PB87-235578

March 31, 198[illegible]

# ACRYLAMIDE

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

## I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for One-day, Ten-day, Longer-term (approximately 7 years, or 10% of an individual's lifetime) and Lifetime exposures based on data describing noncarcinogenic end points of toxicity. Health Advisories do not quantitatively incorporate any potential carcinogenic risk from such exposure. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

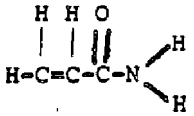
REPRODUCED BY
U.S. DEPARTMENT OF COMMERCE
NATIONAL TECHNICAL
INFORMATION SERVICE
SPRINGFIELD, VA 22161

This HA is based on information presented in the Office of Drinking Water's draft Health Effects Criteria Document (CD) for Acrylamide (U.S. EPA, 1985a). The HA and CD formats are similar for easy reference. Individuals desiring further information on the toxicological data base or rationale for risk characterization should consult the CD. The CD is available for review at each EPA Regional Office of Drinking Water counterpart (e.g., Water Supply Branch or Drinking Water Branch), or for a fee from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Rd., Springfield, VA 22161, PB # 86-117744/AS. The toll-free number is (800) 336-4700; in the Washington, D.C. area: (703) 487-4650.

## II. GENERAL INFORMATION AND PROPERTIES

CAS No. 79-06-1

Chemical Structure



Synonyms:

- 2-Propenamide, acrylic amide, acrylic acid amide, akrylamid, ethylene carboxamide and propinoic acid amide.

Uses:

- As the monomer, in:
  - Grouts
  - Soil stabilizers
- As the polyacrylamide, in:
  - Flocculant production - drinking water and wastewater treatment plants
  - Additive for enhanced oil recovery
  - Fog dissipator
  - Soil stabilizer
  - Paper and paperboard strengthener
  - Adhesive/binder component
  - Metal coating
  - Food packaging
  - Photography applications
  - Chromatography gel
  - Electrophoresis gel
  - Dye applications

Properties (Windholz, 1976; Verschueren, 1983)

| | |
|---|---|
| Chemical Formula | $C_3H_5NO$ |
| Molecular Weight | 71.08 |
| Physical State (room temp.) | white crystals |
| Boiling Point (at 25 mmHg) | 125 °C |
| Melting Point | 84.5 °C |
| Vapor Pressure (25°C) | 0.007 mmHg |

| | |
|---|---|
| Specific Gravity (30°C) | 1.122 g/mL |
| Water Solubility (30°C) | 2155 g/L |
| Chloroform Solubility (30°C) | 26.6 g/L |
| Benzene Solubility (30°C) | 3.46 g/L |
| Octanol/Water Partition Coefficient | -- |
| Taste Threshold (water) | -- |
| Odor Threshold (water) | -- |
| Odor Threshold (air) | |
| Conversion Factor | 1 $mg/m^3$ = 0.34 ppm |
| Conversion Factor | 1 ppm = 2.95 $mg/m^3$ |

Occurrence

- The production of acrylamide in 1982 was estimated to be 86 million pounds (U.S. ITC, 1984). Acrylamide is used primarily in the production of polyacrylamide polymers and co-polymers. It is also used as a grouting agent, and approximately 1 million pounds is used for this purpose (U.S. EPA, 1984).

- Acrylamide monomer occurs as a contaminant in polyacrylamide. The monomer may be released to the environment during its production, its use in manufacturing polymers and during the use of polyacrylamides. However, the major source of release occurs as a result of its use as a grout. No information on production and manufacture releases is available. Due to the low vapor pressure of acrylamide, no releases to air are expected (U.S. EPA, 1984).

- Acrylamide has been shown to biodegrade in surface waters within a few days (Brown and Rhead, 1979). Waters which routinely receive acrylamide releases will degrade it even more readily. Hydrolysis of acrylamide to acrylic acid has been reported to occur, but is likely to be a relatively slow reaction (Brown and Rhead 1979; Brown et al. 1980b).

- Acrylamide has not been surveyed for in U.S. food and drinking water. Based upon standards recommended by EPA for polymers used in drinking water, the levels of acrylamide monomer in drinking water have been reported to occur up to 0.5 ug/L (U.S. EPA, 1980). One study in England has reported tap water levels of acrylamide in the low ug/L range (Brown and Rhead, 1979). No information has been identified on the occurrence of acrylamide in food. Low levels of acrylamide also may occur in some foods from the use of polyacrylamides in the manufacture of those foods (U.S. EPA, 1984).

## III. PHARMACOKINETICS

Absorption

- When acrylamide (10 mg/kg) was administered to rats *per os*, it was absorbed rapidly and completely from the gastrointestinal tract (Miller et al., 1982).

- By comparing the blood levels of acrylamide after iv or dermal administration, it was calculated that approximately 25% of either applied dose (2 or 50 mg/kg) was absorbed through the skin (Ramsey et al., 1984).

- Recently, it was reported that 26% of a 0.5% solution of acrylamide was absorbed through the skin of rats in 24 hours. An additional 35% was present in the skin and, potentially, available for absorption. Using excised skin preparations, they found that 67% (54% absorbed and 13% present in skin after washing) of the acrylamide was either absorbed or available for absorption (Frantz et al., 1985).

Distribution

- After acrylamide was administered to rats by gavage, the highest concentrations were found in red blood cells, with lower amounts found in all other tissues examined (Ramsey et al., 1984).

- Results reported by Hashimoto and Aldridge (1970) indicate that acrylamide is bound covalently to proteins or other cellular macromolecules.

- Acrylamide freely crosses the placenta in pregnant female rats, rabbits, dogs and pigs (Edwards, 1976; Ikeda et al., 1983) and is uniformly distributed throughout dog and pig fetal tissue (Ikeda et al., 1983).

- Autoradiographic studies revealed that, after oral administration of 120 mg/kg, acrylamide was widely distributed in male and female mice. The fetuses of pregnant mice were uniformly labeled, except that there was a concentration of acrylamide in fetal skin (Marlowe et al., 1986).

Metabolism

- In rats, acrylamide is metabolized primarily by conjugation with cellular glutathione (Miller et al., 1982).

- The major metabolite (greater than 50%) of acrylamide is the mercapturic acid, N-acetyl-S-(3-amino-3-oxypropyl) cysteine (detected in the urine of rats given acrylamide orally or intravenously (Miller et al., 1982; Ramsey et al., 1984).

- Another metabolite resembling cysteine-S-propionamide has been tentatively identified (Dixit et al., 1982).

Excretion

- In rats, excretion of acrylamide and its metabolic products occurs primarily via the urine (Miller et al., 1982; Ramsey et al., 1984).

- Over 60% of a dose of acrylamide, administered either orally or iv, appeared in the urine of rats within 24 to 72 hours (Miller et al., 1982; Ramsey et al., 1984).

- Minor routes (less than 6%) of acrylamide elimination in rats include fecal excretion (Miller et al., 1982) and release of the amide carbon as $CO_2$ following oxidation (Hashimoto and Aldridge, 1970; Ramsey et al., 1984).

## IV. HEALTH EFFECTS

### Humans

- Acrylamide intoxication has been reported in five individuals (three adults and two children) exposed via ingestion of drinking water contaminated with 400 ppm acrylamide (Igisu et al., 1975). All three adults exhibited symptoms of widespread central and peripheral nervous system dysfunction. The children apparently consumed less water than the adults and were less severely affected.

- Additional reports on human exposure to acrylamide deal primarily with dermal or inhalation exposure of workers. The predominant effects included dysfunction of the central and/or peripheral nervous systems. Quantitative data on dose and duration of exposure generally were not available in these reports (Auld and Bedwell, 1967; Garland and Patterson, 1967; Fullerton, 1969; Davenport et al., 1976; Kesson et al., 1977).

### Animals

- Evaluation of the toxicological data base for acrylamide indicates that this chemical is a cumulative poison. It has been shown that when the total dose of acrylamide administered over either short or longer periods of time reaches 100 to 150 mg/kg, signs of neuropathology begin to appear in many species tested (U.S. EPA, 1985a).

### Short-term Exposure

- Reported acute oral $LD_{50}$ values for rats, guinea pigs and rabbits range from 150 to 180 mg/kg (McCollister et al., 1964). Acute oral $LD_{50}$ values for mice have been reported to range from 107 to 170 mg/kg (NIOSH, 1976; Hashimoto et al., 1981).

- An acute oral $LD_{50}$ for acrylamide in male F-344 rats was reported to be 202.5 (range of 188.9 to 217.3) mg/kg (Pryor et al., 1983).

- Single doses of acrylamide, administered at levels as low as 25 mg/kg, have been shown to significantly increase binding of the neurotransmitter $^3H$-spiroperidol in rat brains (Agrawal et al., 1981).

- Single doses of acrylamide (1 to 100 mg/kg), administered via ip injection, were shown to cause significant inhibition of retrogade axonal transport in rats at doses of 25 mg/kg or greater. Doses of 1, 5, or 15 mg/kg caused no inhibition of transport (Miller et al., 1983).

- Cats given acrylamide in the diet at levels of 20 mg/kg/day for 2 or 3 weeks developed hind limb weakness and general unsteadiness of the posterior half of the body which usually progressed to hind limb paralysis (Leswing and Ribelin, 1969). Microscopically, the affected nerves exhibited degeneration of myelin and axons.

- Dogs that were given acrylamide orally at levels of 5 mg/kg/day developed ataxia and muscular weakness by day 21 of treatment; de-myelination of nerves was evident after 60 days (Thomann et al., 1974).

- Rats administered acrylamide in their drinking water displayed hind limb splaying after 14 days of treatment at a dose of 30 mg/kg/day. Microscopic changes in peripheral nerves were observed in animals dosed at 10 and 30 mg/kg/day. A NOAEL of 3 mg/kg/day was identified (Gorzinski et al., 1979).

- Monkeys treated with an average dose of 7.1 mg/kg/day (administered orally in fruit juice) developed signs of visual impairment after 28 days; ataxia and motor impairment occurred after 46 to 65 days of exposure (Merigan et al., 1982).

Long-term Exposure

- Most adverse health effects of acrylamide appear to be the result of damage to central or peripheral nerve tissue. The most characteristic effects are weakness and ataxia in hind limbs, progressing to paralysis with continued exposure (Pryor et al., 1983; Thomann et al., 1974; McCollister et al., 1964).

- The subacute (5 days/wk for 4 wks) and subchronic (5 days/wk for 15 wks) $LD_{50}$s for acrylamide are 32.0 (25.8 to 38.2) and 17.0 (15.3 to 18.7) mg/kg, respectively (Pryor et al., 1983).

- Acrylamide administered in drinking water to rats at levels of 1 mg/kg/day for 90 days caused no external signs of toxicity, but histologic evidence of neuropathy was noted (axolemmal invaginations) (Burek et al., 1980). The NOAEL in this study was determined to be 0.2 mg/kg/day.

- Cats receiving oral doses of 1 mg/kg/day for 125 days developed ataxia (Kuperman, 1958).

- Cats fed 0.7 mg/kg/day for 240 days developed hind limb weakness; a NOAEL of 0.2 mg/kg/day was identified in this study (McCollister et al., 1964).

Reproductive Effects

- Mice, dosed orally with acrylamide at 10.1 mg/kg/day for 8 to 10 weeks, displayed testicular atrophy and significant reduction in testes weight with degeneration of the epithelial cells of the seminiferous tubules (Hashimoto et al., 1981).

Developmental Effects

- Acrylamide, administered by gavage at 20 mg/kg/day to pregnant rats on days 7 through 16 of gestation, significantly reduced $^{3}$H-spiroperidol binding in the striatal tissue of 2-week-old pups (Agrawal and Squibb, 1981).

Mutagenicity

- Acrylamide did not elicit mutagenic activity in the Salmonella Ames test in strains TA 98, TA 100, TA 1535 and TA 1537 with or without microsomal activation (Bull et al., 1984a).

- In the hepatocyte primary culture DNA repair test, acrylamide did not exert mutagenic effects (Miller and McQueen, 1986).

- Acrylamide induced chromosome breaks and aberrations in spermatogonia of mice exposed to 75 mg/kg/day in the diet for two or three weeks (Shiraishi, 1978).

- In a dominant lethal study, male rats received acrylamide at 0, 15, 30 or 60 mg/L for 80 days in their drinking water (0, 1.5, 2.8 or 5.8 mg/kg/day; Smith et al., 1986). The males were mated to untreated females which were killed on day 14 of gestation. A significant increase in preimplantation loss was noted in females mated to males treated at 60 mg/L. Significant post-implantation loss was observed in females mated to the mid- and high-dose males (30 and 60 mg/L). The authors concluded that acrylamide produces dominant lethality in the male rat. This effect was noted at dose levels at which no hindlimb splaying was evident or significant histopathological lesions of the sciatic nerve occurred as determined by light microscopy.

Carcinogenicity

- Groups of male and female Fischer 344 rats received drinking water containing acrylamide monomer at 0, 0.01, 0.1, 0.5 or 2.0 mg/kg/day for 2 years (Johnson et al., 1986). After a year, significant depression of body weight was observed in the highest dose males. Distal neuropathy was observed in the peripheral nerves of animals in this group. Tumor incidence was not increased significantly in the groups receiving 0.01 or 0.1 mg/kg/day. Male rats receiving 0.5 mg/kg/day had significantly increased incidences of scrotal mesothelioma. Statistically significant increased incidences of tumors in the following tissues were determined in rats treated at 2.0 mg/kg: Females -- mammary gland (benign and malignant), central nervous system (malignant), thyroid gland follicular epithelium (benign and malignant), mouth (benign), uterus (malignant) and clitoral gland (benign); males -- scrotal mesothelioma (malignant) and thyroid gland follicular epithelium (benign).

- Female Swiss-ICR mice, administered acrylamide orally at doses of 5.4, 10.7 or 21.4 mg/kg/day for 2 weeks had a dose-dependent increase of tumors induced by the phorbal ester TPA (2.5 ug/mouse, 3 times per week for 20 weeks; Bull et al., 1984b).

- Male and female mice that received acrylamide orally or intraperitoneally at average daily doses of 2.7, 5.4 or 10.7 mg/kg/for eight weeks showed statistically significant increases in the incidence of lung adenomas (Bull et al., 1984a). Acrylamide was more potent by gavage than by systemic routes.

## V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for One-day, Ten-day, Longer-term (approximately 7 years) and Lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(NOAEL \text{ or } LOAEL) \times (BW)}{(UF) \times (\_\_\_ \text{ L/day})} = \_\_\_ \text{ mg/L } (\_\_\_ \text{ ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect-Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100 or 1,000), in accordance with NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

No adequate dose-response data representing the oral route of exposure are available from which to develop short term risk assessments. However, in view of substantial chemical disposition evidence showing that acrylamide is absorbed rapidly and completely by virtually any route of exposure, it is considered acceptable to use data generated following exposure via other routes.

### One-day Health Advisory

The results of Miller et al. (1983) are considered appropriate for use in calculating the One-day HA. In this study, male Sprague-Dawley rats (five animals per dose) were injected intraperitoneally with a single dose of acrylamide (1 to 100 mg/kg) and the rate of retrograde axonal transport of iodinated nerve growth factor was measured. The authors determined that significant inhibition of transport occurred at or above doses of 25 mg/kg, while no significant changes were seen at or below 15 mg/kg. A NOAEL of 15 mg/kg was identified.

The One-day HA for the 10 kg child is calculated as follows:

$$\text{One-day HA} = \frac{(15 \text{ mg/kg/day})(10 \text{ kg})}{(100)\ (1 \text{ L/day})} = 1.5 \text{ mg/L } (1500 \text{ ug/L})$$

where:

15 mg/kg/day = NOAEL, based on absence of neurotransport inhibition in rats.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

Ten-day Health Advisory

The results of Gorzinski et al. (1979) are considered appropriate for use in calculating the Ten-day HA. In this study, acrylamide was administered at levels of 0, 1, 3, 10 or 30 mg/kg/day in drinking water to male and female CDF Fischer 344 rats for 21 consecutive days. Based upon histological examination of peripheral nerves using both light and electron microscopy, it was determined that axon degeneration and demylenization occurred at the 10 and 30 mg/kg/day dose levels while no significant changes were apparent at the 0, 1 or 3 mg/kg/day dose levels. A NOAEL of 3 mg/kg/day was identified.

The Ten-day HA for the 10 kg child is calculated as follows:

$$\text{Ten-day HA} = \frac{(3 \text{ mg/kg/day})(10 \text{ kg})}{(100)(1 \text{ L/day})} = 0.3 \text{ mg/L (300 ug/L)}$$

where:

3 mg/kg/day = NOAEL, based on absence of neuropathy in rats.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

Longer-term Health Advisory

The results of Burek et al. (1980) are considered appropriate for use in deriving the Longer-term HA. In this study, acrylamide was administered in drinking water for 90 days to male and female CDF rats at dose levels of 0, 0.05, 0.2, 1, 5 or 20 mg/kg/day. Electron microscopy revealed that animals dosed at 1 mg/kg/day exhibited axolemmal invaginations of peripheral nerves. No significant alterations were observed at the 0, 0.05 and 0.2 mg/kg/day dose levels. Thus, based on the most sensitive measure of toxicity employed in these studies (ultrastructural examination of peripheral motor nerves), it was concluded that 0.2 mg/kg was the NOAEL.

The Longer-term HA for the 10 kg child is calculated as follows:

$$\text{Longer-term HA} = \frac{(0.2 \text{ mg/kg/day})\ (10 \text{ kg})}{(100)\ (1 \text{ L/day})} = 0.02 \text{ mg/L } (20 \text{ ug/L})$$

where:

0.2 mg/kg/day = NOAEL, based on absence of neuropathy in rats.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

The Longer-term HA for the 70 kg adult is calculated as follows:

$$\text{Longer-term HA} = \frac{(0.2 \text{ mg/kg/day})\ (70 \text{ kg})}{(100)\ (2 \text{ L/day})} = 0.07 \text{ mg/L } (70 \text{ ug/L})$$

where:

0.2 mg/kg/day = NOAEL, based on absence of neuropathy in rats.

