UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

March 12, 1985

Commandant of the Marine Corps
Code LFL
Attention Paul Hubbell
Washington, D.C. 20380
Subject: Request for Information

Dear Mr. Hubbell:

In response to your request of March 9, 1985, the following information is enclosed: one set of Office of Drinking Water Health Advisories. The Health Advisory Program is a continuing effort. The Advisories are updated as new information becomes available, and new Health Advisories are being prepared. I trust the enclosed information is responsive to your needs. If you have any questions or require further details, please contact our office at (202) 382-7571.

Very truly yours,

Edward V. Ohanian, Ph.D.
Chief, Health Effects Branch,
ODW (WH-550)

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Advisory Opinion for 1,1-Dichloroethylene
(Vinylidene Chloride)
Office of Drinking Water
U.S. Environmental Protection Agency
Washington, D.C. 20460
June 15, 1981

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) was 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 intra-

gastric 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 inahled [^{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 ahd 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 (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 pharmacolinetic 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).

Carcinogencity

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 a 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 0.33-0.0033 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 0.34-0.0034 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. (1972) study 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.

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Advisory Opinion for Dichloromethane (Methylene Chloride)
Office of Drinking Water
U.S. Environmental Protection Agency
Washington, D.C. 20460
March 14, 1981

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's 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-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

Dichloromethane, commonly known as methylene chloride (CH_2Cl_2) is a colorless, non-flammable solvent, soluble in water (2 gm in 100 ml), with a boiling point of 40.1° C and specific gravity of 1.325. One part per million in air is equivalent to 3.5 mg/m^3.

Inhalation exposure level recommendations for dichloromethane are: OSHA - 500 ppm, ACGIE - 200 ppm, NIOSH - 75 ppm (to be lowered in the presence of carbon monoxide). Dichloromethane at concentrations of 7.5 mg/l in drinking water can be detected by taste and odor (Tugarinova et al. 1965). Dichloromethane has miscellaneous uses as a solvent in certain pharmaceutical applications, for degreasing engine parts in the motor transportation, railway and aircraft industries, in the extraction of natural products, such as edible fats, cocoa butter, decaffeinated coffee and the beer flavoring in hops.

Sources of Exposure:

Humans are exposed to methylene chloride from air, food and water. Urban air in Japan has been reported to contain 0.035 - 32.9 ug/m^3 methylene chloride (Okuno et al. 1974). Concentrations as high as 1.6 ug/l have been detected in U.S. drinking water (U.S. EPA, 1975). Higher levels might be encountered in drinking water as a result of spills or seepage from land fills. Since methylene chloride is being used for extraction of some food material, it has been detected in the oleoresins of several spices: the highest concentrations of 83 mg/kg was detected in Cassia, followed by all-spice, nutmeg and others (Page and Kennedy, 1975). Dichloromethane was detected in the expired air of human subjects at levels of 0.12 - 340 ug/hr (Conkle et al. 1975).

Metabolism:

There is a paucity of data concerning the absorption of ingested dichloromethane, however it is expected to be absorbed

completely considering the physico-chemical properties of this compound. Absorbed dichloromethane vapor is biotransformed to carbon monoxide resulting in the formation of carboxyhemoglobin in human as well as experimental animals (Kubic et al. 1974, Stewart et al. 1972). Dichloromethane and related dihalomethanes are also metabolized to formaldehyde and halide ions in in vitro experiments (Ahmed and Anders, 1976; Kubic and Anders, 1975).

Health Effects:

Experiments in animals, as well as in humans, suggest that exposure to dichloromethane at high dose levels results in central nervous system depression; it also affects the liver and the blood. Carboxyhemoglobin formed as a result of dichloromethane exposure interferes with work performance capability and adversely affects patients with ischemic heart disease.

Acute Exposure:

On ingestion, the lowest recorded lethal dose for humans is 500 mg/kg (NIOSH, 1978). Tugarinova et al. (1965) compared acute toxicity of dichloromethane in mice, rats and guinea pigs. They administered single doses of dichloromethane in oil to the animals and established that guinea pigs were not as sensitive as mice and rats. Toxic symptoms included central nervous system effects characterized by initial excitation leading to convulsions and respiratory disorders and death. Histopathological examination revealed no overt changes in the internal organs with the exception of cerebral hyperemia. The animals that died in the later periods showed signs of liver toxicity. A daily dose of 750 mg/kg for 10 days given to mice resulted in no deaths. At the end of the experiment, the autopsied animals revealed signs and symptoms of liver toxicity.

In another study, Kimura et al. (1971) suggested a maximum permissible single oral dose 0.001 ml/kg, based on their experiments with rats, utilizing a single oral dose of one ml/kg dichloromethane. They observed gross signs of toxicity. Signs and symptoms of toxicity were not described.

Chronic Exposure Including Reproductive Effects:

Information on the long-term exposure of humans to dichloromethane is not available. For a longer-term experiment, the rats and guinea pigs were given dosages of 0.4 and 377 mg/kg 6 days a week for 5-6 months (Tugarinova et al. 1965). Six

animals were used for each dose level. No treatment related toxic symptoms were observed at the low dose level; however, at the high dose level, the ascorbic acid content of the adrenals decreased. The significnace of this effect is not clear.

In another longer-term study, dichloromethane was administered to rats in drinking water at a concentration of 0.125 g/l (15 mg/kg/ day) for 3 months. The animals were examined for changes in behavior, weight, blood and urin chemistries, reproductive function, organ weight/body weight ratio and histology. No significant treatment related effects were observed; however, the urine-albumin test was frequently positive. The authors did not attach any biological significance to this finding (Bornmann and Loeser, 1967).

Mutagenicity and Carcinogenicity:

Dichloromethane was mutagenic in Salmonella typhimurium TA 100 and TA 98 both in the presence and absence of a liver microsomal activation system (Jongen et al. 1978). The carcinogenic potential of dichloromethane was studied by Theiss et al. 1977. Six to eight week old Strain A/St male mice were injected intraperitoneally three times a week (total of 24 injections) at dose levels of 160, 400 and 800 mg/kg body weight. Twenty-four weeks after the first injection the animals were sacrificed and examined for lung adenomas. The observed adenomas in the treated animals were not statistically significant from those of the control.

Other Observations:

Since dichloromethane is metabolized to carbon monoxide in experimental animals as well as in humans, it is appropriate to consider the toxic effects of carbon monoxide. Astrup et al. 1972 studied the effect of carbon monoxide on fetal development in rabbits. Exposure to 180 ppm CO for 30 days (resulting in 16-18 percent carboxyhemoglobin) during pregnancy resulted in a 20 percent decrease of birth weight and a neonatal mortality of 35 percent as against 1 percent in the control group. Exposure to 90 ppm carbon monoxide (8-9 percent carboxyhemoglobin) had a less pronounced effect.

Several reports indicate the adverse health impact of carboxyhemoglobin on the heart, work performance capability and fetal development. In a well conducted study, Anderson and co-workers (1973) exposed human subjects with ischemic heart disease to 50 and 100 ppm carbon monoxide for four hours on five successive days. After each exposure subjects were asked to go through

standard treadmill exercises ECG test. Blood carboxyhemoglobin levels were determined before and after the exposure and the time of onset and duration of angina pain were recorded. The mean duration of exercise before onset of pain was significantly shortened after 50 and 100 ppm CO exposure. Exposure to CO at 50 and 100 ppm for four hours resulted in mean carboxyhemoglobin concentrations of 2.9 and 4.5 percent, respectively. In another study, Putz et al. 1978 studied the effects of carbon monoxide and methylene chloride on human task performance. The effects were assessed by the performance of human subjects on a visual-manual, dual task and an auditory vigilance task. The experimental procedure involved exposing the subjects to about 200 ppm dichloromethane for 4 hours and to 70 ppm CO to achieve desired carboxyhemoglobin concentrations of 5 percent. The authors suggest that 5 percent carboxyhemoglobin significantly impaired human performance under difficult or demanding task conditions.

