possible use in the development of SNARLs for this compound. If these data prove inadequate, further studies will have to be done in order to identify no-effect levels.

Experiments will soon be underway to investigate the effects of 1,2-DCE on clotting mechanisms. This study should provide no-effect levels for this particular end-point of toxicity. Aspects of cardiovascular toxicity may be addressed in the future through a request for initiation of EPA-sponsored research.

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DISCLAIMER

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