70 kg = assumed body weight of an adult.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

2 L/day = assumed daily water consumption of an adult.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed for synthetic organic chemicals and a value of 10% is assumed for inorganic chemicals. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

The study by Burek et al. (1980) is the most appropriate from which to derive the DWEL. The experimental details are described in the Longer-term Health Advisory section. An additional uncertainty factor of 10 is included in order to accommodate for use of a less-than-lifetime study. From the results of the study, a NOAEL of 0.2 mg/kg was identified.

The RfD and DWEL are calculated as follows:

Step 1: Determination of the Reference Dose (RfD)

$$RfD = \frac{(0.2 \text{ mg/kg/day})}{(1{,}000)} = 0.0002 \text{ mg/kg/day}$$

where:

0.2 mg/kg/day = NOAEL.

1,000 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study of less-than-lifetime duration.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$DWEL = \frac{(0.002 \text{ mg/kg/day})(70 \text{ kg})}{(2 \text{ L/day})} = 0.007 \text{ mg/L (7 ug/L)}$$

where:

70 kg = assumed body weight of an adult.

2 L/day = assumed daily consumption of water of an adult.

Step 3: Determination of the Lifetime Health Advisory

Acrylamide may be classified in group B2: Probable Human Carcinogen. Therefore, a Lifetime HA is not recommended for acrylamide.

The estimated excess cancer risk associated with lifetime exposure to drinking water containing acrylamide at 7 ug/L is approximately $7 \times 10^{-4}$. This estimate represents the upper 95% confidence limit from extrapolations prepared by EPA's Carcinogen Assessment Group using the linearized, multistage model. The actual risk is unlikely to exceed this value, but there is considerable uncertainty as to the accuracy of risks calculated by this methodology.

Evaluation of Carcinogenic Potential

- The data from the Bull et al. (1984a,b) and the Johnson et al. (1986) studies in mice and rats show that acrylamide has significant carcinogenic potential.

- On the basis of the results observed in the rat drinking water study (Johnson et al., 1986), EPA's Carcinogen Assessment Group (CAG) has prepared a draft quantitative risk assessment of acrylamide exposure (U.S. EPA, 1985c). In this draft assessment, CAG derived several

carcinogenic potency factors from different sets of dose-response data. CAG recommended, however, that the human potency factor ($q_1^*$) of 3.7 $(mg/kg/day)^{-1}$ derived from the combination of tumor incidence data on mammary gland, thyroid and uterus in the females be used for estimating the increased lifetime risk of human exposure to acrylamide. Assuming that a 70 kg adult ingests 2 L of water per day over a 70-year lifetime, the estimated excess cancer risk at $10^{-4}$, $10^{-5}$ and $10^{-6}$ would be 1 ug/L, 0.1 ug/L and 0.01 ug/L, respectively. (These estimates were made by the Office of Drinking Water). While recognized as statistically alternative approaches, the range of risks described by using any of these modelling approaches has little biological significance unless data can be used to support the selection of one model over another. In the interest of consistency of approach and in providing an upper bound on the potential cancer risk, the Agency has recommended use of the linearized multistage approach.

- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986), acrylamide is classified in Group B2: Probable human carcinogen. Group B2 contains substances with sufficient evidence of carcinogencity in animals and inadequate evidence from human studies.

## VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- Polyacrylamide products used as coagulant aids in the treatment of drinking water should not have a residual monomer content greater than 0.5 ug/L (U.S. EPA, 1980).

## VII. ANALYTICAL METHODS

- There is no standardized method for the determination of acrylamide in drinking water. An analytical procedure for the determination of acrylamide has been reported in the literature (Brown and Rhead, 1979). This procedure consists of bromination, extraction of the brominated product from water with ethyl acetate and quantification using high performance liquid chromatography (HPLC) with an ultraviolet detector. The concentration of the ethyl acetate to dryness and dissolution in a small volume of distilled water prior to HPLC analysis allows the detection of acrylamide at concentrations of 0.2 ug/L.

## VIII. TREATMENT

- Croll et al. (1974) conducted laboratory experiments to determine the effectiveness of conventional treatments such as coagulation and rapid gravity sand filtration for removal of acrylamide. Several 400 ml samples of Thames River water (pH 7.5) containing 25 mg/L kaolin were coagulated by adding 32 mg/L alum and 2 mg/L of an acrylamide-based polymer with a residual acylamide monomer content of 0.19%. Only about 5% of the residual monomer was removed by this method, suggesting that full-scale water plants using conventional treatment techniques would not be successful in removing acrylamide from drinking water.

- The removal of acrylamide from water by adsorption was studied by Brown et al. (1980a) using various adsorbants including granular activated carbon (GAC) and synthetic resins. The data indicated that GAC may be an effective treatment process. GAC removed 94 to 96% of the acrylamide from a sample containing 0.5 mg/L and 68 to 70% from a sample containing 10 mg/L. The adsorption of acrylamide was not affected significantly by changes in pH. No significant adsorption was achieved by any of the resins tested, including the XAD-2 resin.

- In a laboratory experiment conducted by Croll et al. (1974), water containing 6 ug/L acrylamide (at pH 5.0) was dosed with 8 mg/L powdered activated carbon (PAC) and mixed for 30 minutes. Only 13% of the acrylamide was removed. These data indicate that PAC may not be effective for acrylamide removal from drinking water under conditions used generally in water treatment plants.

- No data were found on the removal of acrylamide by aeration. Since its Henry's Law Constant is $4.38 \times 10^{-3}$ atm (at 20°C), aeration probably would not be very effective.

- Croll et al. (1974) evaluated the effects of some chemical oxidative treatments on removal of acrylamide. Potassium permanganate and ozone were found to be highly effective in removing the substance. Additional data to optimize these processes are needed. Oxidative degradation products also should be identified and evaluated for toxicity and reactivity.

- Selection of individual or combinations of technologies to achieve acrylamide reduction must be based on a case-by-case technical evaluation and an assessment of the economics involved.

## IX. REFERENCES

Agrawal, A.K., P.K. Seth, R.E. Squibb, H.A. Tilson, L.L. Uphouse and S.C. Bondy. 1981. Neurotransmitter receptors in brain regions of acrylamide-treated rats. I: Effects of a single exposure to acrylamide. Pharmacol. Biochem. Behav. 14:527-531.

Agrawal, A.K., and R.E. Squibb. 1981. Effects of acrylamide given during gestation on dopamine receptor binding in rat pups. Toxicol. Lett. 7:233-238.

Auld, R.B., and S.F. Bedwell. 1967. Peripheral neuropathy with sympathetic overactivity from industrial contact with acrylamide. Can. Med. Assoc. J. 96:652-654.

Brown, L., and M. Rhead. 1979. Liquid chromatographic determination of acrylamide monomer in natural and polluted aqueous environment. Analyst. 104:391-399.

Brown, L., K.C.C. Brancroft and M.M. Rhead. 1980a. Laboratory studies on the adsorption of acrylamide monomer by sludge, sediments, clays, peat, and synthetic resins. Water Res. 14:779-781.

Brown, L., M.M. Rhead, K.C.C. Bancroft and N. Allen. 1980b. Model studies of the degradation of acrylamide monomer. Water Res. 14:775-779.

Bull, R.J., M. Robinson, R.D. Laurie, G.D. Stoner, E. Greisiger, J.R. Meier and J. Stober. 1984a. Carcinogenic effects of acrylamide in SENCAR and A/J mice. Cancer Res. 44:107-111.

Bull, R.J., M. Robinson and J.A. Stober. 1984b. Carcinogenic activity of acrylamide in the skin and lung of Swiss-ICR mice. Canc. Lett. 24:209-212.

Burek, J.D., R.R. Albee, J.E. Beyer, T.J. Bell, R.M. Carreon, D.C. Morden, C.E. Wade, E.A. Hermann and S.J. Gorzinski. 1980. Subchronic toxicity of acrylamide administered to rats in the drinking water followed by up to 144 days of recovery. J. Environ. Pathol. Toxicol. 4:157-182.

Croll, B.T., G.M. Arkell and R.P.J. Hodge. 1974. Residues of acrylamide in water. Water Res. 8:989-993.

Davenport, J.G., D.F. Farrell and S.M. Sumi. 1976. Giant axonal neuropathy caused by industrial chemicals. Neurology. 26:919-923.

Dixit, R., P.K. Seth and H. Mukhtar. 1982. Metabolism of acrylamide into urinary mercapturic acid and cysteine conjugates in rats. Drug Metab. Disp. 10:196-197.

Edwards, P.M. 1975. The insensitivity of the developing rat foetus to the toxic effects of acrylamide. Chem.-Biol. Interact. 12:13-18.

Frantz, S.W., M.D. Dryzga, N.L. Freshoar and P.G. Watanabe. 1985. In vivo/in vitro determination of cutaneous penetration of residual monomer from polyacrylamides. Toxicologist. 5:39. (Abst.)

Fullerton, P.M. 1969. Electrophysiological and histological observations on peripheral nerves in acrylamide poisoning in man. J. Neurol. Neurosurg. Psychiat. 32:186-192.

Garland, T.O., and M.W.H. Patterson. 1967. Six cases of acrylamide poisoning. Brit. Med. J. 4:134-138.

Gorzinski, S.J., D. C. Morden, R.R. Albee, C.E. Wade, R.M. Carreon, E.A. Hermann, J.E. Beyer and J.D. Burek. 1979. Results of palatability (12-day) and tolerance (21-day) studies on acrylamide monomer administered in the drinking water to rats.

Hashimoto, K., and W.N. Aldridge. 1970. Biochemical studies on acrylamide, a neurotoxic agent. Biochem. Pharmacol. 19:2591-2064.

Hashimoto, K., J. Sakamoto and H. Tanii. 1981. Neurotoxicity of acrylamide and related compounds and their effects on male gonads in mice. Arch. Toxicol. 47:179-189.

Igisu, H., I. Goto, Y. Kawamura, M. Kato, K. Izumi and Y. Kuroiwa. 1975. Acrylamide encephaloneuropathy due to well water pollution. J. Neurol. Neurosurg. Psychiat. 38:581-584.

Ikeda, G.J., E. Miller, P.P. Sapienza, T.C. Michel, M.T. King, V.A. Turner, H. Blumenthal, W.E. Jackson, III and S. Levin. 1983. Distribution of $^{14}C$-labeled acrylamide and betaine in foetuses of rats, rabbits, beagle dogs and miniature pigs. Food Chem. Toxicol. 21:49-58.

Johnson, K.A., S.J. Gorzinski, K.M. Brodner, R.A. Campbell, C.H. Wolf, M.A. Friedman and R.W. Mast. 1986. Chronic toxicity and oncogenicity study on acrylamide incorporated in the drinking water of Fischer 344 rats. Toxicol. Appl. Pharmacol. 85:154-168.

Kesson, C.M., A.W. Baird and D.H. Lawson. 1977. Acrylamide poisoning. Postgrad. Med. J. 53:16-17.

Kuperman, A.S. 1958. Effects of acrylamide on the central nervous system of the cat. J. Pharmacol. Exp. Ther. 123:180-192.

Leswing, R.J., and W.E. Ribelin. 1969. Physiologic and pathologic changes in acrylamide neuropathy. Arch. Environ. Hlth. 18:22-29.

Marlowe, C., M.J. Clark, R.W. Mast, M.A. Friedman and W.J. Waddell. 1986. The distribution of [$^{14}C$]acrylamide in male and female Swiss-Webster mice studied by whole body autoradiography. Toxicol. Appl. Pharmacol. 86:457-465.

McCollister, D.D., F. Oyen, and V.K. Rowe. 1964. Toxicology of acrylamide. Toxicol. Appl. Pharmacol. 6:172-181.

Merigan, W.H., E. Barkdoll and J.P.J. Maurissen. 1982. Acrylamide-induced visual impairment in primates. Toxicol. Appl. Pharmacol. 62:342-345.

Miller, M.J., D.E. Carter and I.G. Sipes. 1982. Pharmacokinetics of acrylamide in Fischer-344 rats. Toxicol. Appl. Pharmacol. 63:36-44.

Miller, M.J., and C.A. McQueen. 1986. The effect of acrylamide on hepatocellular DNA repair. Environ. Mutagen. 8:99-108.

Miller, M.S., M.J. Miller, T.F. Burks and I.G. Sipes. 1983. Altered retrograde axonal transport of nerve growth factor after single and repeated doses of acrylamide in the rat. Toxicol. Appl. Pharmacol. 69:96-101.

Miller, M.S., and P.S. Spencer. 1984. Single doses of acrylamide reduce retrograde transport velocity. J. Neurochem. 43:1401-1408.

NIOSH. 1976. National Institute for Occupational Safety and Health. Criteria for a recommended standard...occupational exposure to acrylamide. U.S. Dept. of Health, Education and Welfare, Public Health, Center for Disease Control.

Pryor, G.T., E.T. Uyeno, H.A. Tilson and C.L. Mitchell. 1983. Assessment of chemicals using a battery of neurobehavioral tests: A comparative study. Neurobehavioral. Toxicol. Teratol. 5:91-117.

Ramsey, J.C., J.D. Young and S.J. Gorzinski. 1984. Acrylamide: Toxicodynamics in rats. Unpublished report. Dow Chemical Co., Midland, MI.

Shiraishi, Y. 1978. Chromosome aberrations induced by monomeric acrylamide in bone marrow and germ cells of mice. Mutation. Res. 57:313-324.

Smith, M.K., H. Zenick, R. Preston, E.L. George and R.E. Long. 1986. Dominant lethal effects of subchronic acrylamide administration in the male Long-Evans rat. Mutat. Res. 173:273-278.

Thomann, P., W.P. Koella, G. Krinke, H. Petermann, F. Zak and R. Hess. 1974. The assessment of peripheral neurotoxicity in dogs: Comparative studies with acrylamide and clioquinol. Agts. Act. 4:47-53.

U.S. EPA. 1980. U.S. Environmental Protection Agency. Coagulant aids in the treatment of drinking water. Office of Drinking Water.

U.S. EPA. 1984. U.S. Environmental Protection Agency. Miscellaneous synthetic organic chemicals. Occurrence in drinking water, food, and air. Office of Drinking Water.

U.S. EPA. 1985a. U.S. Environmental Protection Agency. Draft health effects criteria document for acrylamide. Criteria and Standards Division. Office of Drinking Water.

U.S. EPA. 1985b. U.S. Environmental Protection Agency. Draft technologies and costs for the removal of synthetic organic chemicals from potable water supplies. Science and Technology Branch. Criteria and Standards Division. Office of Drinking Water.

U.S. EPA. 1985c. U.S. Environmental Protection Agency. Assessment of carcinogenic risk of exposure to acrylamide. (Draft). A staff paper prepared by W.C. Pepelko and J. Cagliano for the Office of Health and Environmental Assessment, Office of Research and Development.

U.S. EPA. 1986. U.S. Environmental Protection Agency. Guidelines for carcinogen risk assessment. Federal Register. 51(185):33992-34003. September 24.

U.S. ITC. 1984. United States International Trade Commission. Synthetic organic chemicals. U.S. production and sales - 1983. U.S. ITC Publication No. 1588, Washington, D.C., pp. 255 and 268.

Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals. 2nd Edition. Van Nostrand Reinhold Co., New York.

Windholz, M., ed. 1976. The Merck Index. 10th Edition. Merck and Co., Inc. Rahway, NJ.

# BENZENE

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

## I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

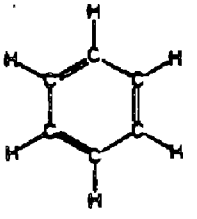
Health Advisories are developed for One-day, Ten-day, Longer-term (approximately 7 years, or 10% of an individual's lifetime) and Lifetime exposures based on data describing noncarcinogenic end points of toxicity. Health Advisories do not quantitatively incorporate any potential carcinogenic risk from such exposure. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

This Health Advisory is based on information presented in the Office of Drinking Water's Draft Health Effects Criteria Documents (CD) for Benzene (U.S. EPA, 1983b, 1985a). The HA and CD formats are similar for easy reference. Individuals desiring further information on the toxicological data base or rationale for risk characterization should consult the CDs. The CDs are available for review at each EPA Regional Office of Drinking Water counterpart (e.g., Water Supply Branch or Drinking Water Branch), or for a fee from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Rd., Springfield, VA 22161, PB # 86-118122/AS. The toll-free number is (800) 336-4700; in the Washington, D.C. area: (703) 487-4650.

## II. GENERAL INFORMATION AND PROPERTIES

CAS No. 71-43-2

Structural Formula



Synonyms

- None

Uses

- Additive to gasoline to increase the octane.
- Chemical intermediate in the synthesis of compounds such as: styrene, synthetic rubber, phenol, alkylarnesulfonate detergent, nitrobenzene (aniline), and cyclohexane.

Properties (Von Gemert and Nettenbreijer, 1977; Windholz, 1983)

| | |
|---|---|
| Chemical Formula | $C_6H_6$ |
| Physical State | Volatile, colorless flammable liquid, aromatic hydrocarbon |
| Boiling Point | 80.100°C |
| Freezing Point | 5.53°C |
| Density at 25°C | 0.8765 g/mL |
| Vapor Pressure at 26°C | 100 mmHg |
| Water Solubility at 25°C | 1.8 g/L |
| Odor Threshold, in air | 4.9 $mg/m^3$ (characteristic odor) |
| Odor Threshold, in water | 2.0 mg/L |

Occurrence

- Benzene is produced at low levels in a number of biological processes and is a component of petroleum (U.S. EPA, 1983a).

- Benzene is produced in large amounts, e.g., 9 billion lbs in 1981 (U.S. ITC, 1984), and is used largely as a feedstock on the production of other chemicals. Small amounts of benzene have been used as a solvent; however, this use has been discontinued. Benzene also is produced indirectly in large volumes, such as during gasoline refining and other operations. The average benzene content of gasoline is less than 1% (Runion, 1975).