EPA-SNARL Development:

Dichloromethane at higher dose levels produces central nervous system and liver effects. It is mutagenic in bacterial test systems and evidence of its carcinogenic potential is inconclusive. The available data suggest that the dichloromethane EPA-SNARL should be developed based on its potential to produce carboxyhemoglobin in humans.

Dichloromethane is metabolized to carbon monoxide as indicated by the formation of carboxyhemoglobin. At 5 percent carboxyhemoglobin level in humans, it is reported to interfere with the work performance as well as adversely affect the subjects with ischemic heart disease (Anderson et al. 1973). At slightly higher carboxyhemoglobin concentrations, it lowers the birth weight of the newborn rabbits, if their mothers are exposed during gestation. Therefore, the dichloromethane EPA-SNARL should be set below the dichloromethane concentration in drinking water that would not maintain 5 percent carboxyhemoglobin for an extended period of time. In fact, it should be at much lower concentrations in order to accommodate exposure to carbon monoxide from other sources.

An experiment to delineate the carcinogenic potential of dichloromethane is in progress at the National Cancer Institute. The results from this experiment or any other would be assessed to update the EPA-SNARL, if necessary.

One-Day EPA-SNARL:

The lowest lethal oral dose of 500 mg/kg (0.38 ml/kg) for

humans has been recorded. This dose cannot be used for the calculation of an EPA-SNARL, since this might have been an isolated incidence and certainly was not a well-controlled study. In addition, the cause of death and other adverse health effects need to be recognized before any degree of confidence is placed on this value. Using the same data base as chosen by the National Academy of Sciences, a one-day EPA-SNARL has been determined. This involves a study by Kimura et al. (1971) where the minimal effective dose of 1 ml/kg (1.3 g/kg) was established. Using a safety factor of 1,000, calculations of an EPA-SNARL for a 10 kg child, consuming one liter of water, are given below:

Calculations

$$\frac{1.3 \text{ g/kg} \times 10}{1000 \times 1 \text{ liter}} = 0.013 \text{ g/liter}$$

where: 10 = 10 kg body weight of a child
1 liter = assumed consumption of drinking water by 10 kg body weight child
1000 = safety factor

Ten-Day EPA-SNARL:

A study by Bornmann and Loeser (1967) appears to be most appropriate to use to determine the 10-day EPA-SNARL. In this study, adult rats were fed dichloromethane (15 mg/kg/day) for three months whereby no observed adverse health effects were identified. Applying a safety factor of 100 instead of 1000 used for longer-term SNARL calculations, to a no observed effect level of 15 mg/kg/day, the ten-day EPA-SNARL is calculated as 1.5 mg/l. This assumes 10 kg body weight of a child consuming one liter of water a day. Another method of calculating the ten-day EPA-SNARL would have been to merely divide the one-day EPA-SNARL by ten indicating a value of 1.3 mg/l.

It is expected that consumption of 13 mg/l and 1.5 mg/l dichloromethane for one and ten days, respectively, would not increase carboxyhemoglobin levels significantly.

The National Academy of Sciences (1980) calculated a one-day and a seven-day NAS-SNARL for dichloromethane in drinking water. They used the study by Kimura et al. (1971) where the minimal effective dose of 1 ml/kg (1.3 g/kg) was established. Using a safety factor of 1000 and a consumption volume of 2 liters of water by an adult the one-day adult NAS-SNARL should be 45 mg/l and consequently a seven day adult NAS-SNARL of 6.4 mg/l. However, the Academy values are 35 mg/l and 5 mg/l for

one-day and seven-day, respectively. There appears to have been a typographical error which was perpetuated in the seven-day NAS-SNARL.

Longer-term EPA-SNARL:

A longer-term EPA-SNARL cannot be estimated with confidence with the present available data; however, in case drinking water containing dichloromethane has to be consumed during an interim period before treatment, a study by Bornmann and Loeser (1967) could be used for determining longer-term dichloromethane EPA-SNARL. In this study, dichloromethane was administered to rats in drinking water at concentrations of 0.125 g/l (15 mg/kg/day) for three months. The animals were examined for changes in behavior, weight gain, blood and urine chemistry, reproductive functions, organ weight/body weight ratio and histology. No significant treatment related effects were observed. Another study by Tugarinova et al. (1965) where dosages of 0.4 and 377 mg/kg six days a week for 5-6 months were used, was not acceptable for these calculations because of inherent problems of statistical significance of the results.

Using a no-observed-effect dose level of 15 mg/kg/day for three months, the following calculations for determining a longer-term EPA-SNARL are made:

Calculations:

$$\frac{15 \text{ mg} \times 10}{1\ 1 \times 1000} = 0.150 \text{ mg/l}$$

where: 15 mg = no observed effect dose level
10 = assumed average body weight of a child
1 1 = assumed consumption of drinking water by 10 kg body weight child
1000 = a safety factor for a three month study

Note: This may be an overly conservative estimate, but this is based on the data available at the present time. Ideally, the study should have three to four dose levels to establish a no adverse effect dose level.

The U.S. EPA's Ambient Water Quality Criteria for Halomethanes (1980) recommended a criterion of 12.4 mg/l dichloromethane. It was calculated from American Conference of Governmental Industrial Hygienists recommended threshold limit value of 200 ppm (694 mg/m^3) for occupational exposure. This criterion applies to ambient water, not drinking water. It is noteworthy that NIOSH recommended a level of 75 ppm dichloromethane

for work-room exposure and suggested that the exposure to dichloromethane should be lowered further if the workers are exposed to carbon monoxide.

Analysis

Dichloromethane can be analyzed by the purge and trap method used for the halogenated hydrocarbons - chloromethanes, chloroethanes, chloroethylenes. The method involves trapping the purgeable halogenated solvents onto a suitable sorbant. The trapped compounds are thermally desorbed from the trap, passed through a programmed gas chromatograph for analysis. Detection is by the use of a microcoulometric or an electrolytic conductivity detector. By using this method, dichloromethane can be detected at 1 ug/l (Bellar & Lichtenberg, 1974, AWWA 66:739).

Treatment

Limited information is available concerning the removal of methylene chloride from drinking water. Studies were conducted to evaluate the capability of granular activated carbon to remove actual mixtures of contaminants, including methylene chloride in drinking water. In one of the studies, an untreated ground water containing low levels of halogenated hydrocarbons (methylene chloride concentration 0.08 ug/l) was passed through granular activated column (1 inch diameter and 30 inches of activated carbon). Empty bed contact time was 6.2 minutes. The water source had a color of approximately 50 color units, a TOC concentration of about 10 mg/l and pH of about 7.1. Methylene chloride was not detected in the effluent (EPA, 1978).

Conclusions and Recommendations

Based on the available data and the state-of-the-art concept in toxicology, the EPA-SNARL for one day is 13 mg/l, for ten-days 1.3 mg/l and the longer-term EPA-SNARL of 0.15 mg/l has been determined. These EPA-SNARLs are based on the acute and sub-acute toxicity data. Furthermore, these EPA-SNARLs would result in a carboxyhemoglobin level much below 5 percent at which level adverse health effects have been observed.

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Advisory Opinion for Benzene
Office of Drinking Water
U.S. Environmental Protection Agency
Washington, D.C. 20460
October 23, 1981

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's 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 eventeual 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

Benzene is an aromatic hydrocarbon, has the molecular formula C_6H_6 and a molecular weight of 78.1 (Weast et al. 1965). Under standard conditions, benzene is a colorless liquid with a very characteristic odor. It is highly flammable (limits of flammability in air of 1.5-8.0% by volume) and volatile (vapor pressure of 100 mm Hg at 26° C). Benzene is relatively soluble in water (1.8 g/l at 25° C) and miscible with a variety of organic solvents. Its density, 0.8737 g/ml at 25° C, is lower than that of water so that undissolved benzene floats on top of water. The pure liquid freezes at -5.553° C and boils at 80.100° C (Ayers and Muder, 1964). The vapors of benzene are nearly three times heavier than air (Lange and Forker, 1961), causing them to settle in low places if the ambient air is relatively still.

Benzene forms a two-phase, minimum boiling azeotrope with water at a benzene concentration of 91% by weight, boiling at 69° C. It also forms ternary azeotropes with other organic compounds and water (Horesly, 1947). This factor must be considered if evaporative purification systems are used to remove benzene from water. A concentration of 1 part per million in air is equivalent to 3.2 mg/m^3. It is noteworthy that the American Conference of Governmental Industrial Hygienists (ACGIH), Occupational Safety and Health Administration (OSHA) and the National Institute for Occupational Safety and Health (NIOSH) recommend threshold limit values for benzene as follows: 32 mg/m^3 (10 ppm), 3.2 mg/m^3 (1 ppm) and 32 mg/m^3 (10 ppm), respectively.

Sources of Exposure

Since benzene is broken down rapidly by bacteria in non-chlorinated water, the levels reported in individual samples may grossly underestimate the actual amount present as a result of decomposition due to sunlight or storage (Brass, 1981). Benzene concentrations in U.S. drinking water have not been surveyed in detail. In the National Organics Monitoring Survey (NOMS), which was conducted from March 1976 through January

1977, benzene analyses were performed on three samplings from community water supplies, which were representative of various types of sources and treatment processes. The numbers of positive benzene analyses per numbers of cities sampled were 0/111, 7/113 (with a mean of 0.4 ug/liter) and 4/16 (with a mean of 0.95 ug/liter) (USEPA, 1978). Four of ten water supplies surveyed by the EPA utilizing volatile organic analysis contained benzene at concentrations of 0.1-0.3 ug/liter (USEPA, 1975). Benzene analyses were performed on samples collected during the National Organics Monitoring Survey (USEPA, 1977). Samples from some of the larger cities using surface waters as their primary water source contained low levels of benzene. The Community Water Supply Survey reported finding that eleven samples out of 230 water supplies analyzed were positive for benzene; the average concentration ranged from 0.4 ug/l in phase 2, to 0.95 ug/l in phase 3 (Brass, 1981). Of the 100 ground water supplies examined, only one was found to contain benzene; the concentration was 0.6 ug/l (ibid).

Benzene can move into surface water from landfills or industrial disposal sites. Three hundred and seven community water supplies using ground water were included in the Community Water Supply Survey. Five of these communities were found to be providing water that contained benzene; the concentration ranged from < 0.5 - 44 ug/l. Since benzene is a major commodity chemical, the potential for exposure to benzene from accidental spills, landfill and industrial leachate remains high.

A review of benzene sampling data by Howard and Durkin (1974) found that only trace levels of benzene had been detected in a few fresh-water samples at that time. For example, a 1972 EPA study cited in the report (USEPA, 1972) identified 53 organic chemicals in the finished waters and organic waste effluents from 11 plants (of 60 sampled) discharging into the Mississippi River. Benzene was not detected in the effluents, but the trace detected in the finished waters suggested another source other than effluent discharge. Dowty et al. (1975) detected benzene in both the raw water (Mississippi River) and finished water at a New Orleans area water treatment plant. It should be noted that these authors also detected benzene and other organics in some commercially bottled artesian waters and deionized charcoal-filtered water. A sampling of five benzene production or consumption plants by Battelle Research Institute found benzene concentrations in water ranging from less than 1 to 179 ppb (plant effluent). The concentrations at 13 upstream and downstream sample locations in nearby receiving waters, however, ranged from less than 1 to 13 ppb, with an average of 4 ppb (Fentiman et al. 1979).

Benzene has been detected in various food categories: fruit, nuts, vegetables, dairy products, meat, fish, poultry, eggs and several beverages. The NCI reported that an individual

could ingest as much as 250 ug/day from these foods (NCI, 1977).

The respiratory route is the primary source of human exposure to benzene. Much of this exposure is to the general population by way of gasoline vapors and automotive emissions. American gasolines contain an average of < 1% (by volume) benzene, e.g. 0.8% (Runion, 1975). Benzene comprises approximately 2.15% (by volume) of the total hydrocarbon emissions from a gasoline engine (Schofield, 1974). Ambient air concentrations of benzene in the vicinity of European gas stations were found to range from 0.8 to 3.2 ppm for gasoline having contents of 3.7% (by volume) (Parkinson, 1971). Assuming U.S. gasolines to be 1% by volume, one would expect atmospheric concentrations ranging from 0.2 ppm to 0.9 ppm at U.S. gas stations. Production, chemical conversion and industrial user emissions constitute another major source of exposure. Lonneman et al. (1968) measured an average benzene concentration of 15 ppb in Los Angeles air, with a maximum of 57 ppb.

Indoor air concentrations of benzene also may represent a significant exposure source for specific segments of the population. Young et al. (1978) stated that consumers may be exposed unknowingly to benzene in the home in the form of paint strippers, carburetor cleaners, denatured alcohol, rubber cememt and art and craft supplies, as well as through use of gasoline as a cleaning solvent.

Smoking may be a very significant benzene exposure source for a portion of the population. Newsome et al. (1965) found that a 40 ml draw of cigarette smoke contained 6.1 ug of benzene. Assuming 15 draws per cigarette, one pack of 20 cigarettes smoked per day and a daily air intake of 20 m^3 (Diem, 1962), the equivalent annual average atmospheric exposure would be 92 ug/m^3 (28 ppb).

Pharmacokinetics

Benzene is absorbed readily through the lungs of humans and has an absorption rate of about 50% after five hours at a dose level of 340 mg/m^3 (Srobova et al. 1950, Teisinger et al. 1952). Inhalation at 166.4 mg/m^3 to 198.4 mg/m^3 for four hours resulted in 30% retention after three hours (Nomiyama and Nomiyama, 1974). Hunter and Blair (1972) reported that humans retained 230 mg after exposure to 80 to 100 mg/m^3 for 6 hours.

Retained benzene is distributed in tissues according to their fat content. Bone marrow, which, in toto, is an organ about two-thirds of the size of the liver, has a high tissue/blood partition co-efficient for benzene. Metabolites are believed to be important in the development of hematotoxicity, partly because of the effect of altered liver metabolism upon leuko-

penia and other hematopoietic responses. But little is known of the metabolite fate of benzene in the bone marrow (Snyder and Kocsis, 1975).