- Releases of benzene to the environment are largely to air due to its volatile nature, with smaller amounts to water and soil. Releases of benzene to water are mainly due to spills of gasoline and other petroleum products and from benzene's previous use as a solvent. Because of the widespread use of petroleum products, releases of benzene occur nationwide (Mara and Lee, 1978; OSHA, 1978).

- Benzene released to surface water rapidly volatilizes to the air.

- Benzene degrades rapidly in air with a half life of less than one day.

- Benzene released to the ground binds somewhat to soil and slowly migrates with ground water. Benzene is biodegraded poorly and is expected to be stable in ground water (Mara and Lee, 1978).

- Benzene occurs in drinking water, food, and air (U.S. EPA, 1983b).

- Benzene occurs in both ground water and surface public water supplies, with higher levels occurring in ground water supplies. Based upon Federal drinking water surveys, approximately 1.3% of all ground water systems are estimated to contain benzene at levels greater than 0.5 ug/L. The highest level reported in the surveys for ground water was 80 ug/L. Approximately 3% of all surface water system are estimated to be contaminated at levels higher than 0.5 ug/L. None of the systems are expected to contain levels higher than 5 ug/L.

- Benzene is found at ppb levels in a large number of foods as a naturally occurring compound (U.S. EPA, 1983b).

- Benzene is found in air in urban and suburban areas, generally at average levels of less than 10 ppb (U.S. EPA, 1983b), but at higher levels in certain metropolitan areas such as Los Angeles where Lonneman et al. (1968) measured an average benzene concentration of 15 ppb with a maximum of 57 ppb. Benzene has been reported to occur in indoor air at levels higher than those found outdoors. Based upon the available evidence, the major source of benzene exposure is believed to be from air.

## III. PHARMACOKINETICS

### Absorption

- As a neutral, low molecular weight, lipid soluble material, benzene is readily absorbed via inhalation and ingestion. It is poorly absorbed through the intact skin (NIOSH, 1974).

- Administration of benzene to rats via inhalation or ingestion results in its rapid uptake and excretion, mainly via exhalation of unchanged benzene (Rikert et al., 1979; Parke and Williams, 1953). The exhalation of unchanged benzene has also been reported in dogs (Schrenk et al., 1941), rabbits (Parke and Williams, 1953) and mice (Andrews et al., 1977a).

- When humans are exposed to benzene in air, absorption via inhalation is approximately 50% (Nomiyama and Nomiyama, 1974 a,b).

Distribution

- Benzene is highly lipid soluble which accounts for its tendency to accumulate in fatty tissue (U.S. EPA, 1983b).

- In mice, benzene is stored in the bone marrow, liver and body fat (Snyder et al., 1978).

Metabolism

- The metabolic pathway for benzene has been thoroughly delineated in benzene background documents including U.S. EPA (1983b, 1985a). In humans, phenol sulfate is the major metabolite of benzene until 400 mg/L levels are reached in the urine. Beyond that level, glucuronide conjugates are also present in the urine (Sherwood, 1972).

Excretion

- The rate of elimination of benzene in humans is biphasic with initially about 16.2% eliminated unchanged via exhalation in 5 hours (Nomiyama and Nomiyama, 1974a,b). The remainder of the benzene is stored in the fatty tissues and is excreted much more slowly. Benzene has a half-life of 0.7 hours in rats (Rickert et al., 1979).

## IV. HEALTH EFFECTS

Humans

- Acute exposure to high levels of benzene produces primarily central nervous system effects such as dizziness, giddiness, exhilaration, nausea, vomiting, headache, drowsiness, staggering, loss of balance, narcosis, coma and death. Exposure to 25,000 ppm in air is rapidly fatal (NAS, 1976). At nonlethal levels, mild central nervous system effects appear to be concentration-dependent and are rapidly reversible. Lower levels of benzene do not seem to elicit these effects no matter how long the exposure (U.S. EPA, 1983b).

- Benzene has been a known hematological poison since the 19th century when cases of aplastic anemia in workers fabricating bicycle tires were described by Santesson (1897).

- Benzene causes bone marrow toxicity resulting in a continuum of changes in the circulating formed blood elements ranging from a mild decrease in platelets to aplastic anemia, a rapidly fatal disease. The lowest level that produced changes in platelet counts in workers appears to be 10 ppm (Doskin 1971; Chang, 1972).

- Benzene causes acute myeloblastic leukemia, acute myelomonocytic leukemia and erythroleukemia (Rinsky et al., 1981). The exposure levels resulting in leukemia have not been determined.

- Epidemiologic studies show that exposure to benzene via inhalation at levels of 10 ppm or lower for approximately one year increases the risk of cancer by 560 fold and exposure for five or more years increases the risk by 2,100 fold (Rinsky et al., 1981).

- Immune system depression resulting from benzene exposure is a well known toxicological phenomenon. Susceptibility to tuberculosis (White and Gammon, 1914) and pneumonia (Winternitz and Hirschfelder, 1913) have been demonstrated to be increased in benzene-treated rabbits.

- Serum levels of IgG and IgA (immunoglobulins) were shown to be decreased in benzene workers (Lange et al., 1973; Smolick et al., 1973).

- These observations in conjunction with the well known ability of benzene to depress leukocytes which play a significant role in protection against infectious agents, may explain why individuals regularly exposed to benzene readily succumb to infection and the terminal event in severe benzene toxicity is often acute overwhelming infection.

- Benzene has caused chromosomal aberrations in exposed workers (Kissling and Speck, 1969; Tough et al., 1970; Forni et al., 1971).

Animals

Short-term Exposure

- Dogs exposed to benzene by inhalation at 600 to 1,000 ppm for 12 to 15 days developed leukopenia (reduction in the number of circulating leukocytes) (Hough and Freeman, 1944).

- Mice exposed to benzene by inhalation at 600 to 1,000 ppm developed fatal anemia within 12 to 15 days (Petrini, 1941).

- When exposed to benzene by inhalation at 80 to 85 ppm, rats (136 doses), guinea pigs (193 doses), rabbits (187 doses) and monkeys (187 doses) developed leukopenia (Wolf et al., 1956).

- Deichmann et al. (1963) conducted a series of experiments in which Sprague-Dawley rats (40/group) were exposed to benzene vapor for 5 hours per day, 4 days per week for 6 to 31 weeks. Average exposure concentrations ranged from 15 to 831 ppm. Rats exposed to benzene vapor at 61, 65 or 831 ppm developed severe leukopenia within 2 to 4

weeks. At 44 and 47 ppm, moderate leukopenia was observed, especially in females, in 5 to 8 weeks, and no leukopenia was observed when animals were exposed to 29 or 31 ppm for 4 months. Therefore, 31 ppm (96 mg/$m^3$) is identified as the NOAEL for this study.

Long-term Exposure

- Sprague-Dawley rats and both AKR/J and C57BL/6J mice were exposed to benzene by inhalation at concentrations of either 100 ppm or 300 ppm 6 hours per day, 5 days per week for life by Snyder et al. (1980). Both rats and mice exhibited lymphocytopenia, anemia and decreased survival time. In mice these effects were accompanied by granulocytosis and reticulocytosis. A later evaluation of the same study showed preliminary evidence of carcinogenicity, bone marrow hypoplasia, anemia and lymphocytopenia (Snyder et al., 1980).

Reproductive Effects

- There is no strong evidence that benzene produces teratogenic effects. It is a potent inhibitor of growth in utero (U.S. EPA, 1983b).

Mutagenicity

- Benzene was found not to be mutagenic in Drosophila melanogaster by Nylander et al. (1978). In this study, newly hatched larvae were exposed to media containing benzene at a concentration of 1% or 2%. Mutation, as measured by a shift in eye pigmentation, was not noted at either concentration.

- Benzene at 20 or 600 ug/plate was shown not to be mutagenic in Salmonella typhimurium when tested with or without metabolic activation in strains TA100, TA98, TA1535, TA1537 and TA1538. Levels up to 880 ug/plate with activation were not mutagenic in strains TA98 and TA1000 (Dean, 1978).

- Benzene oxide , the presumed initial metabolite of benzene, was mutagenic without activation in an Ames test using S. typhimurium (Pulkrabek et al., 1980).

- A marked increase in sister chromatid exchanges (SCE) was reported in DBA/2 mice exposed to benzene at 3100 ppm by inhalation for 4 hours (Tice et al., 1980).

Carcinogenicity

- Benzene has produced both solid tumors and leukemias in Sprague-Dawley rats (Maltoni and Scartano, 1979). Benzene dissolved in olive oil was administered by gavage to 13 week old Sprague-Dawley rats at doses of 50 or 250 mg/kg/day 4 to 5 days a week for 52 weeks. The animals were then allowed to live until spontaneous death. The high dose group consisted of 35 rats of each sex; the low dose and vehicle control goups consisted of 30 rats of each sex. After 20 weeks of exposure, the denominators were corrected (numbers of animals

surviving) to reflect compound-related deaths. The 250 mg/kg group then consisted of 33, males and 32 female rats; the 50 mg/kg and control groups consisted of 28 male and 30 female rats each. At the end of 144 weeks, 25% of the females had Zymbal gland tumors, 6.2% had skin carcinomas and and 12.1% had leukemias.

## V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for One-day, Ten-day, Longer-term (approximately 7 years) and Lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(NOAEL \text{ or } LOAEL) \times (BW)}{(UF) \times (\_\_\_ \text{ L/day})} = \_\_\_ \text{ mg/L } (\_\_\_ \text{ ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect-Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100 or 1,000), in accordance with NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

### One-day Health Advisory

Insufficient data are available to calculate a One-day HA for benzene. Similarly, the National Academy of Sciences (1982) has stated that there are insufficient data to determine a one-day SNARL. The Ten-day HA (0.235 mg/L or 235 ug/L) is considered to be adequately protective for a one-day exposure as well.

### Ten-day Health Advisory

The calculation of the Ten-day HA is based on the study of Deichman, et al. (1963) who exposed Sprague-Dawley rats to benzene by inhalation 6 hours per day, 4 days per week, at a broad range of concentrations and monitored their hematology weekly. By the second week of treatment, there was definite hematological impairment, including severe leukopenia, at the 61, 65 and 631 ppm exposure concentration and moderate leukopenia, especially in females, at the 44 and 47 ppm exposure concentrations. Leukopenia was not observed, however, at 29 or 31 ppm.

Using the NOAEL of 31 ppm (96 $mg/m^3$), the Ten-day HA is calculated as follows:

Step 1: Determination of the Total Absorbed Dose (TAD)

$$TAD = \frac{(96\ mg/m^3)\ (6\ m^3)\ (0.5)\ (4)}{(70\ kg)\qquad\qquad (7)} = 2.35\ mg/kg/day$$

where:

96 mg/m3 = 31 ppm exposure; NOAEL for leukopenia in rats.

6 m3 = volume of air inhaled during 6 hours of exposure; based upon equivalent lung to whole body ratios for adult humans and rats (Olson and Gehring, 1976).

0.5 = pulmonary absorption factor for benzene (Nomiyama and Nomiyama, 1974a,b).

4/7 = conversion of total weekly dose to equivalent daily dose.

Step 2: Determination of the Ten-day Health Advisory

$$\text{Ten-day HA} = \frac{(2.35\ mg/kg/day)(10\ kg)}{(100)\ (1\ L/day)} = 0.235\ mg/L\ (235\ ug/L)$$

where:

2.35 mg/kg/day = TAD.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

Longer-term Health Advisories

Longer-term Health Advisories have not been calculated because of the carcinogenic potency of benzene.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body

weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed for synthetic organic chemicals and a value of 10% is assumed for inorganic chemicals. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

A Lifetime Health Advisory has not been calculated because of the carcinogenic potency of benzene.

Evaluation of Carcinogenic Potential

- Benzene is a known human carcinogen.
- U.S. EPA (1985a) has estimated that excess upper-bound lifetime cancer risks of $10^{-4}$, $10^{-5}$ and $10^{-6}$ correspond to benzene in drinking water at concentrations of 70, 7 and 0.7 ug/L, respectively.
- IARC (1982) has classified benzene as a Group 1: Human carcinogen.
- Applying the criteria in the EPA guidelines for assessment of carcinogenic risk (U.S. EPA, 1986), benzene may be classified as a Group A: human carcinogen. This category is for substances for which there is sufficient evidence from epidemiologic studies to support the causal association between exposure to the agents and cancer.

## VI. OTHER CRITERIA, STANDARDS AND GUIDANCE

- The National Academy of Sciences has not calculated SNARLS or ADIs for benzene (NAS, 1982).
- The current OSHA recommendation for a 10-hour time-weighted average (TWA) exposure to benzene in air is 3.2 ug/L (1 ppm) and is a lowest feasible level in the work place. This level would allow a daily dose of 16 mg.

## VII. ANALYTICAL METHODS

- Analysis of benzene is by a purge-and-trap gas chromatographic procedure used for the determination of volatile aromatic and unsaturated organic compounds in water (U.S. EPA, 1985b). This method includes the bubbling of an inert gas through the sample and trapping benzene on an adsorbent material which is then heated to drive off benzene onto a gas chromatographic column. The gas chromatograph is temperature-programmed to separate the resulting analytes which are then detected by the photoionization detector. This method is applicable to the measurement of benzene over a concentration range of 0.02 to 1500 ug/L. Confirmatory analysis is by mass spectrometry (U.S. EPA, 1985c), which has a detection limit of 0.2 ug/L for benzene.

## VIII. TREATMENT TECHNOLOGIES

- Treatment technologies which will remove benzene from water include granular activated carbon (GAC) adsorption, air stripping and boiling.

- Dobbs and Cohen (1980) developed adsorption isotherms for several organic chemicals including benzene. It was reported that Filtrasorb® 300 carbon columns exhibited adsorptive capacities of 0.007 mg, 0.03 mg, 1 mg and 40 mg benzene/g carbon (Beaudet et al., undated, Bilello and Beaudet, 1981).

- Air stripping is an effective, simple and relatively inexpensive process for removing benzene and other organics from water. Benzene is amenable to air stripping on the basis of its Henry's Law Constant of 240 atm at 20°C (Kavanaugh and Trussel, 1980). Cummins (1985) reported that benzene could be removed from water contaminated by a gasoline spill by packed column air stripping. In this field study, 24' x 2' columns packed with plastic saddles were used to treat water containing 190 ug/L benzene and other contaminants. Removal efficiencies of 70 to 100% were obtained using air-to-water ratios of 8.1:1 to 87:1. At air-to-water ratios of 17:1 or greater, efficiencies were 97% or better. Use of this process, however, transfers the contaminant directly to the air stream. When considering the use of air stripping as a treatment process, it is suggested that careful consideration be given to the overall environmental consequences and various hazards associated with release of this chemical into the air.

- Boiling also is effective in eliminating benzene from water. Studies have shown that 10 minutes of vigorous boiling will remove 99% of the benzene (Love et al., 1983).

## IX. REFERENCES

Andrews, L.S., E.W. Lee, C.M. Witmer, J.J. Kocsis and R. Snyder. 1977. Effects of toluene on the metabolism, disposition and hemopoietic toxicity of $^{3}$H-benzene. Biochem. Pharmacol. 26:293-300.

Beaudet, B.A., E.M. Keller, L.J. Bilello and R.J. Turner. Undated. Removal of specific organic contaminants from industrial wastewaters by granular activated carbon adsorption. Incomplete citation.

Bilello, L.J., and B.A. Beaudet. 1981. Evaluation of activated carbon by the dynamic mini-column adsorption technique. Incomplete citation.

Chang, I.W. 1972. Study on the threshold limit value of benzene and early diagnosis of benzene poisoning. J. Cath. Med. Coll. 23:429.

Cummins, M.D. 1985. Field evaluation of packed column air stripping. U.S. EPA.

Dean. B.J. 1978. Genetic toxicology of benzene, toluene, xylenes and phenols. Mut. Res. 47:75.

Deichmann, W.B., W.E. MacDonald and E. Bernal. 1963. The hemopoietic tissue toxicity of benzene vapors. Toxicol. Appl. Pharmacol. 5:201-224.

Dobbs, R.J., and J.M. Cohen. 1980. Carbon isotherms for toxic organics. U.S. EPA.

Doskin, T.A. 1971. Effect of age on the reaction to a combination of hydrocarbons. Hygiene and Sanitation. 36:379.

Forni, A., E. Pacifico and A. Limonta. 1971. Chromosome studies in workers exposed to benzene or toluene or both. Arch. Environ. Health. 22:373-354.

Gemert Von, L.J., and A.H. Nettenbreijer. 1977. Compilation of odor threshold values in air and water. National Institute for Water Supply, Voorburg, Netherlands.

Gerarde, H.W. 1960. Toxicology and biochemistry of aromatic hydrocarbons. Elsevier Publishing Company., N.Y.

Hough, H., and S. Freeman. 1944. Relative toxicity of commercial benzene and a mixture of benzene, toluene and xylene. Fed. Proc. 3:20.

IARC. 1982. International Agency for Research on Cancer. IARC monographs, some industrial chemicals and dyestuffs. 29, 83.

Kavanaugh, M.C., and R.P. Trussel. 1980. Design of aeration towers to strip volatile contaminants from drinking water. JAWWA. Dec.

Kissling, M., and B. Speck. 1969. Chromosome aberrations in experimental benzene intoxication. Helv. Med. Acta 36:59.

Lange, A.R., Smolick, W. Zatonski and J. Syzmanska. 1973. Serum immunoglobulin levels in workers exposed to benzene, toluene and xylene. Int. Arch. Arbeitsmed. 31:248.

Lonneman, W.A., T.A. Bellar and A.P. Altshuller. 1968. Aromatic hydrocarbons in the atmosphere of the Los Angeles basin. Environ. Sci. Technol. 2(11):1017.

Love, O.T., R.J. Miltnen, R.G. Eilers and Fronk-Leist. 1983. Treatment of volatile organic compounds in drinking water. U.S. EPA, MERL, Cincinnati, OH 45268. EPA-600/8-83-019.

Maltoni, C., and C. Scartano. 1979. First experimental demonstration of the carcinogenic effects of benzene: Long term bioassays on Sprague-Dawley rats by oral administration. Med. Lav. 70:352-357.