Whether administered by inhalation, orally, or by another route, benzene is eliminated rapidly by expiration and excretion in the urine. Parke and Williams (1953) administered ^{14}C-labeled benzene orally to rabbits (0.34-0.5 g/kg) and collected samples over three days. Benzene expired in air accounted for 43% of the dose; 34.5% was excreted in the urine as glucuronide or ethereal sulfate conjugates of metabolic oxidation products phenol, quinol, catechol and hydroxyquinol together with small amounts of other products; and 5% to 10% remained in the tissues. Benzene is metabolized similarly in humans (Laskin and Goldstein, 1977).

Health Effects

Short-term exposure to relatively high levels of benzene produces central nervous system effects. Such effects include dizziness, giddiness, exhilaration, nausea, vomiting, headache, drowsiness, staggering, loss of balance, narcosis, coma and death.

It has been known since the 19th century that long-term low-level exposure to benzene produces adverse hematological effects; Santesson (1897) described cases of aplastic anemia in workers fabricating bicycle tires. The original association of acute leukemia with benzene exposure was made in 1928 (Delore and Borgomano, 1928) and it has been postulated that benzene may be a cause of acute myeloblastic leukemia (Goldstein, 1981; OSHA, 1978b; NAS, 1980). Other hematological diseases also have been reported to be associated with benzene exposure (Goldstein, 1977).

Short-Term Exposure

Gerarde (1960) provides a table summarizing acute effects in which it is stated that 19,000-20,000 ppm for 5-10 minutes is a fatal benzene level; "7,500 ppm for 30 minutes is dangerous to life; 1,500 ppm for 60 minutes produces serious symptoms; 500 ppm for 60 minutes leads to symptoms of illness; 50-150 ppm for five hours produces headache, lassitude and weakness."

Mild central nervous system effects appear to be rapidly reversible following cessation of exposure. There is no evidence that they result in chronic brain damage. Also of importance is that these effects appear to be concentration-dependent. Lower levels of benzene do not seem to elicit these responses

no matter how long the exposure (at 480 mg/m^3) (Goldstein, 1977). Therefore, for acute (single dose or one day) exposures, a study that evaluates acute effects is required.

In animal studies, effects similar to those described for humans have been noted. Six rabbits exposed by inhalation to 112,000 to 144,000 mg/m^3 underwent anesthesia after 3.7 minutes and showed other effects in the central nervous system until death, which ensued after 22.5 to 71 minutes (Carpenter et al. 1944).

Kimura et al. (1971) studied acute oral toxicity in Sprague-Dawley rats. They used 6 to 12 rats of both sexes per group in testing newborn and 14-day old rats, and 6 male rats per group for the other older ages. Single dose LD_{50} values for 14-day old, young adult, and old adult rats were 3.0, 3.3 and 4.9 g/kg body weight, respectively. Withey and Hall (1975) performed an initial range finding study of ten male Sprague-Dawley rats (150-200 gm) using five dose levels: 2.00, 2.99, 4.47, 6.69 and 10.0 gm/kg. The benzene was administered via gavage. A separate study then was initiated on 20 male rats at each of five dose levels (3.00, 4.25, 6.00, 8.46 and 11.92 g/kg). The LD_{50} in both experiments was the same: 5.96 g/kg. Three of the dose levels used (2.00, 2.99 and 3.0) had no deaths.

Longer-Term Exposure

The toxicity of benzene to the hematopoietic system of humans experiencing chronic exposure to benzene is well documented. Reported effects include myelocytic anemia, thrombocytopenia, or leukopenia (occurring either separately or in cases of pancytopenia) and leukemia, particularly acute myelogenous and monocytic leukemia. In many of these studies, humans were exposed to benzene along with other solvents at relatively high concentrations. Data on the level and duration of exposure are inadequate for deriving dose-response relationships of chronic benzene toxicity (Vigliani and Forni, 1976). While it is impossible to determine a no-effect dose, it is highly probable that continuous exposure to benzene at low levels will result in the above noted effects. Infante et al. (1977) reported a retrospective cohort study of two populations of workers who were involved in production of rubber sheeting (Pliofilm). Benzene was the only material in their work environment that was known to be associated with blood disorders. In both plants during 1940-1949, the occupational exposure of 561 workers to benzene was apparently well within the maximum allowable concentration of 100 ppm that was usually recommended. Vital status to 1975, which was obtained for 75% of the workers, showed a significant excess of leukemia in those exposed to benzene, indicating a 10-fold increase in risk of death from

myeloid and monocytic leukemia.

The onset of leukemia is usually preceded by many observable effects on the hematopoietic system (Snyder and Kocsis, 1975). It is not known whether benzene causes leukemia as one aspect of its hematotoxic effects, whether the leukemia is a consequence of benzene-induced damage to immunological components of the bone marrow, or whether the leukemic effects are unrelated to the other hematopoietic manifestations (Laskin and Goldstein, 1977).

Benzene mixed with equal parts of olive oil was administered to rats by subcutaneous injection (Latta and Davies, 1941); Gerarde, 1956). Weight loss and leukopenia resulted from doses of 880 mg benzene/kg body weight, which were given daily for 14 days (Gerarde, 1956), and from doses of 1.32 g benzene/kg body weight, which were given daily for 3 to 60 days (Latta and Davies, 1941). In Latta and Davies' study, a rat that died after 10 days had hyperplastic bone marrow, and one that died at 21 days had acute leucopenia and hypoplastic bone marrow. Oral administration of benzene to rats in daily doses of 1, 10, 50 and 100 mg/kg body weight during 132 days over 6 months resulted in leucopenia and erythrocytopenia at the lowest minimal effect level of 10 mg/kg and above (Wolf et al. 1956).

Leucopenia is the most commonly observed effect of chronic benzene intoxication in laboratory animals. Deichmann et al. (1963) exposed 40 male and 40 female Sprague-Dawley rats by inhalation to six different levels of benzene for 5 hours to 7 hours per day, four days a week for six to 31 weeks. Tail blood was collected weekly or biweekly and analyzed for total peripheral white blood cell count, red blood cell count and benzene concentrations. All rats were examined for gross pathologic tissue changes and, in a few instances, the nucleated cell populations of femoral bone marrow were determined. The dose levels were 0, 50, 96, 103, 146, 156 and 2760 mg/m^3. The most significant and constant pathological changes were found in the lung (chronic bronchopneumonia) and spleen (hemosiderosis). The splenic hemosiderosis was more severe and occurred more frequently in females when compared to controls, but was not dose related. Leucopenia developed at 146 mg/m^3 and above. This effect was dose related and occurred with greater severity and at earlier times in females. In addition, there was some indication, also in females, that the circulating white blood cell count was depressed at 103 mg/m^3. However, at lower exposures, a fall in leukocyte causes cyclical fluctuations. Moreover, there is normally wide variation among cell counts during diurnal cycles and among individual animals.

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Teratogenicity

Only one study of teratogenicity has been noted. In this study, Watanabe and Yoshida (1970) gave subcutaneous injections of acute toxic doses of benzene (2.62 mg/kg body weight) to pregnant mice on days 11 through 15 of gestation. Malformations were most prevalent in the group that was treated on the 13th day. Four of 15 litters, involving 10 of 127 fetuses, had cleft palate, agnathia, or micrognathia. Decreased white cell count and weight gain in the benzene-treated mice were the same whether the litters were normal or included malformed fetuses. As an indication of the toxicity of the dose used in this experiment, five male mice that received benzene at 2.62 mg/kg body weight survived, while four of five male mice that had been injected with 3.49 mg/kg died within 3 days. Therefore, teratogenicity occurs in mice exposed to benzene, though at doses very close to lethal.

Mutagenicity

Toxic effects on bone marrow cells of rats and other laboratory animals include changes in chromosome number and chromosome breakage that resemble those in humans. There is no clear evidence for dose-dependent response (Laskin and Goldstein, 1977). Lyon (1975) used the Ames assay with Salmonella typhimurium strains TA98 and TA100 to test benzene for mutagenicity in doses ranging from 0.1 to 1.0 ul/plate, both without and with microsomal fractions at concentrations from 1 to 50 ul/plate. Postmitochondrial supernatant suspensions of microsomes were prepared from liver homogenates from normal rats and from rats that had been treated with phenobarbital and 3-methylcholanthrene (MCA), and from the bone marrow of normal and MCA-treated rats. Benzene was uniformly negative in all of these assays and was also inactive in the dominant lethal assay in rats.

Carcinogenicity

Maltoni and Scarnato (1979) administered by gavage benzene dissolved in virgin olive oil to 13 week old Sprague-Dawley rats. The material was administered at doses of 50 and 250 mg/kg for 4-5 days a week for 52 weeks. The animals then were allowed to live until spontaneous death. Each high dose group consisted of 35 male and 35 female rats and controls and low dose groups were composed of 30 male and 30 female rats. After 20 weeks of exposure, Maltoni and Scarnato corrected the denominators (number of animals surviving) to reflect "nonexperimentally" caused deaths. The 250 mg/kg dose level group then consisted of 33 male and 32 female rats; the 50 mg/kg and olive oil control

group then consisted of 28 male and 30 female rats. The authors reported their results after 144 weeks. At the 250 mg/kg dose level, 25% (8/32) of the female rats and Zymbal gland tumors, 6.2% (2/32) had skin carcinomas, 21.9% (7/32) had mammary carcinomas, 3.1% (1/32) had leukemias. The male rats in the 250 mg/kg dose group had no Zymbal gland tumors, no skin carcinomas and no mammary gland tumors; however, they had 12.1% leukemias (4/33), one subcutaneous angiosarcoma (3.0%) and one hematoma (3.0%). In the rats remaining after the 20 week adjustments, the following carcinogenic effects were noted. At the 50 mg/kg dose level, only female rats had tumors which were Zymbal gland carcinoma, 6.7% (2/25) and mammary carcinoma, 13.3% (4/25). The control group had tumors only in female rats, which were: mammary carcinoma 10.0% (3/30), leukemias 3.3% (1/30). The authors concluded that benzene "appears to cause Zymbal gland carcinomas, at the two studied dose levels with a dose response relationship. Moreover, a dose correlated increase of hemato-lympho reticular neoplasias (leukemias) and mammary carcinomas has also been observed."

Ward et al. (1975) subcutaneously injected male C57BL/6N mice repeatedly with benzene dissolved in corn oil. Eighty benzene treated mice, while initially divided into four dose groups ranging from 0.5-2.0 mg/kg, were eventually combined and reported as a single experimental group. Three control groups were used with twenty male mice per group: a no treatment control, a corn oil only control, and a positive control using butylnitrosourea. The animals were injected twice weekly for 44 weeks, then once weekly until 54 weeks. At 104 weeks after the first injection, all surviving mice were sacrificed (108 weeks of age) and a complete necropsy was performed, as had been done with all the mice that died. The toxic lesions included a bone marrow depleted of hematopoietic cells and hepatonecrosis. A granulocytic leukemia was also noted. After reviewing the data from that study, the National Academy of Sciences Safe Drinking Water Committee concluded that the increase in pathology was not statistically significant, even when time to response was incorporated into the analysis (National Academy of Sciences, 1977).

EPA-SNARL Development

The Office previously released an emergency SNARL for kerosene and fuel oil #2 based, in part, on their benzene content. The present document supercedes all previous ODW benzene guidances. The Office of Drinking Water will, from time to time, as data and other relevant information become available, update these guidances to reflect the most recent scientific reports.

The available data suggest that the EPA-SNARL for benzene

should be based on the potential of this compound to produce hematopoietic damage. This decision is justified by the following factors:

1. The hematopoietic system appears to be the most sensitive indicator of benzene toxicity.

2. Benzene-induced leukopenia and fatal anemia develop in days; rabbits, guinea pigs, rats and mice sometimes develop anemia within 12-15 days (Hough and Freeman, 1944; Petrini, 1941; Wolf et al. 1956).

The ten-day and longer-term SNARL values calculated for benzene do not take into account the suggested carcinogenicity of benzene and are based on data from papers in which benzene toxicity was evaluated. In some of the studies, dose-response information is available, whereas, in others a single dose was chosen to produce a toxic effect. In the cases reported here, the effects were related to bone marrow toxicity. Where possible, studies were selected where benzene was administered orally.

One-Day EPA-SNARL

The EPA determined that there were insufficient data to compute a one-day SNARL. Similarly, the National Academy of Sciences (1981) stated that there are insufficient data to determine a one-day SNARL.

Ten-day SNARL

Calculation of the ten-day SNARL is based on the study of Deichman et al. (1963) who exposed rats to benzene four days a week by inhalation and monitored their hematology weekly. By the second week of treatment, there was definite hematological impairment at the 2659 mg/m^3 exposure concentration and some indication, especially in females, that white blood cells were depressed at the 103 mg/m^3 exposure concentration. No effect was seen, however, at 96 mg/m^3. The following equation was applied to provide a ten-day SNARL of 0.23 mg/l.

Step 1

$$\frac{(96\ mg/m^3)(6\ m^3)(0.5)(4)(10\ kg)}{(100)(1/day)\ x\ 7\ (70\ kg)} = 0.23\ mg/l$$

where: (96 mg/m^3) = 29 ppm exposure
6 m^3 = volume of air inhaled over 6 hours exposure based upon equivalent lung/whole body ratios for adult humans and rats (Olson and Gehring, 1976)
0.5 = absorption factor
4/7 = conversion of total weekly dose to equivalent daily dose
$\frac{10}{70}$ = child/adult body weight ratio
1 l = liter of water consumed per day by 10 kg child
100 = safety factor

Longer-term SNARL

Longer-term SNARLs are not for lifetime exposures. These SNARLs apply only to contamination levels during interim periods of exposure.

A longer-term SNARL can be calculated using data from Wolf et al. (1956) who gavaged female rats at doses of 1, 10, 50 and 100 mg/kg over a 187 day period. No effects were seen at 1 mg/kg but a slight leucopenia was observed at 10 mg/kg given 132 times over the 187 days. The no-effect level would appear to lie between these values.

$$\frac{(1 \text{ mg/kg})(10 \text{ kg})(100\%)(5)}{(100)(7)} = 0.07 \text{ mg/liter}$$

where: 1 mg/kg = assumed no effect dose
10 kg = 10 kilogram child
100% = absorption factor
1 l = 1 liter of water consumed per day by 10 kg child
100 = safety factor
5/7 = factor to correct from 5 days/week to 7 days

The National Academy of Sciences derived its 10-day SNARL using the Wolf data. They chose the 50 mg/kg as the no effect dose, five times the 10 mg/kg dose which showed a slight leucopenia.

No chronic SNARL was calculated for benzene by the National Academy of Sciences because, in their opinion, benzene is a suspect human carcinogen.