Mara, S.J., and S.S. Lee. 1978. Assessment of human exposures to atmospheric benzene. U.S. Environmental Protection Agency, Research Triangle Park, NC. EPA-450/3-78-031.

NAS. 1976. National Academy of Sciences. Health effects of benzene: A review. Committee on Toxicology, Assembly of Life Sciences, National Research Council. Wash. D.C.

NAS. 1982. National Academy of Sciences. Drinking Water and Health. Volume 4. National Academy Press, Washington, D.C..

NIOSH. 1974. National Institute of Occupational Safety and Health. Criteria for a recommended standard . . . occupational exposure to benzene. U.S. DHEW, Washington, DC. PB246 700.

Nomiyama, K., and H. Nomiyama. 1974a. Respiratory retention uptake and excretion of organic solvents in man. Benzene, toluene, n-hexane, trichloroethylene, acetone, ethyl acetate, and ethyl alcohol. Int. Arch. Arbeitsmed. 32:75-83.

Nomiyama, K., and H. Nomiyama. 1974b. Respiratory elimination of organic solvents in man. Benzene, toluene, n-hexane, trichloroethylene, acetone, ethyl acetate, and ethyl alcohol. Int. Arch. Arbeitsmed. 32:85-91.

Nylander, P., H. Olaffsson, B. Rasmuson and H. Svahlin. 1978. Mutagenic effects of petrol in Drosphila melanogaster. I. Effects of benzene and 1,2-dicloroethane. Mut. Res. 57:163.

OSHA. 1978. Occupational Safety and Health Administration. Final environmental impact statement. Benzene. U.S. Dept. of Labor, Washington, DC.

Parke, D.V., and R.T. Williams. 1953. Studies in detoxication. The metabolism of benzene containing $^{14}C$ benzene. Biochem. J. 54:231-238.

Petrini, M. 1941. Investigations on acute and subacute poisoning by benzene. Rass. Med. Ind. 12:435-476. (In Italian)

Pulkrabek, P., T. Kinoshita and A.M. Jeffery. 1980. Benzene oxide: In vitro mutagenic and toxic effects. Proc. 16th Ann. Meeting Amer. Soc. Clin. Oncol. 21:107.

Rinsky, R.A., R.J. Young, A and B. Smith. 1981. Leukemia in benzene workers. Amer. J. Ind. Med. 2:217-245.

Rickert, D.E., T.S. Baker, J.S. Bus, C.S. Barrow and R.D. Irons. 1979. Benzene disposition in the rat after exposure by inhalation. Toxicol. Appl. Pharmacol. 49:417-423.

Runion, H.E. 1975. Benzene in gasoline. Am. Indust. Hyg. Assn. J. 36:338-350.

Santesson, C.G. 1897. Uber chronische vergiftung mit steinkohlentheerbenzin; vir todesfalle. Arch. Hyg. Berl. 31:336.

Schrenk, H.H., W.P. Yant, S.J. Pearce, F.A. Patty and R.R. Sayers. 1941. Absorption, distribution and elimination of benzene by body tissues and fluids of dogs exposed to benzene vapor. J. Ind. Hyg. Toxicol. 23:20-34.

Sherwood, R.J. 1972. Benzene: The interpretation of monitoring results. Ann. Occup. Hyg. 15:409-421.

Smolick, R., K.Grzybek-Hryncewica, A. Lange and W. Zatonski. 1973. Serum complement level in workers exposed to benzene, toluene and xylene. Int. Arch. Arbeitmed. 31:243.

Snyder, R., E.W. Lee and J.J. Kocsis. 1978. Binding of labeled benzene metabolites to mouse liver and bone marrow. Res. Commun. Chem. Pathol. Pharmacol. 20:191-194.

Snyder, C.A., B.D. Goldstein and A.R. Sellakumar. 1980. Hematotoxicity of inhaled benzene to Sprague-Dawley rats and AKR mice at 300 ppm. J. Toxicol. Environ. Health. 4:605-618.

Tice, R.R., D.L. Costa and R.T. Drew. 1980. Cytogenetic effects of inhaled benzene in murine bone marrow: Induction of sister chromatid exchanges, chromosomal aberrations, and cellular proliferation inhibition in DBA/2 mice. Proc. Natl. Acad. Sci. USA 77:21483152B.

Tough, I.M., P.G. Smith, W.M. Court Brown and D.G. Harnden. 1970. Chromosome studies on workers exposed to atmospheric benzene: The possible influence of age. Europ. J. Cancer 6:49-55.

U.S. EPA. 1979. U.S. Environmental Protection Agency. Water related environmental fate of 129 priority pollutants. Office of Water Planning and Standards, EPA-440/4-79-029, December 1979.

U.S. EPA. 1983a. U.S. Environmental Protection Agency. Benzene occurrence in drinking water, food, and air. Office of Drinking Water. Washington, DC.

U.S. EPA. 1983b. U.S Environmental Protection Agency. Benzene draft criteria document. Office of Drinking Water. Washington, DC.

U.S. EPA. 1984a. U.S. Environmental Protection Agency. Intermedia priority pollutants guidance documents. Office of Toxic Substances. Washington, DC.

U.S. EPA. 1984b. U.S. Environmental Protection Agency. National primary drinking water regulations; Volatile synthetic organic chemicals; Proposed rulemaking. Fed. Reg. 49(114):24330-24355. June 12.

U.S. EPA. 1985a. U.S. Environmental Protection Agency. Proposed RMCL background document for Benzene for the Office of Drinking Water, Criteria and Standards Division. Washington, DC.

U.S. EPA. 1985b. U.S. Environmental Protection Agency. Method 503.1. Volatile aromatic and unsaturated organic compounds in water by purge and trap gas chromatography. Environmental Monitoring and Support Laboratory, Cincinnati, Ohio. June 1985.

U.S. EPA. 1985c. U.S. Environmental Protection Agency. Method 524.1. Volatile organic compounds in water by purge and trap gas chromatography/ mass spectrometry. Environmental Monitoring and Support Laboratory, Cincinnati, Ohio. June 1985.

U.S. EPA. 1986. U.S. Environmental Protection Agency. Guidelines for carcinogenic risk assessment. Fed. Reg. 51(185):33992-34003. September 24.

U.S. ITC. 1984. U.S. International Trade Commission. Synthetic organic chemicals. United States production, 1983. U.S. ITC Publication 1422. Washington, D.C.

White, W.C., and A.M. Gammon. 1914. The influence of benzol inhalation on experimental pulmonary tuberculosis in rabbits. Trans. Assoc. Amer. Phys. 29:332-337.

Windholz, M. 1983. The Merck Index. 10th Edition. Merck and Co., Inc. Rahway, NJ.

Winternitz, M.C., and A.D. Hirschfelder. 1913. Studies on experimental pneumonia in rabbits: Parts I-III. J. Exptl. Med. 17:664.

Wolf, M.A., V.K. Rowe, D.D. McCollister, R.L. Hollingsworth and F. Oyen. 1956. Toxicological studies of certain alkylated benzenes and benzene. Arch. Ind. Health. 14:387-389.

March 31, 1987

# CARBON TETRACHLORIDE

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

## I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

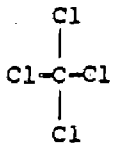
Health Advisories are developed for One-day, Ten-day, Longer-term (approximately 7 years, or 10% of an individual's lifetime) and Lifetime exposures based on data describing noncarcinogenic end points of toxicity. Health Advisories do not quantitatively incorporate any potential carcinogenic risk from such exposure. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

This Health Advisory (HA) is based on information presented in the Office of Drinking Water's Health Effects Criteria Document (CD) for carbon tetrachloride (U.S. EPA, 1985a). The HA and CD formats are similar for easy reference. Individuals desiring further information on the toxicological data base or rationale for risk characterization should consult the CD. The CD is available for review at each EPA Regional Office of Drinking Water counterpart (e.g., Water Supply Branch or Drinking Water Branch), or for a fee from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Rd., Springfield, VA 22161, PB #85-118155/AS. The toll-free number is (800) 336-4700; in the Washington, D.C. area: (703) 487-4650.

## II. GENERAL INFORMATION AND PROPERTIES

CAS No. 56-23-5

Structural Formula



Synonyms

- Methane tetrachloride, tetrachloromethane, $CCl_4$, perchloroethane.

Uses

- The major use of $CCl_4$ is in the production of chlorofluorocarbons, which are used as refrigerants, foam-blowing agents and solvents. Carbon tetrachloride also is used in fumigants, as a solvent in metal cleaning and in manufacture of paints and plastics (Rams, et al., 1979). It is being replaced in grain fumigation by other registered pesticides (U.S. EPA, 1980a).

Properties (U.S. EPA, 1985a)

| | |
|---|---|
| Chemical Formula | $CCl_4$ |
| Molecular Weight | 153.8 |
| Physical State | Colorless liquid |
| Boiling Point | 76.5°C |
| Melting Point | -23°C |
| Density | $d_4^{20}$ 1.594 |
| Vapor Pressure | 115.2 mm Hg at 25°C |
| Water Solubility | 800 mg/L |
| Taste Threshold | not available |
| Odor Threshold | 0.52 mg/L (Amoore and Hautala, 1983) |
| Conversion Factor | 6.4 mg/$m^3$ = 1 ppm |

## Occurrence

- Carbon tetrachloride ($CCl_4$) is a synthetic chemical with no natural sources (U.S. EPA, 1983).

- Production of $CCl_4$ was approximately 600 million lbs in 1983 (U.S.ITC, 1983). Carbon tetrachloride also is produced as a by-product of the manufacture of a number of other chlorinated materials.

- Current major sources of $CCl_4$ released to the environment are from accidental releases from production and uses. Previously, large amounts of $CCl_4$ were released from its use as a solvent. Most of the releases of $CCl_4$ occur to the atmosphere by evaporation because of its high volatility. Some $CCl_4$ may be released to the environment during the disposal of wastes in landfills or surface waters. The majority of releases will occur in the areas near its production and use (U.S. EPA, 1983).

- Carbon tetrachloride released to: (1) the environment is fairly stable; (2) the air, degrades slowly; (3) surface waters, migrates to the atmosphere in a few days or weeks; and (4) the land, does not sorb onto soil and migrates readily to ground water. Carbon tetrachloride is expected to remain in ground water for months to years. Unlike more highly chlorinated compounds, $CCl_4$ does not bioaccumulate in individual animals or food chains (U.S. EPA, 1979).

- Carbon tetrachloride occurs ubiquitously in the air but at concentrations of less than 10 ppt. Carbon tetrachloride is a fairly rare contaminant in ground and surface waters, with higher levels found in ground water. The Agency estimates that less than 1% of all ground waters derived drinking water systems have levels of $CCl_4$ greater than 0.5 ug/L and less than 0.2 % greater than 5 mg/L (U.S. EPA, 1983).

- Very limited information is available on the occurrence of carbon tetrachloride in food. In the past, $CCl_4$ has been used as a grain fumigant and low levels have been reported to occur in some foods from this use (U.S. EPA, 1983).

- The major source of exposure to $CCl_4$ is from contaminated air. Water and food are only a minor sources.

# III. PHARMACOKINETICS

## Absorption

- Carbon tetrachloride is absorbed readily from the gastrointestinal tract, the respiratory tract and the skin. About 60% of an oral dose (1600 mg/kg) was absorbed by rats within six hours (Reddrop et al., 1981), and 65 to 86% of oral doses of 2,000-4,000 mg/kg were absorbed by rats within 24 hours (Paul and Rubinstein, 1963; Seawright and McLean, 1967; Marchand et al., 1970).

Absorption from the lung has been reported as about 30% in monkeys exposed to 290 mg $CCl_4/m^3$ for 139, 344 or 300 minutes (McCollister et al., 1952).

° Bruckner et al. (1986a) assessed potential effects of different vehicles on the pharmacokinetics of $CCl_4$. Fasted 200 g male Sprague-Dawley rats with indwelling arterial cannulas received 25 mg/kg $CCl_4$ by gavage: in corn oil; as an aqueous emulsion; in water; and as pure undiluted chemical. A 25 mg/kg dose was given intravenously for calculation of bioavailability. Serial blood samples were taken and analyzed for $CCl_4$. Peak concentrations of $CCl_4$ in the blood were reached within 8 minutes after dosing in the emulsion and saturated water groups. These peak levels were slightly higher than in the pure $CCl_4$ group and substantially higher than in the corn oil group. There was evidence of later secondary peaks of lesser magnitude in the corn oil group. The absolute bioavailability for the emulsion and saturated water groups was higher than for the corn oil and pure chemical groups, and comparable to the intravenous group.

Distribution

° Carbon tetrachloride appears to be distributed to all major organs following absorption (U.S. EPA, 1985a). Carbon tetrachloride has been found in fat, liver, blood, brain, kidney and muscle, with particularly high concentrations in fat. Carbon tetrachloride reaches maximal concentrations in most tissues at approximately two to four hours following intragastric administration (Marchand et al., 1970).

Metabolism

° Carbon tetrachloride metabolism occurs primarily in the liver. The first step is thought to be formation of a trichloromethyl radical in the cytochrome heme moiety. This trichloromethyl radical undergoes a variety of reactions, including hydrogen abstraction to form chloroform, dimerization to form hexachloroethane and addition to cellular molecules. Further metabolism of the heme-bound trichloromethyl radical is postulated to result in the eventual formation of carbonyl chloride (phosgene) (Shah et al., 1979 with an in vitro study with rat liver).

° After a single oral dose of $CCl_4$ in Wistar rats, Bini et al. (1975) proposed that the trichloromethyl free radical was the main metabolite of $CCl_4$ after they found chloroform and hexachloroethane as metabolites in the rats. Fowler (1969) found these metabolites in rabbits given $CCl_4$ orally. McCollister et al. (1951) detected labeled carbon dioxide exhaled by monkeys exposed to $^{14}C$-$CCl_4$ by inhalation.

Excretion

° Carbon tetrachloride and its volatile metabolites are excreted primarily in exhaled air and also in the urine and feces (U.S. EPA, 1985a). Elimination of orally ingested $CCl_4$ occurs with an estimated half-time of four to six hours, and most of an oral dose is excreted

within one to two days. No reports were located regarding the tissue accumulation and retention of $CCl_4$ during chronic exposure.

## IV. HEALTH EFFECTS

### Humans

- The effects of $CCl_4$ exposure in humans are similar to effects seen in animals, with the liver, kidney and lungs being most sensitive.
- Single oral doses of 2.5 to 15 mL (57 to 343 mg/kg) are usually without effect, although changes may occur in liver and kidney (U.S. EPA, 1985a). Some individual adults suffer adverse effects (including death) from ingestion of as little as 1.5 mL (34 mg/kg), and 0.18 to 0.92 mL may be fatal in children (29 to 150 mg/kg) (U.S. EPA, 1985a).
- Inhalation exposure also results in central nervous system depression and renal and hepatic damage (U.S. EPA, 1985a). No ill effects result from three hours of exposure to 63 mg/m$^3$, but 70 minutes of exposure to 2,309 mg/m$^3$ may produce liver effects. High levels (1,500 mg/m$^3$) may produce severe poisoning and death.

### Animals

#### Short-term Exposure

- Carbon tetrachloride is toxic to animals, with oral $LD_{50}$ values ranging from 1,000 to 12,800 mg/kg (U.S. EPA, 1985a).
- The tissue most affected by $CCl_4$ is the liver. Using release of liver enzymes into serum and histological examination as end-points, single oral doses (in corn oil) of 40 mg $CCl_4$/kg did not produce adverse effects, while doses of 80 mg/kg or higher did in male Sprague-Dawley rats (Bruckner et al., 1986b). Numerous studies have found that oral doses ranging from about 100 to 4,000 mg/kg produce fatty infiltration, loss of cytochrome P-450 and other enzymes, inhibition of protein synthesis and histological alterations in the liver. When damage is severe, hepatocellular necrosis may result, but the effects observed following lower doses are largely reversible (U.S. EPA, 1985a).
- Kidney and lung also are affected following oral exposure to $CCl_4$ (U.S. EPA, 1985a). Single doses of about 4,000 mg/kg result in lesions of the renal proximal tubule in rats and pulmonary Clara cells and endothelial cells in rats and/or mice. These changes also appear to be reversible when damage is not too severe.
- Bruckner et al. (1986b) found hepatotoxic effects (increased serum enzymes, pathology) in rats given $CCl_4$ in corn oil at daily doses of 20 mg/kg and higher by gavage for 9 days in an 11-day study.

- Hayes et al. (1986) observed hepatotoxicity (increased serum enzymes, increased organ weight) in male and female CD-1 mice given $CCl_4$ in corn oil by gavage at doses of 625, 1,250 or 2,500 mg/kg for 14 consecutive days.

- The objective of a study by Kim et al. (1986) was to assess the influence of dosing vehicles on the acute hepatotoxicity of $CCl_4$. Fasted 200 g male Sprague-Dawley rats were given 0, 10, 25, 50, 100, 250, 500, 1,000 or 2,000 mg $CCl_4$/kg by gavage in: corn oil; as an aqueous emulsion; as the undiluted chemical; and in the 10 and 25 mg/kg doses only in water. Blood and liver samples were taken 24 hrs after dosing for measurement of serum and microsomal enzymes. Pathological examination of liver samples was also conducted. Dose-dependent increases in serum enzyme levels and pathological changes, and dose-dependent decreases in microsomal P-450 and glucose-6-phosphatase activity were observed in each vehicle group. $CCl_4$ was less hepatotoxic at each dosage level when given in corn oil than when given as an emulsion or as the pure chemical. $CCl_4$ in corn oil was also less toxic than $CCl_4$ in water at the 10 and 25 mg/kg doses.

Long-term Exposure

- The effects of longer-term exposure to $CCl_4$ are similar to the effects of short-term exposure: the liver is the most sensitive tissue, showing fatty infiltration, release of liver enzymes, inhibition of cellular enzyme activities, inflammation and, ultimately, cellular necrosis (U.S. EPA, 1985a).

- Rats exposed by gavage to $CCl_4$ in corn oil at doses of 1 mg/kg 5 days/week for 12 weeks did not show measurable adverse effects, while doses of 10 or 33 mg/kg resulted in enzyme release, centrilobular vacuolization and necrosis in liver (Bruckner et al., 1986b).

- Condie et al. (1985) investigated the effects of a corn oil vehicle as well as Tween-60 on the subchronic hepatotoxicity of carbon tetrachloride ($CCl_4$). Male and female CD-1 mice were given 0, 1.2, 12 and 120 mg/kg $CCl_4$ by gavage in either corn oil as a solution or 1% Tween-60 as a suspension once daily for five consecutive days per week for 90 days. Hepatotoxicity was greater in the corn oil vehicle groups of mice than in the Tween-60 groups. Significant increases in serum enzyme activities were detected in the 12 mg/kg $CCl_4$ corn oil male and female groups but not in the corresponding Tween-60 groups. When comparing the serum enzyme activities in the high dose groups, there were dramatic increases in both the male and female corn oil groups as compared to the corresponding Tween-60 groups. Liver and liver/body weights were significantly greater in each high dose group. Histopathological findings indicated that hepatocellular changes occurring during the administration of $CCl_4$ at the 12 mg/kg (hepatocellular cytomegaly, fat and necrosis) and 120 mg/kg (necrosis and fat) dose levels were more frequently observed when $CCl_4$ was given in corn oil than when it was administered in Tween-60. The experimental findings indicate that the corn oil vehicle lowered the no-observed-adverse-effect level (NOAEL) from $CCl_4$ exposure by an

order of magnitude (from 12 mg/kg to 1.2 mg/kg) compared to the Tween-60 vehicle and also enhanced the hepatotoxicity of $CCl_4$ in the high dose treatment groups.

- Hayes et al. (1986) reported hepatotoxic effects (increased serum enzymes, increased organ weight, pathological lesions) in male and female CD-1 mice given $CCl_4$ in corn oil by gavage at doses of 12, 120, 540 or 1,200 mg/kg for 90 consecutive days.

- Alumot et al. (1976) fed 18 male and 18 female rats (strain not given) 0, 80 or 200 ppm $CCl_4$ in the diet until final sacrifice at two years. The authors equated 200 ppm to 10-18 mg/kg body weight/day. No adverse effects from exposure to $CCl_4$ were observed. However, tissues were not examined microscopically, liver weights were not taken, and survival was below 50% at 21 months. In an earlier 6-week study, Alumot et al. (1976) found no effect with 22 mg/kg and increased lipid and triglyceride in liver with 40 and 76 mg/kg. Only body weight was additionally measured.

- Prendergast et al. (1967) found hepatotoxicity in guinea pigs, rats, monkeys, rabbits and dogs exposed to 515 mg $CCl_4/m^3$ air eight hours/day, five days/week for six weeks. Liver effects were also found in these species after continuous exposure to 61 mg/$m^3$ for 90 days but not to 6.1 mg/$m^3$. After inhalation exposure of Wistar rats to $CCl_4$ eight hours/day, five days/week for ten months, Smyth et al. (1936) found liver toxicity with levels above 315 mg/$m^3$ and kidney changes with at least 315 mg/$m^3$ (lowest level tested). Adams et al. (1952) noted liver damage in Wistar rats, guinea pigs, and rabbits at some inhalation exposures ranging from 32.5 to 2,600 mg/$m^3$, seven hours/day, five days/week for 258 days and no observable effect in a Rhesus monkey similarly exposed to 25 mg/$m^3$ for 212 days, but the study cannot be adequately assessed from the limited details reported.

Reproductive Effects

- No reproductive evvects were noted in rats fed diets containing $CCl_4$ at 80 and 200 ppm for up to two years (Alumot et al., 1976)

Developmental Effects

- No evidence was located to demonstrate that $CCl_4$ is teratogenic (U.S. EPA, 1985a). Newborn rats appear to be less sensitive to liver damage by $CCl_4$ than 7-day-old rats (Dawkins, 1963). An intraperitoneal dose of 2,400 mg/kg has resulted in adverse effects on testicular function in rats (Chatterjee, 1966).

Mutagenicity

- No evidence of mutagenic activity for $CCl_4$ has been found in bacterial test systems or in cultured liver cells (U.S. EPA, 1985a), except that Sina et al. (1983) found $CCl_4$ weakly positive at cytotoxic levels in an alkaline elution/rat hepatocyte assay to measure DNA single-strand breaks. Increased gene crossover and mitotic recombination were

observed in yeast cells exposed to $CCl_4$ at 3,300 to 5,400 mg/L buffer (Callen et al., 1980). Amacher and Zelljadt (1983) concluded $CCl_4$ as positive for cell transformation in Syrian hamster embryo cells.

- In an in vivo-in vitro hepatocyte DNA repair assay by Mirsalis, et al. (1985), $CCl_4$ failed to induce unscheduled DNA synthesis in male and female $B_6C_3F_1$ mice but did significantly elevate hepatic cell proliferation. The latter effect was also induced by $CCl_4$ in male Fischer 344 rats but at higher doses.

Carcinogenicity

- Carbon tetrachloride is carcinogenic in animals, producing mainly hepatic neoplasms. Doses of about 30 mg/kg/day or higher for six months or longer have been found to produce an increased frequency of hepatocellular tumors in mice, rats and hamsters (U.S. EPA, 1985a).

- In an exploratory study of a large number of solvents and cancers in rubber industry workers, Wilcosky et al. (1984) associated exposure to carbon tetrachloride with lymphosarcoma and lymphatic leukemia, but they stressed cautious interpretation because of the modest number of cases and biases.

## V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for One-day, Ten-day, Longer-term (approximately 7 years) and Lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(NOAEL \text{ or } LOAEL) \times (BW)}{(UF) \times (\_\_\_ \text{ L/day})} = \_\_\_ \text{ mg/L } (\_\_\_ \text{ ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect-Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100 or 1,000), in accordance with NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

The acute animal study by Bruckner et al. (1986b) has been selected to serve as the basis for the One-day Health Advisory in the 10-kg child because this study clearly defined a one-day NOAEL (40 mg/kg) and LOAEL (80 mg/kg)

for $CCl_4$ based on changes in BUN, GPT, SDH and OCT and histopathological changes in the liver and kidneys of rats sacrificed 24 hours after dosing. The abstract report of the study by Kim et al. (1986) does not provide sufficient details for assessment as a basis for the One-day HA.

The One-day HA for a 10-kg child is calculated as follows:

$$\text{One-day HA} = \frac{(40 \text{ mg/kg/day})\ (10 \text{ kg})}{(100)\ (1 \text{ L/day})} = 4.0 \text{ mg/L } (4{,}000 \text{ ug/L})$$

where:

40 mg/kg day = NOAEL based on absence of liver toxicity following one-day exposure in rats.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with ODW/NAS guidelines for use with a NOAEL from an animal study.

1 L/day = assumed water consumption of a child.

Ten-day Health Advisory

The short-term study by Bruckner et al. (1986b) has been selected to serve as the basis for the Ten-day HA for the 10-kg child. This study identified a LOAEL of 20 mg/kg/day in rats given 9 doses over 11 days, based on significant increases in serum enzyme levels and hepatic midzonal vacuolization by 11 days. Higher doses of $CCl_4$ caused even more extensive liver damage. The 14-day study by Hayes et al. (1986) is not selected because all doses used were effect levels above those in the Bruckner et al. (1986b) study.

The Ten-day HA for a 10-kg child is calculated as follows:

$$\text{Ten-day HA} = \frac{(20 \text{ mg/kg/day})\ (10 \text{ kg})\ (9)}{(1{,}000)\ (1 \text{ L/day})\ (11)} = 0.16 \text{ mg/L } (160 \text{ ug/L})$$

where:

20 mg/kg/day = LOAEL based on liver toxicity in rats.

9/11 = factor accounting for 9 doses given over 11 days.

10 kg = assumed body weight of a child.

1,000 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a LOAEL from an animal study.

1 L/day = assumed water consumption of a child.

Longer-term Health Advisory

The 12-week study by Bruckner et al. (1986b) has been selected to serve as the basis for calculation of the Longer-term HA. Bruckner and co-workers dosed rats with $CCl_4$ in corn oil by gavage five times weekly for 12 weeks with doses of 1, 10 or 33 mg/kg. This study identified a NOAEL of 1 mg/kg/day and a LOAEL of 10 mg/kg day for hepatotoxicity. Condie et al. (1985) obtained similar results with a NOAEL of 1.2 mg/kg/day and a LOAEL of 12 mg/kg/day in CD-mice given $CCl_4$ in corn oil by gavage five times weekly for 90 days. In the same study, Condie et al. (1985) found a NOAEL of 12 mg/kg/day with $CCl_4$ suspended in Tween-60, but these data are not selected for the Longer-Term HA calculation because of use of a rather insoluble form of $CCl_4$ (suspension) as the method of dosing. The 90-day study by Hayes et al. (1986) is not selected because a NOAEL was not found, although the LOAEL of 12 mg/kg/day approximates the 10 mg/kg/day LOAEL in the Bruckner et al. (1985) study.

The Longer-term HA for a 10-kg child is calculated as follows:

$$\text{Longer-term HA} = \frac{(1\ \text{mg/kg/day})\ (10\ \text{kg})\ (5)}{(100)\ (1\ \text{L/day})\ \ (7)} = 0.071\ \text{mg/L}\ (71\ \text{ug/L})$$

where:

1 mg/kg/day = NOAEL based on absence of liver toxicity in rats.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

5/7 = factor to account for dosing five days per week.

1 L/day = assumed daily water consumption of a child.

The Longer-term HA for a 70-kg adult is calculated as follows:

$$\text{Longer-term HA} = \frac{(1\ \text{mg/kg/day})\ (70\ \text{kg})\ (5)}{(100)\ (2\ \text{L/day})\ \ (7)} = 0.25\ \text{mg/L}\ (250\ \text{ug/L})$$

where:

1 mg/kg/day = NOAEL based on absence of liver toxicity in rats.

70 kg = assumed body weight of an adult.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

5/7 = factor to account for dosing five days per week.

2 L/day = assumed daily water consumption of an adult.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed for synthetic organic chemicals and a value of 10% is assumed for inorganic chemicals. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

The 12-week study by Bruckner et al. (1986b) described under Longer-term Health Advisory is the most appropriate from which to derive the DWEL in that the available animal toxicity studies with chronic exposure to $CCl_4$ are concluded to be insufficient for use in the DWEL calculation. From these results, a NOAEL of 1 mg/kg was identified.

The two-year study in rats by Alumot et al. (1976) was not chosen because the assessment of $CCl_4$ toxicity was deficient with respect to tissue examination. The inhalation studies by Prendergast et al. (1967), Smyth et al. (1936), and Adams et al. (1952) were not used since inhalation data are less desirable for HA development.

Using the NOAEL of 1 mg/kg, the DWEL is derived as follows:

Step 1: Determination of the Reference Dose (RfD)

$$RfD = \frac{(1\ mg/kg/day)\ (5)}{(1{,}000)\quad (7)} = 0.0007\ mg/kg/day$$

where:

1 mg/kg/day = NOAEL based on absence of liver toxicity in rats orally given $CCl_4$ for 90 days.

1,000 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study of less-than-lifetime duration.

5/7 = factor to account for dosing 5 days per week.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$DWEL = \frac{(0.0007 \text{ ug/kg/day})\ (70 \text{ kg})}{(2 \text{ L/day})} = 0.025 \text{ mg/L } (25 \text{ ug/L})$$

where:

0.0007 ug/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Carbon tetrachloride may be classified in Group B: Probable human carcinogen. The estimated excess cancer risk associated with lifetime exposure to drinking water containing carbon tetrachloride at 25 ug/L is approximately $8 \times 10^{-5}$. This estimate represents the upper 95% confidence limit from extrapolations prepared by EPA's Carcinogen Assessment Group using the linearized, multistage model. The actual risk is unlikely to exceed this value, but there is considerable uncertainty as to the accuracy of risks calculated by this methodology.

Evaluation of Carcinogenic Potential

- The IARC (1979) classified carbon tetrachloride as a 2B carcinogen with sufficient animal evidence and inadequate human evidence.

- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986a), carbon tetrachloride may be classified in Group B2: Probable human carcinogen. This category is for agents for which there is inadequate evidence from human studies and sufficient evidence from animal studies.

- U.S. EPA calculated a unit risk estimate (the 95% upper limit by the linearized multistage model) of $0.37 \times 10^{-5}$ for a human continuously exposed to 1 ug $CCl_4$ per liter of water (U.S. EPA, 1984). The corresponding $10^{-6}$, $10^{-5}$ and $10^{-4}$ risks are associated with 0.3, 2.7 and 27 ug/L, respectively.

- It should be noted that this approach, which involved using the geometric mean of risk estimates based on four studies, for calculating unit risk estimates for $CCl_4$ is from U.S. EPA (1984) which was reviewed by the U.S. EPA's Science Advisory Board.

- There was an attempt to compare risk estimates derived with the multistage model with other models in U.S. EPA, 1984. Of the studies used (Della Porta et al., 1961; Edwards et al., 1942; NCI rat and mouse, 1976), risk estimates could not be calculated with the Weibull and log probit models, and a time-to-tumor model was successful only with the NCI (1976) data which gave 95% upper confidence limits similar to those obtained with the multistage model. Unit (ingestion of 1 ug $CCl_4$/L water/lifetime) risk estimates (95% upper confidence limits) with individual studies and the multistage model were $3.4 \times 10^{-5}$

(Della Porta et al., 1961), $9.4 \times 10^{-6}$ (Edwards et al., 1942), $1.8 \times 10^{-6}$ (NCI mouse, 1976) and $3.1 \times 10^{-7}$ (NCI rat, 1976). Unit risk estimates (maximum likelihood estimates) with individual studies and the multistage model were $2.1 \times 10^{-5}$ (Della Porta et al., 1961), $7.1 \times 10^{-6}$ (Edwards et al., 1942), $1.4 \times 10^{-6}$ (NCI mouse, 1976) and $1.9 \times 10^{-7}$ (NCI rat, 1976). While recognized as statistically alternative approaches, the range of risks described by using any of these modeling approaches has little biological significance unless data can be used to support the selection of one model over another. In the interest of consistency of approach and in providing an upper bound on the potential cancer risk, the EPA has recommended use of the linearized multistage approach.

## VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- Data from the animal studies have been used by NAS (1977) and U.S. EPA (1980b, 1984) to calculate the upper 95% bound on the number of additional cancer cases that may occur when $CCl_4$ is consumed in drinking water over a 70-year lifetime. By these methods, a $10^{-6}$ lifetime excess cancer risk was associated with $CCl_4$ in drinking water at levels of 4.5 ug/L by the NAS (1977), 0.4 ug/L by the U.S. EPA (1980a) and 0.3 ug/L by the U.S. EPA (1984).

- The criteria for the U.S. EPA, OHEA and NAS risk calculations differ in two respects: (1) NAS used the multistage model, while U.S. EPA used an "improved" multistage model; and (2) NAS used the data set from the National Cancer Institute (NCI) study in male rats while U.S. EPA initially used the data set from the NCI study in male mice (U.S. EPA, 1980b) and subsequently used a geometric mean of four studies (NCI, 1976 - mice; NCI, 1976 - rats; Edwards et al., 1942 - mice; and Della Porta et al., 1961 - hamsters) (U.S. EPA, 1984).

- Ambient water quality criteria for $CCl_4$ calculated by the EPA (U.S. EPA 1980b) were based on increased lifetime cancer risk estimates of $10^{-5}$ (4.0 ug/L), $10^{-6}$ (0.40 ug/L), and $10^{-7}$ (0.04 ug/L). It is noteworthy that these estimates were derived by assuming a lifetime consumption of both drinking water (2 L/day) and aquatic species (6.5 g fish and shellfish/day) taken from waters containing the corresponding $CCl_4$ levels. Specifically, daily $CCl_4$ exposure assumptions were as follows: 94% from ingesting drinking water and 6% from consuming seafood "fish factor." The corresponding "drinking water only" concentrations were 4.41, 0.44, and 0.04 ug/L, respectively.

- Using the carcinogenicity data set and a linear multistage model, WHO (1984) derived a recommended tentative limit for $CCl_4$ of 3 ug/L as a level which should result in less than one additional cancer per 100,000 population ($10^{-5}$) for a lifetime of exposure assuming daily consumption of two liters of drinking water.

- The U.S. EPA (1981) and NAS (1980) previously calculated SNARLS (Suggested No-Adverse-Response Levels) for $CCl_4$ in drinking water. These guidelines are summarized in Table 1.

TABLE 1

Summary of Existing Guidelines for $CCl_4$

| | USEPA[a] | NAS[b] |
|---|---|---|
| One-day | 0.2 mg/L | 14 mg/L |
| Seven-day[c] | - | 2 mg/L |
| Ten-day[c] | 0.02 mg/L | - |
| Long-term | None[d] | None[e] |

[a]U.S. EPA (1981) used a LOAEL of 20 mg/kg (Korsrud et al., 1972) as the basis for their calculations.
[b]NAS (1980) used a LOAEL of 400 mg/kg (Murphy and Malley, 1969) as the basis for their calculations.
[c]In the absence of subacute oral data, the NAS (1980) and U.S. EPA (1981) calculated 7- and 10-day SNARLS by dividing their one-day values by 7 and 10, respectively.
[d]The U.S. EPA (1981) did not calculate a long-term SNARL due to a lack of acceptable chronic oral exposure data at that time.
[e]The NAS (1980) did not determine a long-term SNARL because of NAS policy at that time not to calculate such values for animal carcinogens.