Carcinogenic Risk Estimate

The National Academy of Sciences, in Drinking Water and Health,

Volume 3, 1980) states:

> There are no data from animal models for use in extrapolation. Occupational studies on human exposure (Aksoy et al. 1972, 1974 a, b, 1976; Ishimaru et al. 1971; Thorpe, 1974) do not contain adequate information on degree of exposure or size of population at risk. In addition, the workers in benzene-related occupations typically were exposed to other chemicals, as in the study reported by Ott et al. 1978. Consequently, extrapolation of benzene-induced cancer risk from such data as these would be tenuous.
>
> In a study by Infante et al. 1977, workers were exposed to benzene as the sole chemical suspected of affecting the hematopoietic system. In these cases, benzene concentrations apparently were high during the first years of exposure and were lower thereafter. There are no data indicating how often short exposures at elevated levels may have occurred. Estimates of actual exposure are inadequate for extrapolation for risk of benzene-induced leukemia.

The EPA's Carcinogen Assessment Group (CAG) has determined a carcinogenic risk estimate by using the following considerations.

> Three epidemiology studies of workers exposed to benzene vapors on their jobs, performed by Infante, Ott and Aksoy, were reviewed by the CAG for the Office of Air Quality Planning and Standards (USEPA, 1979). Their result was that the potency for humans breathing benzene continuously is B = 0.02407. This means that the lifetime risk of getting leukemia, R, equals 0.024074 times the lifetime average continuous exposure, X, measured as ppm of benzene by volume in air, or R = BX. Therefore, the air concentration, X, resulting in a risk of 10^{-5} is X = R/B = $10^{-5}/0.024074$ = 4.1539×10^{-4} ppm.
>
> Since the air concentration corresponding to 1 ppm of benzene is 3.25 mg/m^3 and assuming a respiratory rate of 20 m^3/day and a respiratory absorption coefficient of 0.50, the daily intake that would result in a risk of 10^{-5} is:
>
> 4.154×10^{-4} ppm x 3.25×10^3 ug/m^3 per ppm x 20 m^3/day x 0.5 = 13.5 ug/day

If it is assumed that the fraction of benzene absorbed is the same between inhalation and ingestion of water and fish, a daily benzene intake of 13.5 ug through drinking water would cause a leukemia risk of 10^{-5}. The water concentration given

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retention time for benzene is 199 seconds and the lower limit of detection is 0.02 ug/l.

Treatment

(Forthcoming from STB)

Conclusions and Recommendations

Benzene at high levels is extremely toxic to the central nervous system. Its toxicity at lower levels is the result of bone marrow effects which may result in pancytopenia with fatal outcomes. As stated above, the recommended guidance levels for benzene are:

Ten-Day - 0.23 mg/l
Longer-term - 0.07 mg/l

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Advisory Opinion for Trans-1,2-Dichloroethylene
Office of Drinking Water
U.S. Environmental Protection Agency
Washington, D.C. 20460
September 21, 1982

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's 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 exployed 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/-^{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 *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 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

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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 (800 mg/m^3) (the currently-established TLV/MAC in a number of countries) and at 1000 and 3000 ppm (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 (800 mg/m^3) yielded an increased incidence

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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 of the 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

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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 2.5mM.

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.

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SNARL for Tetrachloroethylene
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U.S. Environmental Protection Agency
Washington, D.C. 20460
February 10, 1980

THE OFFICE OF DRINKING WATER "SNARLS" PROGRAM

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 with a margin of safety; it is called a SNARL (suggested no adverse response level). Normally values are provided for one-day, 10-day and longer-term exposure periods where available data exists. 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 when they have been found.

In the absence of a formal drinking water standard for tetrachloroethylene, the Office of Drinking Water has estimated a suggested no adverse response level (SNARL) following the state-of-the-art concepts in toxicology for non-carcinogenic risk for short and long term exposures. For carcinogenic risk, a range of risk estimates is provided for life-time exposures using a model and computations from the NAS Report (1979) entitled "Toxicity of selected drinking water contaminants". However, SNARLs are given on a case-by-case basis in emergency situations such as spills and accidents. The SNARL calculations for short-term and chronic exposures ignore the possible carcinogenic risk that may result from those exposures. In addition, SNARLs usually do not consider the health risk resulting from possible synergistic effect of other chemicals in drinking water, food and air.

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 a national standard or Maximum Contamination Level (MCL). 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 SNARL purposes might differ from an eventual MCL. The SNARLs may also change as additional information becomes available. In short SNARLs are offered as advice to assist those that are dealing with specific contamination situations to protect public health.

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General Information and Health Effects

Substantial quantities of tetrachloroethylene are being produced (700 million pounds in the U.S. in 1973). Tetrachloroethylene (perchloroethylene) is used as a dry cleaning and degreasing solvent, heat-transfer medium, and in the manufacture of fluorocarbons. This chemical is slightly soluble in water (0.01% by volume).

Little work has been done to delineate the uptake, distribution, metabolism and excretion patterns following oral exposures to tetrachloroethylene. For our purposes, an assumption is being made that 30% is absorbed via respiration and almost 100% via the gastrointestinal tract, as has been shown for trichloroethylene. Only a small fraction of tetrachloroethylene is metabolized to trichloroacetic acid and/or trichloroethanol. The urinary half-life of tetrachloroethylene is markedly longer (144 hours) than that of trichloroethylene indicating some level of bioaccumulation.

Tetrachloroethylene, like other halogenated hydrocarbons at high doses, has been reported to produce liver and kidney damage and central nervous system disturbances in mammals, including humans. In addition, tetrachloroethylene has been demonstrated to lower the DNA and RNA content of several organ systems of rats. High concentrations of this chemical result in growth inhibition and mortality as demonstrated in animal inhalation studies.

Investigations of chronic toxicity of tetrachloroethylene in animals have all involved inhalation exposure, with the exception of an assessment of carcinogenesis which involved oral dosing (NCI, 1977). The National Cancer Institute has reported tetrachloroethylene-induced hepatocellular carcinomas in male and female mice, but not in male or female rats.

Schwetz et al. (1975) reported that tetrachloroethylene was not teratogenic to rats and Swiss Webster mice after inhalation exposures of 300 ppm for seven hours per day on days six-15 of gestation. Careful examination of their data, however, indicate that there were a number of modest but statistically significant deviations of adverse health effect parameters from control animals, including increased body maternal weights, decreased body weight of mouse fetuses, increased fetal resorptions and increased incidence of split sternebrae, subcutaneous edema and delayed ossification of skull bones in mouse fetuses. Schumacher et al. (1962) exposed three week old mice for eight hours/day, three days each to 200, 400, 800 and 1600 ppm perchloroethylene. The exposures produced significant mortality and growth inhibition in survivors.

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Tetrachloroethylene SNARL

Tetrachloroethylene is a carcinogen in mice, and also causes non-carcinogenic bioeffects at high doses. One-day, 10-day, and chronic SNARL values based on non-carcinogenic bioeffects are computed incorporating appropriate factors of safety. Estimates of concentrations projected to increase the lifetime cancer risk by one in 100,000 and one in a 1,000,000 are also provided using the NAS model. The non-carcinogenic SNARL recommendations are made considering the child and other sensitive members of the population.

A one-day SNARL of 2.3 mg/l can be calculated using a study by Kylin (1963). In this study mice were exposed to 200 ppm tetrachloroethylene in air for a period of four hours. Histological examinations of the liver demonstrated fatty infiltration but not cellular necrosis. Even though the exposure levels ranged from 200 to 1600 ppm tetrachloroethylene, the no-adverse-effect level was not established.

Using the method by Olsen and Gehring (1976) whereby the lung/whole body ratios for humans and animals are assumed to be roughly equivalent, the total exposure of 200 ppm (1358 mg/m^3) for four hours via inhalation, could be used to determine the one-day SNARL:

$$\frac{(1358\ mg/m^3)(4\ m^3/day)(0.30)\qquad (1)}{(1\ l/day)(100\ \text{uncertainty factor})(7)} = 2.3\ mg/l$$

where:
- 1/7 = child/adult body weight ratio
- 0.30 = absorption factor
- 1 l/day = child's daily water consumption
- 100 uncertainty factor because of animal experiment
- 1358 mg/m^3 = (200 ppm)(6.79 conversion factor)
- $4m^3$ = according to Olsen and Gehring whereby the lung/whole body ratios for humans (adults) and rats (adults) are assigned to be roughly equivalent

An uncertainty factor of 100 was chosen rather than 1,000 even though the SNARL is based upon an animal experiment in which the no-observed-effect level was not identified. It was felt that the index of toxicity, namely fatty infiltration of the liver, is a delicate disorder in itself which is reversible and not life-threatening after a short exposure, therefore an additional margin of safety was not warranted.

The National Academy of Sciences (NAS, 1979) has computed a one-day SNARL of 172 mg/l and 24.5 mg/l for the seven-day SNARL. Calculations used by the NAS to determine a one-day SNARL were based on hepatotoxicity at a dose level of 490 mg/kg body weight given intraperitoneally to the animals. The calculations were made for a 70 kg man and the drinking water was

considered to be the sole source of exposure. The seven-day NAS SNARL was calculated by dividing the one-day SNARL value by the appropriate number of days.

The NAS chose to work with data in animals given intraperitoneal injections. The Office of Drinking Water selected an inhalation study in animals for extrapolation of its SNARL and calculated the SNARL for the 10 kg child. Animal studies and a human case history suggest that, in this case, children appear to be a sensitive population which needs to be protected from the adverse health effects.

The Office of Drinking Water 10-day SNARL was calculated using an inhalation study by Savolainen et al. (1977) in which inhalation exposures of adult male rats to 200 ppm of tetrachloroethylene six hours daily for five days caused diminished brain RNA content. The 10-day SNARL of 175 ug/l was thus determined:

$$\frac{(1358\ mg/m^3)(6\ m^3)(0.30)(1)(1)}{(1\ l/day)(1000)\qquad\qquad(7((2)} = 175\ ug/l$$

where: $1358\ mg/m^3$ = (200 ppm)(6.79 conversion factor)
$6\ m^3$ = according to Olsen and Gehring whereby the lung-whole body ration for humans (adults) and rats (adults) are assumed to be roughly equivalent
0.30 = absorption factor
1 l/day = child's daily consumption of drinking water
1000 = uncertainty factor due to animal experiment where the no-observed-effect level was not identified
1/7 = child/adult body weight ratio
1/2 = factor to provide for equivalent toxicity on day 10 as noted on day five

As a matter of interest, "Medical World News" contained a report of a six week old baby with jaundice and an enlarged liver; the baby was breast fed by a mother who was frequently exposed to tetrachloroethylene in a dry cleaning establishment (Anonymous, 1978). The mother's milk contained perchloroethylene levels up to one mg %. The child's symptoms vanished when breast feeding was discontinued.

Longer-Term SNARL

A longer-term SNARL of 20 mg/l (rounded from the computation) can be estimated from a study by Navrotskii et al. (1971). The authors reported increased urinary urobilinogen and pathological changes in the parenchyma of the liver and kidneys of rabbits after inhalation exposure to 100 mg/m^3 perchloroethylene for three to four hours/day for seven to 11 months.

The calculations for a longer-term SNARL are:

$$\frac{(100\ mg/m^3)(4\ m^3/day)(0.30)}{(1\ l/day)(1000\ uncertainty\ factor)(7)} \quad \frac{(1)}{} = 0.017\ mg/l$$

where: $100\ mg/m^3$ = observed effect level
$4m^3$ = according to Olsen and Gehring whereby the lung-whole body ratio for humans (adults) and rats (adults) are assumed to be roughly equivalent
0.30 = absorption factor
1 l/day = child's consumption of drinking water
1/7 = child/adult body weight ratio
1000 = uncertainty factor due to animal study where health effect was observed

Since tetrachloroethylene is considered a carcinogen, at least for mice, and using the risk estimates generated by the National Academy of Sciences (NAS), it is possible to identify that range of tetrachloroethylene concentrations that would increase the risk of one excess cancer per 10^6 or 10^5 people exposed over a lifetime. From the NAS model it is estimated that consuming 2 l/day over a lifetime having a tetrachloroethylene concentration of 3.5 ug/l or 35 ug/l would increase the risk by one excess cancer/million exposed or one excess cancer/100,000 exposed, respectively. This is the range of risks where many EPA regulatory values for other carcinogens have been.

These risk extrapolations were based on an assumption that there is no threshold effect level for carcinogens. The state-of-the-art at the present time is such that no experimental tools can accurately define the absolute numbers of excess cancer deaths attributable to tetrachloroethylene in drinking water. Due to biological variability and the number of assumptions required, each of the risk estimating procedures leads to a different value. There is wide variation between these estimates and also in their interpretation. For this reason, we report the results of the NAS risk computations, which is a conservative approach, as a range of values from one in 100,000 to one in 1,000,000 incremental risk (risk above background) for a carcinogen. The NAS risk estimates are based on the multistage model concept. "At low dose, the multistage model is often mathematically equivalent to the linear or single hit model. Therefore, its use for extrapolation is consistent with the conservative linear risk estimation. If the precise mechanism of carcinogenesis is represented by a threshold or log-normal dose response relationship, the multistage model may considerably overestimate the risk at low dose levels. However, this possibility cannot be reasonably quantified" (NAS 1979).

In summary, the one-day, ten-day and longer-term SNARL values for tetrachloroethylene are 2300 ug/l, 175 ug/l and 20 ug/l,

respectively, if drinking water is the only source of exposure. The concentrations resulting in a lifetime risk of 10^{-6} and 10^{-5} are 3.5 ug/l and 35 ug/l, respectively, if the contaminated drinking water was consumed over a lifetime. The longer-term SNARL of 20 ug/l tetrachloroethylene in drinking water may result in excess cancer risk of approximately six in one million, if the exposure was for a lifetime (70 years).

SNARL For Trichloroethylene
Health Effects Branch, Criteria and Standards Division
Office of Drinking Water
U.S. Environmental Protection Agency
Washington, D.C. 20460
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In the absence of a formal drinking water standard for trichloroethylene, the Office of Drinking Water has estimated a suggested no adverse response level (SNARL) following the state-of-the-art concepts in toxicology for non-carcinogenic risk for short and long term exposures. For carcinogenic risk a range of risk estimates are provided for life-time exposures using a model and computations from the National Academy of Sciences Report: Drinking Water and Health (1977). However, SNARLs are given on a case-by-case basis in emergency situations such as spills and accidents. The SNARL calculations for short-term and chronic exposures ignore the possible carcinogenic risk that may result from those exposures. In addition SNARLs usually do not consider the health risk resulting from possible synergistic effect of other chemicals in drinking water, food and air.

General Information and Health Effects

Trichloroethylene is used primarily as a metal degreasing agent. It is also used, however, in dry-cleaning as a solvent, and in refrigerants and fumigants. Trichloroethylene is slightly soluble in water.