- The final RMCL by the U.S. EPA Office of Drinking Water is 0, the proposed MCL is 5 ug/L, and the practical quantitation level is 5 ug/L (U.S. EPA, 1985e).
- The U.S. EPA Office of Pesticide Programs has published a notice of intent to cancel registrations of grain fumigation products containing $CCl_4$ (U.S. EPA, 1986b).
- The OSHA standard in 10 ppm (TWA), and the ACGIH (1983) has recommended a TLV of 5 ppm and an STEL of 20 ppm.
- The U.S. EPA (1985d) has published a notice of intent to list $CCl_4$ under Section 112 of the Clean Air Act.

## VII. ANALYTICAL METHODS

- Analysis of $CCl_4$ is by a purge-and-trap gas chromatographic procedure used for the determination of volatile organohalides in drinking water (U.S. EPA, 1985b). This method calls for the bubbling of an inert gas through the sample and trapping $CCl_4$ on an adsorbent material. The adsorbent material is heated to drive off the $CCl_4$ onto a gas chromatographic column. This method is applicable to the measurement of $CCl_4$ over a concentration range of 0.03 to 1500 ug/L. Confirmatory analysis for carbon tetrachloride is by mass spectrometry (U.S. EPA,

1985c). The detection limit for confirmation by mass spectrometry is 0.3 ug/L.

## VIII. TREATMENT TECHNOLOGIES

- Treatment techniques which will remove carbon tetrachloride from drinking water include granular activated carbon adsorption, boiling, and aeration (Combs, 1980).

- Pilot plant studies by EPA's Drinking Water Research Division have shown consistently that conventional treatment processes (coagulation, sedimentation, filtration), even when augmented by the addition of powdered activated carbon, provide little removal of carbon tetrachloride.

- The use of powdered activated carbon was only partially effective at doses as high as 30 ug/L (Love et al., 1983; Symons et al., 1979; Lykins et al., 1980).

- Carbon tetrachloride at a raw water concentration of 12 ug/L treated using Filtrasorb® 400 granular activated carbon exhibited breakthrough after three weeks. The empty bed contact time reported was 5 minutes. When the empty bed contact time was increased to 10 minutes, breakthrough occurred at 14 to 16 weeks (Symons, 1978).

- A full-scale installation investigation conducted by Calgon using twin granular activated carbon beds in series (EBCT of 130 minutes) reported that, along with other chemicals, carbon tetrachloride was removed to below detection from an influent concentration of 73 ug/L (O'Brien et al., 1981).

- A study demonstrated that the synthetic resin (Ambersorb XE-340) removed carbon tetrachloride from treated drinking water with an effectiveness similar to Filtrasorb® 400 (Symons et al., 1979). It should be noted that these resins are not commercially available.

- Boiling also is effective in eliminating carbon tetrachloride from a solution. Studies have shown that five minutes of vigorous boiling will remove upwards of 99% of the carbon tetrachloride originally present (Combs, 1980; Love and Eilers, 1981).

- Finally, aeration may be used to remove carbon tetrachloride from water. Laboratory studies conducted by Love et al. (1983) showed that a diffused air aerator could remove 91% of the carbon tetrachloride in the water using a 4:1 air to water ratio.

- Air stripping is an effective, simple, and relatively inexpensive process for removing carbon tetrachloride and volatile organics from water. However, use of this process then transfers the contaminant directly to the air stream. When considering use of air stripping as a treatment process, it is suggested that careful consideration be given to the overall environmental occurrence, fate, route of exposure, and various hazards associated with the chemical.

## IX. REFERENCES

ACGIH. 1983. American Conference of Governmental Industrial Hygienists, Inc. Documentation of the threshold limit values. 4th ed. Cincinnati.

Adams, E.M., H.C. Spencer, V.K. Rowe, D.D. McCollister and D.D. Irish. 1952. Vapor toxicity of carbon tetrachloride determined by experiments on laboratory animals. Arch. Indust. Hyg. Occup. Med. 6:50-66.

Alumot E., E. Nachtomi, E. Mandel and P. Holstein. 1976. Tolerance and acceptable daily intake of chlorinated fumigants in the rat diet. Food Cosmet. Toxicol. 14:105-110.

Amacher, D.E., and I. Zelljadt. 1983. The morphological transformation of Syrian hamster embryo cells by chemicals reportedly nonmutagenic to Salmonella typhimurium. Carcinogenesis. 4(3):291-296.

Amoore, J.E., and E. Hautala. 1983. Odor as an aid to chemical safety: Odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. J. Appl. Toxicol. 3:272-290.

Bini, A., G. Vecchi, G. Vivioli, V. Vannini and C. Cessi. 1975. Detection of early metabolites in rat liver after administration of $CCl_4$ and $CBrCl_3$. Pharmacol. Res. Commun. 7:143-149.

Bruckner, J.V., H.J. Kim, C.E. Dallas, R. Ramanathan, S. Muralidhara and J.M. Gallo. 1986a. Effect of dosing vehicles on the pharmacokinetics of orally administered carbon tetrachloride ($CCl_4$). Society of Toxicology 1987 Annual Meeting. (In press) (Abstract)

Bruckner, J.V., W.F. MacKenzie, S. Muralidhara, R. Luthra, G.M. Kyle and D. Acosta. 1986b. Oral toxicity of carbon tetrachloride: acute, subacute and subchronic studies in rats. Fund. Appl. Toxicol. 6:16-34.

Callen, D.F., C.R. Wolfe and R.M. Philpot. 1980. Cytochrome P-450 mediated genetic activity and cytotoxicity of seven halogenated aliphatic hydrocarbons in Saccharomyces cerevisiae. Mutation Res. 77:55-63.

Chatterjee, A. 1966. Testicular degeneration in rats by carbon tetrachloride intoxication. Experientia. 22:394-396.

Combs, W.S. 1980. Removal of chlorinated solvents from water by boiling. State of Rhode Island and Providence Plantations Dept. of Health, Providence, RI. (MIMEO)

Condie, L.W., R.D. Laurie, M. Robinson and J.F. Bercy. 1985. Effect of corn oil gavage on hepatotoxicity of carbon tetrachloride in CD-1 mice. Fund. Appl. Toxicol. In press.

Dawkins, M.J.R. 1963. Carbon tetrachloride poisoning in the liver of the newborn rat. J. Pathol. Bacteriol. 85:189-196.

Della Porta, G., B. Terracini and P. Shubik. 1961. Induction with carbon tetrachloride of liver cell carcinomas in hamsters. J. Natl. Cancer Inst. 26:855-863.

Dobbs, R.A., and J.M. Cohen. 1980. Carbon adsorption isotherms for toxic organics. EPA 600/880-023, Office of Research and Development, Cincinnati, OH.

Edwards, J.E., W.E. Heston and A.J. Dalton. 1942. Induction of the carbon tetrachloride hepatoma in strain L. mice. J. Natl. Cancer Inst. 3:297-301.

Fowler, J.S.L. 1969. Carbon tetrachloride metabolism in the rabbit. Brit. J. Pharmacol. 37:733-737.

Hayes, J.R., L.W. Condie, Jr., and J.F. Borzelleca. 1986. Acute, 14-day repeated dosing, and 90-day subchronic toxicity studies of carbon tetrachloride in CD-1 mice. Fund. Appl. Toxicol. 7:454-463.

IARC. 1979. International Agency for Research on Cancer. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Man. 20:371-399.

Kim, H.J., S. Odend'hal, R. Ramanathan, C.E. Dallas, S. Muralidhara and J.V. Bruckner. 1986. Effect of oral dosing vehicles on acute hepatotoxicity of carbon tetrachloride ($CCl_4$) in rats. Society of Toxicology 1987 Annual Meeting. (In press) (Abstract)

Korsrud, G.O., H.C. Grice and J.M. McLaughlan. 1972. Sensitivity of several serum enzymes in detecting carbon tetrachloride-induced liver damage in rats. Toxicol. Appl. Pharmacol. 22:474-483.

Love, O.T., Jr., and R.G. Eilers. 1981. Treatment for the control of trichloroethylene and related industrial solvents in drinking water. U.S. EPA, Office of Research and Development, Cincinnati, OH.

Love, O.T., Jr., R.J. Miltner, R.G. Eilers and C.D. Pronk-Leist. 1983. Treatment of volatile organic compounds in drinking water. U.S. EPA, Municipal Environmental Research Laboratory. EPA-600/8-83-019.

Lykins, B.W., and J. DeMarco. 1980. An overview of the use of powdered activated carbon for removal of trace organics in drinking water. U.S. EPA, Office of Research and Development, Cincinnati, OH. (Draft)

Marchand, C., S. McLean and G.L. Plaa. 1970. The effect of SKF 525A on the distribution of carbon tetrachloride in rats. J. Pharmacol. Exp. Ther. 174:232-238.

McCollister, D.D., W.H. Beamer, G.J. Atchison and H.C. Spencer. 1951. The absorption, distribution and elimination of radioactive carbon tetrachloride by monkeys upon exposure to low vapor concentrations. J. Pharmacol. Exp. Ther. 102:112-124.

Mirsalis, J.C., C.K. Tysn, E.N. Loh, D.K. Spek and J.W. Spalding. 1985. Induction of hepatic cell proliferation and unscheduled DNA synthesis in mouse hepatocytes following in vivo treatment. Carcinogenesis. 6:1521-1524.

Murphy, S.D., and S. Malley. 1969. Effect of carbon tetrachloride on induction of liver enzymes by acute stress or corticosterone. Toxicol. Appl. Pharmacol. 15:117-130.

NAS. 1977. National Academy of Sciences. Drinking Water and Health. Volume 1. Safe Drinking Water Committee. National Research Council. National Academy Press. Washington, D.C. pp. 703-707.

NAS. 1980. National Academy of Sciences. Drinking water and health. Vol. 3. Safe Drinking Water Committee. Board on Toxicology and Environmental Health Hazards, Assembly of Life Sciences, National Research Council. Washington, DC: National Academy of Sciences. pp. 96-98.

NCI. 1976. National Cancer Institute. Report on carcinogenesis bioassay of chloroform. Bethesda, Maryland: Carcinogenesis Program, Division of Cancer Cause and Prevention.

O'Brien, R.P., D.M. Jordan and W.R. Musser. 1981. Trace organic removal from contaminated groundwaters with granular activated carbon. Presented to: American Chemical Society, Atlanta, GA. March, 1981.

Paul, B.P., and D. Rubinstein. 1963. Metabolism of carbon tetrachloride and chloroform by the rat. J. Pharmacol. Exptl. Therap. 141:141-148.

Prendergast, J.A., R.A. Jones, L.J. Jenkins and J. Seigel. 1967. Effects on experimental animals of long-term inhalation of trichloroethylene, carbon tetrachloride, 1,1,1-trichloroethane, dichlorodifluoromethane, and 1,1-dichloroethylene. Toxicol. Appl. Pharmacol. 10:270-289.

Rams, J.M., M. Pilgrim, S. Rauth, G. Hunt, T. Shannon and K. Slimak. 1979. Draft report, Level I materials balance: carbon tetrachloride. Prepared by JRB Associates for Office of Pesticides and Toxic Substances, U.S. Environmental Protection Agency, Washington, D.C.: U.S. Environmental Protection Agency. Contract No. 68:01-5793.

Reddrop, C.J., W.Riess and T.F. Slater. 1981. Interactions of carbon tetrachloride and promethazine in the rat. II. Elimination of carbon tetrachloride and chloroform in expired air as indications of their metabolism in the intact animal. Biochem. Pharmacol. 30:1449-1455.

Seawright, A.A., and A.E.M. McLean. 1967. The effect of diet on carbon tetrachloride metabolism. Biochem. J. 105:1055-1060.

Shah, H., S. Hartman and S. Weinhouse. 1979. Formation of carbonyl chloride in carbon tetrachloride metabolism by rat liver in vitro. Cancer Res. 39:3942-3947.

Sina, J.F., C.L. Bean, G.R. Dysart, V.I. Taylor and M.O. Bradley. 1983. Evaluation of the alkaline elution/rat hepatocyte assay as a predictor of carcinogenic/mutagenic potential. Mutat. Res. 113:357-391.

Smyth, H.F., H.F. Smyth, Jr. and C.P. Carpenter. 1936. The chronic toxicity of carbon tetrachloride: Animal exposure and field studies. J. Indust. Hyg. Toxicol. 18:277-298.

Symons, J.M. 1978. Interim treatment guide for controlling organic contaminants in drinking water using granular activated carbon. U.S. EPA, Office of Research and Development, Cincinnati, OH.

Symons, J.M., J.K. Carswell, J. DeMarco and O.T. Love, Jr. 1979. Removal of organic contaminants from drinking water using techniques other than granulated activated carbon alone - a progress report. In: Proceedings, Practical Applications of Adsorption Techniques in Drinking Water, EPA/NATO, Challenges of Modern Society, Reston, VA. (In press)

U.S. EPA. 1979. Water related environmental fate of 129 priority pollutants. Office of Water Planning and Standards. EPA-440/4-79-029.

U.S. EPA. 1980a. U. S. Environmental Protection Agency. Carbon tetrachloride; Pesticide Programs; rebuttable presumption against registration and continued registration of certain pesticide products. Federal Register 45(201). Part IV:68534-68584. (Oct. 15).

U.S. EPA. 1980b. U. S. Environmental Protection Agency. Ambient water quality criteria for carbon tetrachloride. Environmental Protection Agency. Office of Water Regulations and Standards, Criteria and Standards Division. Washington, D.C.

U.S. EPA. 1981. U.S. Environmental Protection Agency. Advisory opinion for carbon tetrachloride. Office of Drinking Water, Washington, D.C.

U.S. EPA. 1983. U.S. Environmental Protection Agency. Carbon tetrachloride occurrence in drinking water, food, and air. Office of Drinking Water.

U.S. EPA. 1984. U.S. Environmental Protection Agency. Health assessment document for carbon tetrachloride. Cincinnati, OH: EPA Publ. No. 600/8-82-001F, Environmental Criteria and Assessment Office.

U.S. EPA. 1985a. U.S. Environmental Protection Agency. Final draft criteria document for carbon tetrachloride. TR-540-131A. Office of Drinking Water.

U.S. EPA. 1985b. U.S. Environmental Protection Agency. Method 502.1. Volatile halogenated organic compounds in water by purge and trap gas chromatography. Environmental Monitoring and Support Laboratory, Cincinnati, Ohio 45268. June 1985.

U.S. EPA. 1985c. U.S. Environmental Protection Agency. Method 524.1. Volatile organic compounds in water by purge and trap gas chromatography/mass spectrometry. Environmental Monitoring and Support Laboratory, Cincinnati, Ohio 45268. June 1985.

U.S. EPA. 1985d. U.S. Environmental Protection Agency. Assessment of carbon tetrachloride as a potentially toxic air pollutant. Federal Register. 50(156):32621-32627.

U.S. EPA. 1985e. U.S. Environmental Protection Agency. National primary drinking water regulations; Volatile synthetic organic chemicals; Final rule and proposed rule. Federal Register 50(219):46880-46933. November 13.

U.S. EPA. 1986a. U.S. Environmental Protection Agency. Guidelines for carcinogenic risk assessment. Federal Register 51(185):33992-34003. September 24.

U.S. EPA. 1986b. U.S. Environmental Protection Agency. Pesticide products containing carbon tetrachloride; Notice of intent to cancel registrations and notice of transmittal and availability of draft notice to cancel. Federal Register. 51(78):15372-15373. April 23.

U.S. ITC. 1983. U.S. International Trade Commission. Synthetic organic chemicals, United States production. USITC Publication 1422. Washington, D.C.

Wilkosky, C., H. Checkoway, E.G. Marchall and H.A. Tyroler. 1984. Cancer mortality and solvent exposures in the rubber industry. Am. Indust. Hyg. J. 45:809-811.

WHO. 1984. World Health Organization. Guidelines for drinking water quality. Volume I, Recommendations. EPP/82.39.

# CHLOROBENZENE

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

## I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

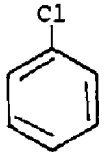
Health Advisories are developed for One-day, Ten-day, Longer-term (approximately 7 years, or 10% of an individual's lifetime) and Lifetime exposures based on data describing noncarcinogenic end points of toxicity. Health Advisories do not quantitatively incorporate any potential carcinogenic risk from such exposure. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

This Health Advisory (HA) is based on information presented in the Office of Drinking Water's draft Health Effects Criteria Document (CD) for Chlorobenzene (U.S. EPA, 1985a). The HA and CD formats are similar for easy reference. Individuals desiring further information on the toxicological data base or rationale for risk characterization should consult the CD. The CD is available for review at each EPA Regional Office of Drinking Water counterpart (e.g., Water Supply Branch or Drinking Water Branch), or for a fee from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Rd., Springfield, VA 22161, PB #86-117769/AS. The toll-free number is (800) 336-4700; in the Washington, D.C. area: (703) 487-4650.

## II. GENERAL INFORMATION AND PROPOERTIES

CAS No. 108-90-7

Structural Formula




Synonyms

- Monochlorobenzene, benzene chloride, chlorobenzol, phenyl chloride.

Uses

- Production of chloronitrobenzene and diphenyl ether; rubber intermediates; solvent in adhesives, paints, waxes, polishes; and inert solvent.

Properties: (Irish, 1963)

| | |
|---|---|
| Chemical Formula | $C_6H_5Cl$ |
| Molecular Weight | 112.6 |
| Physical State (room temp.) | Colorless, neutral liquid |
| Boiling Point | 132°C |
| Melting Point | -45°C |
| Density | -- |
| Vapor Pressure | 11.8 mm Hg (at 25°C) |
| Specific Gravity | 1.106 (at 25°C) |
| Water Solubility | 500 mg/L (at 20°C) |
| Oil/Water Coefficient | 918 (Sato and Nakajima, 1979) |
| Log Octanol/Water Partition Coefficient | 2.84 (Leo et al., 1971) |
| Odor/Taste Threshold (water) | 0.41-1.5 ug/L (Tarkhova, 1965)<br>10-20 ug/L (Varshavskaya, 1968) |
| Odor Threshold (water) | 50 ug/L (Amoore and Hautala, 1983) |
| Odor Threshold (medium unknown) | 0.21 mg/L (A.D. Little, 1968) |
| Conversion Factor (air) | 1 ppm = 4.7 $mg/m^3$ |

Occurrence

- There are no natural sources of chlorobenzene.

- Chlorobenzene production in 1984 was 256 million lbs (USITC, 1985). The majority of releases result from chlorobenzene's use as a solvent. Due to chlorobenzene's volatility, most of its environmental releases occur to air. Chlorobenzene is released to water and the ground during the disposal of waste solvent. Because chlorobenzene is used in metal cleaning operations, releases occur in industrial areas nationwide (U.S. EPA, 1987).

- Chlorobenzene released to the atmosphere is expected to degrade slowly by free radical oxidation. Chlorobenzene released to surface water is expected to partition rapidly to air where it also is expected to degrade. Chlorobenzene has been shown to be relatively resistant to biodegradation. Based on limited studies, EPA estimates the half-life of chlorobenzene in soil to be several months. When released to the ground, chlorobenzene is expected to bind to soil and to migrate slowly to ground water. Chlorobenzene has been reported to bioaccumulate in fish, aquatic invertebrates and algae. In higher organisms, chlorobenzene has been shown to be metabolized to other compounds (U.S. EPA, 1979).

- Chlorobenzene rarely occurs as an environmental contaminant. Federal surveys of drinking waters derived from surface water have not reported the presence of chlorobenzene. A few groundwater systems have been found with chlorobenzene levels in the low ppb range. No information of the occurrence of chlorobenzene in food has been identified. Chlorobenzene has been identified as a contaminant of air at very low levels (less than 1 ppb) in urban and suburban areas. Even with the low levels of chlorobenzene in air, inhalation is probably the major route of environmental exposure (U.S. EPA, 1983).

## III. PHARMACOKINETICS

Absorption

- No data are available which demonstrate the percentage of the dose absorbed following oral exposure. Based upon what is known about the high lipid solubility of chlorobenzene along with absorption characteristics of benzene and the smaller chlorinated ethanes and ethylenes which are also highly lipid soluble, it will be assumed, for the purpose of the development of Health Advisories, that 100% of any orally administered dose is absorbed, while 60% of a dose inhaled over a period of one to several hours is absorbed and retained (Astrand, 1975; Dallas et al., 1983).

Distribution

- Sullivan et al. (1983) studied the distribution of $^{14}C$-chlorobenzene in male Sprague-Dawley rats following single or multiple 8-hour inhalation exposures at 100, 400 or 700 ppm (460, 1,880 or 3,290

mg/m$^3$). The highest concentrations were found in the fat (epididymal and perirenal). The kidneys and liver also showed significant amounts. The amounts found in these tissues were proportional to dose except for adipose tissue which showed greatly exaggerated accumulation with dose when compared to the other tissues. The $^{14}C$ burden of adipose tissue increased with increasing exposure concentrations. In addition, there also was a tendency for multiply-exposed rats to exhibit higher tissue burdens than rats exposed only once.

Metabolism

- The metabolic transformation of chlorobenzene has been studied in several mammalian species, including the human (Williams et al., 1975). While absolute quantities and ratios differ between species, the principal metabolites for each species are p-chlorophenol, p-chlorocatechol and p-chlorophenyl-mercapturic acid.

- Because of its lipophilicity (log P =2.96), chlorobenzene tends to bioaccumulate in adipose tissue as exposure continues (Sullivan, et al., 1983). Upon termination of exposure, the chemical would be expected to be released from the fat stores and become available for metabolic activation and potential continuation of induction of toxicity.

Excretion

- The chlorophenol metabolite is excreted as the ethereal sulfate or the glucuronide (Spencer and Williams, 1950; Azouz, et al, 1953). Other excretion products include the chlorophenyl mercapturic acid, 4-chlorocatechol, and to a lesser degree in some species, phenol and hydroquinone (Williams et al., 1975; Sullivan et al., 1983).

- When the metabolic pathways for chlorobenzene biotransformation become saturated, increasing amounts of the chemical are exhaled unchanged (Sullivan et al., 1983). In rats exposed to 100 ppm (470 mg/m$^3$) (a dose which did not saturate metabolic pathways) in air for 8 hours, 5% was excreted via inhalation and 95% in the urine. Repeated dosing (8 hr/day for 4 or 5 days) at 700 ppm (a dose that does saturate metabolic pathways) results in 32% being exhaled and 68% excreted in the urine.

## IV. HEALTH EFFECTS

Humans

- The only information available on the effects of chlorobenzene in the human comes from case reports of poisonings or occupational exposures. No data on actual exposure concentrations are presented in any of these reports.

- Inhalation exposure to chlorobenzene has been observed to result in signs of central nervous depression (sedation and narcosis) as well

as irritation of the eye and respiratory tract (Rozenbaum et al., 1947; Girard et al., 1969; Smirnova and Granik, 1970).

- Rozenbaum et al. (1947) also noted thrombocytopenia and leukopenia in some of the workers described in their study. The question arises as to whether this effect was induced by the chlorobenzene or some contaminant.

- Cardiac effects such as chest pain, bradycardia and ECG irregularities and toxemia of pregnancy have been noted in individuals exposed to chemicals used in the production of chlorobenzene (Dunaeveskii, 1972; Petrova and Vishnevskii, 1972). Chlorobenzene cannot be identified as the causative agent since these workers were exposed to mixtures of substances over varying periods of time.

Animals

Short-term Exposure

- Reported oral $LD_{50}$'s in adult animals range from 2.8 to 3.4 g/kg (Irish, 1963; Vecerek et al., 1976). Reported inhalation $LC_{50}$'s range from 0.05 (guinea pig) to 20 mg/l (mouse-2 hour exposure) (Rozenbaum et al., 1947; Lecca-Radu, 1959).

- In rats, single subcutaneous doses greater than 5 g/kg produced hyperexcitability and muscle spasms, followed by CNS depression and death (Rozenbaum, et al, 1947; von Oettingen, 1955).

- Chlorobenzene causes necrosis of the liver and interferes with porphyrin metabolism (Rimington and Ziegler, 1963; Khanin, 1969; Knapp et al., 1971). Oral doses of 1140 mg/kg/day administered to rats for 5 days resulted in increases in urinary excretion of coproporphyrin III, uroporphyrin and porphobilinogen (Rimington and Ziegler, 1963). Delta-aminolevulinic acid levels also were increased as were liver protoporphyrin and uroporphyrin.

- Kidneys of rabbits receiving 2 to 20 doses of chlorobenzene at 0.9 mg/kg by injection over a two-week period showed swelling of the tubular and glomerular epithelia (Rozenbaum et al., 1947).

- Chlorobenzene has been shown to produce alterations in bile duct-pancreatic flow (a phenomenon of unexplained significance)(Yang et al., 1979), and blood dyscrasias such as leukopenia and lymphocytosis (Cameron et al. 1937; Rozenbaum et al., 1947; Zub, 1979). As noted for the human, there is a question as to whether these hematopoietic effects resulted from chlorobenzene or a contaminant.

- Administration of chlorobenzene in corn oil by gavage for 14 consecutive days to male and female F344/N rats and $B6C3F_1$ mice was ineffective in rats and mice at doses of 500 mg/kg/day. Rats were also given 1,000 and 2,000 mg/kg/day doses, which were fatal. Survival, body weights and necropsies data were obtained. Histopathology was not performed.

Long-term Exposure

- Adolescent dogs (6/sex/group) were exposed to chlorobenzene vapors at target levels of 0, 0.78, 1.57 or 2.08 mg/l air for 6 hr/day, 5 days/week for 6 months (Monsanto, 1980). Significant changes included a decrease in absolute adrenal weights in males at the mid- and high-dose levels, an increase in liver:body weight ratio in females at the mid- and high-doses, a sex-independent, dose-related increased incidence in emesis and an increase in the frequency of abnormal stools in treated females. The NOAEL is 0.78 mg/L.

- Oral administration of chlorobenzene by capsule at doses of 0, 27.25, 54.5 or 272.5 mg/kg/day to male and female beagle dogs daily, 5 days/week, until sacrifice at 93 days resulted in observable effects (mortality, lesions, various toxic effects) only at the high dose (Knapp et al., 1971; Hazelton, 1967a). The NOAEL is 54.5 mg/kg/day.

- Oral dosing of rats at levels of 14.4, 144 or 288 mg/kg/day, 5 days/week for 6 months yielded significant increases in liver and kidney weights and histopathological changes in the livers of mid- and high-dose animals (Irish, 1963). No changes were observed at the low dose. The NOAEL is 14.4 mg/kg/day.

- Male and female rats were fed chlorobenzene in their diets at levels equal to 12.5, 50, 100 or 150 mg/kg/day for 90 to 99 days (Knapp, et al., 1971; Hazelton, 1967b). Males showed retarded growth at the highest dose. At the mid- and high dose levels, significant increases in liver and kidney weights were noted. The two lowest dose produced no adverse effects. The NOAEL is 50 mg/kg/day.

- In subchronic (90 or 91 day) studies in which both sexes of rats and mice received chlorobenzene in corn oil by gavage five times weekly with 0, 60, 125, 250, 500 or 750 mg/kg/day (NTP, 1985; Battelle, 1978a,b). Rats and mice showed depressed body weight gain at the highest three doses. In rats, polyuria and porphyria were noted at the two highest doses. Histopathology was noted in the liver, kidney and lymphoid tissue in both species at the three highest doses. Liver and liver/body weights were increased in male mice and female rats at doses above 60 mg/kg. The NOAEL is 60 mg/kg/day.

- The only chronic exposure study available on chlorobenzene is the NTP gavage bioassay in rats and mice (NTP, 1985). On five days/week, both sexes of rats and female mice received 60 or 120 mg chlorobenzene/kg day in corn oil; male mice received 30 or 60 mg/kg/day. Significant changes included equivocal mild to minimal liver necrosis in the rats and a decrease in the survival rate for low dose male mice, but not high dose male mice. The NOAEL is 60 mg/kg/day.

Reproductive Effects

- There are no available data on reproductive effects of chlorobenzene.

Developmental Effects

- John et al. (1984) and Hayes et al. (1982) have reported the results of a two-phase teratology study in which pregnant rats and rabbits were exposed via inhalation to 0, 75, 210 or 590 ppm chlorobenzene, 6 hr/day, during the period of major organogenesis (days 6 through 15 for rats;days 6 through 18 for rabbits). In the rats, maternal toxicity (decreased body weight gain) was observed at the highest dose. No teratological changes were observed in fetuses from rats exposed at any dose. Rabbits showed maternal toxicity (statistically significant increase in relative and absolute liver weights) at the mid and high doses. Again, no structural malformations were noted in the fetuses. However, since the control group exhibited malformations at levels higher than historically noted, the rabbit study was repeated, using doses of 0, 10, 30, 75 or 590 ppm. In this study, no significant changes in rates and types of malformations were observed.

Mutagenicity

- Chlorobenzene has been shown to cause mitotic disturbances in Allium cepa (Ostergen and Levan, 1943) and reverse mutations in Streptococcus antibioticus (Koshkinova, 1968) and Aspergillus nidulans (Prasad and Pramer, 1968;Prasad, 1970).

- Chlorobenzene was not mutagenic in the Ames Salmonella assay or in E. coli, either with or without metabolic activation (Monsanto, 1976a; Dupont, 1977;Merck, 1978; Simmon et al., 1979).

- Chlorobenzene did not induce specific locus forward mutations in mouse lymphoma L5178Y cells, either with or without activation (Monsanto, 1976b).

- Chlorobenzene did induce reciprocal recombination in the yeast Saccharomyces cerevisiae strain D3 in the presence of the metabolic activation system (Simmon et al. 1979).

Carcinogenicity

- Chlorobenzene has been tested for carcinogenic potential in rats and mice in the NTP Bioassay Program (NTP, 1985). The report of these studies states that the chemical produced a statistically significant increase in the incidence of neoplastic nodules of the liver in high dose (120 mg/kg/day) male rats. Incidences of neoplastic nodules in male rats were 2/50 in untreated controls, 2/50 in vehicle controls, 4/49 in low dose and 8/49 in high dose. However, there were also hepatocellular carcinomas in two vehicle control male rats, and combining these with the neoplastic nodule data results in an increase in high dose males of borderline significance ($P = 0.048$) by one statistical test (life table) of the three used (also incidental tumor test and Fischer's exact test) by the NTP. No increased incidence was observed in numbers of hepatocellular carcinomas in male rats or of neoplastic nodules or hepatocellular carcinomas in female rats or mice of either sex.

## V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for One-day, Ten-day, Longer-term (approximately 7 years) and Lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(NOAEL \text{ or } LOAEL) \times (BW)}{(UF) \times (\_\_\_ L/day)} = \_\_\_ mg/L \ (\_\_\_ ug/L)$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect-Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100 or 1,000), in accordance with NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

### One-day and Ten-day Health Advisories

No satisfactory data are available from which to calculate One-day and Ten-day HAs for the 10 kg child. The 14-day studies in rats and mice by the NTP (1985) are not selected because of inadequate assessment of toxicity in these studies. It is recommended that, for this duration of exposure, the Longer-term HA for a 10-kg child be applied. Therefore, the One-day and Ten-day Health Advisories are 4.3 mg/L (4,300 ug/L).

### Longer-term Health Advisory

Subchronic studies were conducted in which both rats and mice were dosed by gavage five times weekly with chlorobenzene at 0, 60, 125, 250, 500 or 750 mg/kg in corn oil (10 animals/species/sex/dose level) (NTP, 1985; Battelle, 1978a,b). Deaths were found with the three highest doses in mice and the two highest doses in rats. Food consumption did not vary among the groups in mice, but it was lower in the two highest dose rat groups. Body weight gain was affected in both species, with significant changes observed in mice and rats at the three highest doses. No clinically significant chlorobenzene-related changes were observed in any of the hematological parameters measured in either species. None of the clinical chemistry parameters measured in mice were changed. However, in the rats, alkaline phosphatase and GGPT levels were slightly elevated at 500 and 750 mg/kg. Urinalyses of the controls and two highest dose groups revealed a dose-dependent polyuria with concomitant decreases in specific gravity and creatinine concentration. At the two highest doses, urinary coproporphyrin excretion was increased in rats. In mice, this increase was observed only in females at 250 and 500 mg/kg. Liver and body weight ratios were increased significantly in female mice at 250 and 500 mg/kg and in male mice at 125 and 250 mg/kg. Both male and female rats at 250 and

500 mg/kg and females at 125 mg/kg showed these increases. Absolute and organ/body weights for spleen were decreased in all treated groups of male rats but with no clear dose response. Mice and rats at the three highest doses (250, 500 and 750 mg/kg) all exhibited significant histopathological changes including hepatic necrosis, nephrosis, myeloid depletion, lymphoid depletion and lymphoid necrosis. The 60 mg/kg/day NOAEL with 5 days/week treatment of rats and mice in the NTP (1985) study is equivalent to the 54.5 mg/kg/day, 5 days/week NOAEL in dogs and the 50 mg/kg/day, 7 days/week NOAEL in the Hazelton (1967a,b) studies.

From the NTP (1985) data, a NOAEL of 60 mg/kg/day was identified.

A Longer-term Health Advisory is calculated as follows:

For the 10-kg child:

$$\text{Longer-term HA} = \frac{(60\ \text{mg/kg/day})\ (10\ \text{kg})\ (5)}{(100)\ (1\ \text{L/day})\ \ (7)} = 4.3\ \text{mg/L}\ (4{,}300\ \text{ug/L})$$

where:

60 mg/kg/day = NOAEL, based upon absence of various effects at higher doses in rats and mice.

10 kg = assumed body weight of a child.

5/7 = conversion of 5 day/week exposure to 7 day/week exposure.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

For the 70-kg adult:

$$\text{Longer-term HA} = \frac{(60\ \text{mg/kg/day})\ (70\ \text{kg})\ (5)}{(100)\ (2\ \text{L/day})\ \ (7)} = 15.0\ \text{mg/L}\ (15{,}000\ \text{ug/L})$$

where:

60 mg/kg/day = NOAEL, based upon absence of various effects at higher doses in rats and mice.

70 kg = assumed body weight of an adult.

5/7 = conversion of 5 day/week exposure to 7 day/week exposure.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

2 L/day = assumed daily water consumption of an adult.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed for synthetic organic chemicals and a value of 10% is assumed for inorganic chemicals. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

The data base used for the derivation of the Longer-term Health Advisories also is selected for deriving the Lifetime Health Advisory in that more toxicologic endpoints and species were assessed in the subchronic studies compared to the NTP (1985) carcinogenicity bioassay.

The Lifetime Health Advisory is calculated as follows:

Step 1: Determination of the Reference Dose (RfD)

$$RfD = \frac{(60\ mg/kg/day)(5)}{(1{,}000)\quad(7)} = 0.043\ mg/kg/day$$

where:

60 mg/kg/day = NOAEL based upon absence of various effects at higher doses.

5/7 = conversion of 5 day/week exposure to 7 day/week exposure.

1,000 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study of less-than-lifetime duration.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$DWEL = \frac{(0.043\ mg/kg/day)\ (70\ kg)}{(2\ L/day)} = 1.51\ mg/L\ (1{,}510\ ug/L)$$

where:

0.043 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

Lifetime HA = 1.5 mg/L x 20% = 0.3 mg/L (300 ug/L)

It is important to note that the taste and odor threshold in water has been identified at levels ranging from 0.41 to 1.5 ug/L (Tarkhova, 1965) to 10 to 20 ug/L (Varshavskaya, 1967). All of the Health Advisories derived in this document have been developed on the basis of toxicity, not on the aesthetic characteristics of the water quality. Any guidance developed on a site-specific basis may, however, require one to consider the aesthetic, in addition to the toxic, consequences following exposure to chlorobenzene in the drinking water.

Evaluation of Carcinogenic Potential

- The EPA Carcinogenic Assessment Group (CAG) did not derive a carcinogenic potency factor or range of risk estimates for chlorobenzene (U.S. EPA, 1985b).