Trichloroethylene, like other halogenated hydrocarbons at high dose levels, has been reported to produce liver and kidney damage and central nervous system disturbances in mammals, including humans. These effects have been observed as a result of short-term exposures and the intensity of the response was dependent upon the dosage levels. Salvini et al. (Brit. J. Med. 1971. 28:293) observed psychophysiological changes in human volunteers in a controlled inhalation study using trichloroethylene at as low a level as 110 ppm for two four-hour periods.

Long-term exposures of mice to trichloroethylene produced carcinogenic effects in both male and female animals (National Cancer Institute, 1976). In addition to the carcinogenic effect, trichloroethylene has been reported to be mutagenic in microorganisms, transforms cultured mammalian cells to carcinogenic cells, and binds with tissue macromolecules, thus supporting the carcinogenic potential of trichloroethylene.

There has been some controversy over the current eivdence

linking trichloroethylene and carcinogenicity in animal studies. Although the NCI bioassay was positive, others have argued that the effects may have been due to contaminants (epichlorohydrin and epoxybutane) in the tested trichloroethylene. NCI has agreed to retest. The NAS in its 1979 report, however, recognizing the issue, accepted the NCI result and computed a risk value based upon carcinogenic potential.

Recent studies on the metabolism and elimination of trichloroethylene in rats and human volunteers reveal that the metabolites of trichloroethylene, namely trichloroethanol and trichloroacetic acid, are not immediately eliminated from the body. Trichloroethanol was found to have a half-life of 12 hours in human volunteers. This would mean that repeated daily exposure to trichloroethylene via drinking water would result in some accumulation of trichloroethanol in the body. Moreover, the metabolite trichloroacetic acid has been reported to bind to plasma proteins. This property of trichloroacetic acid may result in interaction with drugs and chemicals having similar properties, thereby resulting in toxic effects. (Ertle et al. Arch. Toxicol. 29, 171-188, 1972.)

SNARL Development

Trichloroethylene is a carcinogen in mice, and also causes non-carcinogenic bioeffects. One-day, 10-day and chronic SNARL values based on non-carcinogenic bioeffects are computed incorporating appropriate factors of safety. Estimates of concentrations projected to increase the lifetime cancer risk by one in 100,000 and one in a 1,000,000 are also provided using the NAS model. The non-carcinogenic SNARL recommendations are made considering the child and other possibly sensitive members of the population.

Using a study where human volunteers were exposed via inhalation to 110 ppm (590 mg/m^3) of trichloroethylene for an 8-hour period where psychophysiological symptoms were observed, a one-day SNARL value of 2 mg/l could be calculated for the child.

$$\frac{(590\ mg/m^3)(8\ m^3/day)(0.30)}{(1\ l/day)(100\ \text{uncertainty factor})} \times \frac{1}{7} = 2.02\ mg/l$$

where:
- 1/7 = child/adult body weight ratio
- 0.30 = absorption factor
- 1 l/day = child daily water consumption
- 100 = uncertainty factor via 10 factor because a human experiment was used and 10 factor because data did not specify the no observed adverse effect level

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To calculate a SNARL for 10 days metabolic and pharmacokinetics data are required. Since that data is not available, a conservative method would be to divide the one-day SNARL of 2 mg/l by 10 whereby the 10-day SNARL value would become approximately 200 ug/l.

Since the one-day and 10-day SNARL values are determined for emergencies and spills for a short period of time, it should be assumed that drinking water would be the primary or sole source of human intake of trichloroethylene. This is in opposition to that for a chronic SNARL where a lesser contribution from drinking water may be appropriate. Therefore, a relative source contribution factor has not been incorporated into the suggested one-day and 10-day SNARL values of 2 mg/l and 0.2 mg/l, respectively.

The NAS (1979) has computed a one-day SNARL of 105 mg/l and 15 mg/l for the seven-day SNARL. Their calculations were based upon the observation of intoxication of adults and the application of uncertainty factors. Our calculations, however, were based upon psychophysiological parameters and extrapolated to the child with the appropriate uncertainty factors.

The NAS chose to work with uncontrolled case histories where trichloroethylene was accidentally ingested. The study which the Office of Drinking Water chose to evaluate and extrapolate, while being an inhalation study, was conducted under controlled conditions.

A longer exposure SNARL for trichloroethylene, can be calculated using a study by Kimmerle and Eben entitled "Metabolism, Excretion and Toxicology of Trichloroethylene after Inhalation." This study evaluated the subacute exposure to trichloroethylene via inhalation in adult rats for some 14 weeks following exposure to 55 ppm (300 mg/m^3), five days a week. Indicies of toxicity include hematological investigation, liver and renal function tests, blood glucose and organ/body weight ratios. Liver weights were shown to be elevated while the other test values were not different from controls. The elevated liver weights could be interpreted to be the result of hydropic changes or fatty accumulation. The no-observed-effect level was not identified.

Using the method of Olsen and Gehring (1976) whereby the lung-whole body ratios for humans (adults) and rats (adults) are assumed to be roughly equivalent, tne total dose of trichloroethylene to the child can be determined and a longer term SNARL can be calculated to be approximately 75 ug/l when the principal source of trichloroethylene is assumed to be from drinking water.

$$\frac{(300\ mg/m^3)\ 8\ m^3/day\ (5)(1)(0.30)}{(1\ l/day)\ (7)\ (7)\ (1000)} = 73.5\ ug/l$$

where: 55 ppm (5.46) = 300 mg/m^3 minimum effect level
8 m^3 = according to Olsen/Gehring
5/7 = fraction converting from 5 to 7-day exposure
1/7 = child/adult body weight ratio
0.30 = absorption rate
1 l/day = child consumption per day
1000 = uncertainty factor due to animal study where minimal effect was reported

In cases where other sources of exposure are prevalent and, for example, drinking water is assumed to account for a portion of the total exposure, say 20%, of the trichloroethylene intake, then the SNARL value would become 15 ug/l. By-and-large, however, the 75 ug/l SNARL would be assumed to be appropriate under normal circumstances in the absence of other major sources of TCE.

A chronic SNARL approximately equivalent to the SNARL of 75 ug/l can be justified on the basis that (1) long-term exposure to low doses of trichloroethylene probably does not bioaccumulate much more over a lifetime than in 3-6 months, and (2) the SNARL was calculated for the child and not the adult thus providing a somewhat larger safety margin.

Since trichloroethylene is considered a carcinogen, at least for mice, and using the risk estimates generated by the National Academy of Sciences (NAS), it is possible to identify that range of trichloroethylene concentrations that would increase the risk of one excess cancer per 10^6 or 10^5 people exposed over a lifetime. From the NAS model it is estimated that consuming 2 l/day over a lifetime having a trichloroethylene concentration of 4.5 ug/l or 45 ug/l would increase the risk by one excess cancer/million exposed or one excess cancer/100,000 exposed, respectively. This is the range of risks where many EPA regulatory values for other carcinogens have been.

These risk extrapolations were based on an assumption that there is no threshold level for carcinogens. The state-of-the-art at the present time is such that no experimental tools can accurately define the absolute numbers of excess cancer deaths attributable to trichloroethylene in drinking water. Due to the biological variability and a number of assumptions required, each of the risk estimating procedures lead to a different value. There is wide variation among these estimates and also in their interpretation. For this reason we report the results of the NAS risk computations, which is a conservative approach, as a range of values in the one in one hundred thousand to one in one million incremental risk (risk above background) for a carcinogen. The NAS risk estimates are based on the multistage

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