- EPA has classified chlorobenzene as to its carcinogenic potential, using the weight of evidence classification scheme in its risk assessment guidelines for carcinogens (U.S. EPA, 1986). The Agency has placed the chemical in Group D: Inadequate evidence. EPA's Carcinogen Assessment Group has not derived a carcinogenicity potency factor ($q_1^*$) or a range of excess lifetime cancer risk estimates.

## VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- EPA (1980) proposed ambient water quality criteria for chlorobenzene, one based upon available toxicity data (488 ug/L) and one based upon organoleptic effects (20 ug/L). These criteria were derived for the 70 kg adult, assumed to drink 2 liters of water per day and eat 6.5 g of contaminated fish and seafood per day. The toxicity-based criteria were calculated using the 14.4 mg/kg/day NOAEL from the study by Irish et al. (1963) and an uncertainty factor of 1,000.

- ACGIH (1982) has adopted a TLV of 75 ppm (350 mg/$m^3$) for chlorobenzene in the workplace.

- On the basis of a 1983 draft of the NTP report (NTP, 1985), the National Academy of Sciences performed a quantitative risk assessment to estimate excess lifetime cancer risk (NAS, 1983). The upper 95% confidence limit estimate of that risk was $2.13 \times 10^{-7}$ per ug/L of drinking water. This corresponds to a drinking water concentration of 2.35 ug/L being equivalent to a 1 in a million excess risk.

Assumptions were defined for a 70-kg adult, drinking 2 liters of water per day.

- WHO (1984) recommended a guideline for chlorobenzene of 3 ug/L based upon avoidance of taste and odor problems.

- The U.S. EPA Office of Drinking Water proposed an RMCL of 0.06 mg/L (U.S. EPA, 1985c).

## VII. ANALYTICAL METHODS

- Analysis of chlorobenzene is by the purge-and-trap gas chromatographic procedure used for the determination of volatile organohalides in drinking water (U.S. EPA, 1984a). This method calls for the bubbling of an inert gas through the sample and trapping chlorobenzene on an adsorbant material. The adsorbant material is heated to drive off the chlorobenzene onto a gas chromatographic column. This method is applicable to the measurement of chlorobenzene over a concentration range of 0.05 to 1500 ug/L. Confirmatory analysis for chlorobenzene is by mass spectrometry (U.S. EPA, 1985d). The detection limit for confirmation by mass spectometry is 0.3 ug/L.

## VIII. TREATMENT TECHNOLOGIES

- Treatment techniques which are effective in removing chlorobenzene from drinking water include adsorption on granular activated carbon (GAC) or powdered activated carbon (PAC). Aeration, reverse osmosis and boiling also are capable of removing chlorobenzene.

- Dobbs and Cohen (1980) developed adsorption isotherms for a number of organic chemicals, including chlorobenzene. They found that Filtrasorb ® 300 carbon had a capacity of 91 mg of chlorobenzene per gram of carbon at an equilibrium concentration of 1.0 mg/L and 9.3 mg/g at a concentration of 100 ug/L.

- PAC gave inconsistent removal rates when it was added to well water containing several contaminants including chlorobenzene (U.S. EPA, 1985b).

- Conventional coagulation filtration treatment does not appear to be effective in chlorobenzene removal. Limited data collected at Water Factory 21 indicated that there was an 18.2% removal of chlorobenzene when only filtration was used (U.S. EPA, 1985b). Another study of conventional treatment practices found them to be completely ineffective in chlorobenzene removal (Love et al., 1983).

- The Henry's Law Constant for chlorobenzene is 145 atm at 20°C (U.S. EPA, 1985b). This indicates that the chemical might be amenable to removal by aeration. In a bench-scale study, a diffused air aerator reduced the chlorobenzene in a 97 ug/L solution by 90% using a 15:1 air-to-water ratio (Love et al., 1983).

- Air stripping is an effective, simple and relatively inexpensive process for removing chlorobenzene and other volatile organics from water. However, the use of this process then transfers the contaminant directly into the air stream. When considering use of air stripping as a treatment process, it is suggested that careful consideration be given to the overall environmental occurrence, fate, route of exposure and various hazards associated with the chemical.

- Degradation with ozone is ineffective as a method for removing chlorobenzene (U.S. EPA, 1985d).

- Reverse osmosis appears to have the potential for use in chlorobenzene removal. A laboratory study reviewed by EPA reported successful decontamination with 97 to 100% of the chlorobenzene removed.

## IX. REFERENCES

ACGIH. 1982. American Conference of Government Industrial Hygienists. TLVs. Threshold limit values for chemical substances and physical agents in the work environment with intended changes for 1982. Cincinnati, Ohio. p. 13.

Amoore, J.E., and E. Hautala. 1983. Odor as an aid to chemical safety: Odor threshold compounds with threshold unit values and volatilities for 714 industrial chemicals in air and water dilution. J. Appl. Toxicol. 3:272-290.

Astrand, I. 1975. Uptake of solvents in the blood and tissue of man. Scand. J. Work Environ. Hlth. 1:199-218.

Azouz, W.M., D.V. Parke and R.T Williams. 1953. Studies in detoxication. 51: The determination of catechols in urine, and the formation of catechols in rabbits receiving halogenobenzenes and other compounds, dihydroxylation in vivo. Biochem. J. 55(1):146-151.

Battelle. 1978a. Battelle's Columbus Laboratories. Chlorobenzene. Prechronic test phase review - mouse. Establishment of doses for subchronic. Unpublished report. NTP Subcontract No. 76-34-106002.

Battelle. 1978b. Battelle's Columbus Laboratories. Chlorobenzene. Prechronic test phase review - rat. Establishment of doses for subchronic. Unpublished report. NTP Subcontract No.76-34-106002.

Cameron, G.R., J.C. Thomas, S.A. Ashmore, J.L. Buchan, E.H. Warren and A.W. McKenny Hughes. 1937. The toxicity of certain chlorine derivatives of benzene with special reference to o-dichlorobenzene. J. Path. Bact. 44:281-296.

Dallas, C.E., F.W. Weir, S. Feldman, L. Putcha and J.V. Bruckner. 1983. The uptake and disposition of 1,1-dichloroethylene in rats during inhalation exposure. Toxicol. Appl. Pharmacol. 68:140-151.

Dobbs, R.A., and J.M. Cohen. 1980. Carbon adsorption isotherms for toxic organics. EPA 600/8-80-023. MERL, Cincinnati, Ohio.

Dunaeveskii, G.A. 1972. Functional condition of circulatory organs in workers employed in the production of organic compounds. Gig. Tr. Prof. Zabol.16:48.

Dupont, 1977. Mutagenic activity of monochlorobenzene in the Salmonella-microsome assay. Haskell Laboratory for Toxicology and Industrial Medicine. Unpublished Report.

Girard, R., F. Tolot, P. Martin and J. Bourret. 1969. Serious blood disorders and exposure to chlorine derivatives of benzene (A report of seven cases). J. Med. Lyon 50(1164):771-773. (Fr.)

Hayes, W.C, T.S. Gushaw, K.A. Johnson, T.R. Hanley, Jr., J.H. Ouellette and J.A. John. 1982. Monochlorobenzene inhalation teratology study in rats and rabbits. Unpublished Report. Toxicology Research Laboratory. Dow Chemical Company. 115 pp.

Hazelton Laboratories. 1967a. 13-Week oral administration -- dogs. Monochlorobenzene. Final report. Submitted to Monsanto Company. Project No. 241-105. February 24.

Hazelton Laboratories. 1967b. Three-month subacute oral study -- rats. Monochlorobenzene. Final report. Submitted to Monsanto Company. Project No. 241-104. March 9.

Irish, D.D. 1963. Halogenated hydrocarbons. II. Cyclic In: Patty's Industrial Hygiene and Toxicology. Volume II. D.W. Fassett and D.D. Irish, eds. Interscience Publishers. New York, N.Y. pp. 1333-1362.

John, J.A., W.C. Hayes, T.R. Hanley, Jr., K.A. Johnson, T.S. Gushow and K.S. Rao. 1984. Inhalation teratology study on monochlorobenzene in rats and rabbits. Toxicol. Appl. Pharmacol. 76:365-373.

Khanin, A.G. 1969. Pathohistological changes in the central nervous system and internal organs of experimental animals after chronic, 24-hour inhalation of toxic substances. T. Tsent. Inst. Vsoversh, Vrachei. 135:97-106. (Russ.)

Knapp, W.K., W.M. Busey and W. Kundzins. 1971. Subacute oral toxicity of monochlorobenzene in dogs and rats. Toxicol. Appl. Pharmacol. 19:393 (Abstract).

Koshkinova, D.V. 1968. The effect of dimethylcyclodiazomethane in chlorobenzene solution on mutagenesis in Actinomyces antibiotius 400. Genetika. 4(8):121-125. (Russ.)

Lecca-Radu. 1959. Modifications of blood carbonic anhydrase and leucocytic indophenol oxidase in chronic benzene and monochlorobenzene intoxication. Igiena 8:231-240.

Leo, A., C. Hansek and B. Elkins. 1971. Partition coefficients and their uses. Chem. Rev. 71(6):525-616.

Little, A.D. 1968. Research of chemical odors: Part I. Odor thresholds for 53 commercial chemicals. Manufacturing Chemists Association, Washington, D.C., pp. 22-23, October.

Love, G.T., R.J. Miltner, R.G. Eilers and C.D. Pronk-Leist. 1983. Treatment of volatile organic compounds in drinking water. U.S. EPA. MERL. EPA 600/8-83-019.

Merck. 1978. Monochlorobenzene: Bacterial mutagen test (Ames test). West Point, PA. Merck and Co., Inc. Unpublished.

Monsanto Company. 1976a. Mutagenicity evaluation of B10-76-86-CP-5535 (WGK). Final report. LBI Project No. 2547. Kensington, MD. Litton Bionetics. Unpublished.

Monsanto Company. 1976b. Mutagenicity evaluation of B10-76-86-CP-5535 (LOX). Final report. LBI Project No. 2547. Kensington, MD. Litton Bionetics. Unpublished.

Monsanto Company. 1980. Subchronic inhalation toxicity study of monochlorobenzene to male and female dogs. Environmental Health Laboratory Report. Number R80-53. Project #790015/DMEH ML-79-025. October, 30. Unpublished.

NAS. 1983. National Academy of Sciences. Drinking Water and Health. Volume 5. National Academy Press, Washington, DC. pp. 28-33.

NTP. 1985. National Toxicology Program. Toxicology and carcinogenesis studies of dichlorobenzene (CAS No. 108-90-7) in F344/N rats and B6C3F1 mice (gavage studies). U.S. Department of Health and Human Services. Public Health Service. National Institutes of Health. NTP No. 261. NIH Publication No. 83-2517.

Ostergren, G., and A. Levan. 1943. The connection between C-mitotic activity and water solubility in some monocyclic compounds. Hereditas. 29:496-498.

Petrova, N.L., and A.A. Vishnevskii. 1972. Course of pregnancy and deliveries in women working in the organosilicon varnish and enamel industries. Nauch Jr. Inrutsk. Med. Inst. 115:102.

Prasad, I. 1970. Mutagenic effects of the herbicide 3,4-dichloropropionanilide and its degradation products. Can. J. Microbiol. 16:369-372.

Prasad, I., and D. Pramer. 1968. Mutagenic activity of some chloroanilines and chlorobenzenes. Genetics. 20:212-

Rimington, G.E., and G. Ziegler. 1963. Experimental porphyria in rats induced by chlorinated benzenes. Biochem. Pharmacol. 12:1387-1397.

Rozenbaum, N.D., R.S. Block, S.N. Kremneva, S.L. Ginzburg and I.V. Pozhatiskii. 1947. Use of chlorobenzene as a solvent from the standpoint of industrial hygiene. Gig. Sanit. 12(1):21-24. (Russ.)

Sato, A., and T. Nakajima. 1979. A structure-activity relationship of some chlorinated hydrocarbons. Arch. Environ. Health. (March-April) 69-75.

Simmon, V.F., E.C. Ricco and M.V. Pierce. 1979. In vitro microbiological genotoxicity assays of chlorobenzene, m-dichlorobenzene, o-dichlorobenzene and p-dichlorobenzene. Final report. Menlo Park, CA. SRI International. Unpublished.

Smirnova, N.A., and N.P. Granik. 1970. Remote consequences of acute occupational poisoning by some hydrocarbons and their derivatives. Gig. Truda i Prof. Zabol. 5:50-51. (Russ.)

Spencer, B., and R.T. Williams. 1950. Studies in detoxication. 33. The metabolism of halogenobenzenes. A comparison of the glucuronic acid, etheral sulfate and mercapturic acid. Conjugation of chloro-, bromo-, and iodobenzene and of the o-, m-, and p-chlorophenyl glucuronides. Biochem. J. 47:279-284.

Sullivan, T.M., G.S. Born, G.P. Carlson and W.V. Kessler. 1983. The pharmacokinetics of inhaled chlorobenzene in the rat. Toxicol. Appl. Pharmacol. 71:194-203.

Tarkhova. 1965. Cited in: Compilation of odour threshold values in air and water. L.J. van Gemert and A.H. Nettenbreijer, eds. National Institute for Water Supply. Voorburg, Netherlands. 1977.

U.S. EPA. 1979. U.S. Environmental Protection Agency. Water related environmental fate of 129 priority pollutants. Office of Water Planning and Standards. EPA-440/4-79-029. December.

U.S. EPA. 1980. U.S. Environmental Protection Agency. Ambient water quality criteria for chlorinated benzenes. Office of Water Regulations and Standards. Criteria and Standards Division. Washington, D.C. EPA 440/5-80-028.

U.S. EPA. 1983. U.S. Environmental Protection Agency. Chlorobenzene occurrence in drinking water, food, and air. Office of Drinking Water.

U.S. EPA. 1984. U.S. Environmental Protection Agency. Method 502.1. Volatile halogenated organic compounds in water by purge and trap gas chromatography. Environmental Monitoring and Support Laboratory, Cincinnati, Ohio 45268. June.

U.S. EPA. 1985a. U.S. Environmental Protection Agency. Draft health effects criteria document for chlorobenzene. Criteria and Standards Division, Office of Drinking Water, Washington, DC.

U.S. EPA. 1985b. U.S. Environmental Protection Agency. Health assessment document for chlorinated benzenes. Office of Health and Environmental Assessment. EPA 600/8-84-015F.

U.S. EPA. 1985c. U.S. Environmental Protection Agency. National primary drinking water regulations; Synthetic organic chemicals, inorganic chemicals and microorganisms; Proposed rule. Federal Register. 50(219):469341-47022. November 13.

U.S. EPA. 1985d. U.S. Environmental Protection Agency. Method 524.1. Volatile organic compounds in water by purge and trap gas chromatography/ mass spectrometry. Enviromental Monitoring and Support Laboratory, Cincinnati, Ohio. June.

U.S. EPA. 1986. U.S. Environmental Protection Agency. Guidelines for carcinogenic risk assessment. Federal Register. 51(185):33992-34003. September 24.

U.S. EPA. 1987. U.S. Environmental Protection Agency. Occurrence of synthetic organic chemicals in drinking water, food, and air. Office of Drinking Water.

USITC. 1985. U.S. International Trade Commission. Synthetic organic chemicals, United States production and sales, 1984 (Investigation No. 332-135), USITC Publication 1745. U.S. Government Printing Office. Washington, D.C.

Varshavskaya, S.P. 1968. Comparative toxicological characteristics of chlorobenzene and dichlorobenzene (ortho- and para- isomers) in relation to the sanitary protection of water bodies. Gig. Sanit. 33(10):17-23.

Vecerek, B., G.I. Kondraskin, K. Hatle, L. Kyslikova and K. Jojkova. 1976. Xenobiological characteristics of chlorobenzene. Bratisl. lek. Listy. 65(1):9-14.

von Oettingen, W.F. 1955. The halogenated aromatic hydrocarbons. In: The halogenated aliphatic, olefinic, cyclic, aromatic and aliphatic aromatic hydrocarbons, including the halogenated insecticides, their toxicity and potential dangers. U.S. Dept. Health, Education and Welfare, Rockville, MD. No. 414:283-299.

WHO. 1984. World Health Organization. Guidelines for drinking-water quality. Vol.1 Recommendations. Geneva. p. 73.

Williams, R.T., P.C. Hirom and A.G. Renwick. 1975. Species variation in the metabolism of some organic halogen compounds. In: Ecological Toxicological Research. A.D. McIntrye and C.F. Mills, eds. Plenum Press, New York, N.Y. pp. 99-105.

Yang, K.H., R.E. Peterson and J.M. Fujimoto. 1979. Increased bile duct-pancreatic flow in benzene and halogenated benzene-treated rats. Toxicol. Appl. Pharmacol. 47:505-514.

Zub, M. 1979. Reactivity of the white blood cell system to toxic action of benzene and its derivatives. Acta Biol. Cracov Serv. Zool. 21(2):163-174.

# ORTHO-, META-, AND PARA-DICHLOROBENZENES

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

## I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

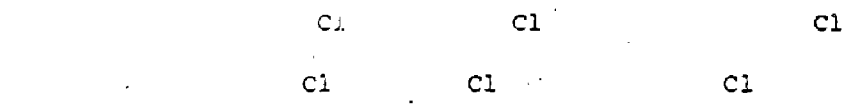
Health Advisories are developed for One-day, Ten-day, Longer-term (approximately 7 years, or 10% of an individual's lifetime) and Lifetime exposures based on data describing noncarcinogenic end points of toxicity. Health Advisories do not quantitatively incorporate any potential carcinogenic risk from such exposure. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

This Health Advisory (HA) is based on information presented in the Office of Drinking Water's Health Effects Criteria Document (CD) for ortho-, meta-, and para-dichlorobenzenes (U.S. EPA, 1987). The HA and CD formats are similar for easy reference. Individuals desiring further information on the toxicological data base or rationale for risk characterization should consult the CD. The CD is available for review at each EPA Regional Office of Drinking Water counterpart (e.g., Water Supply Branch or Drinking Water Branch), or for a fee from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Rd., Springfield, VA 22161, PB #86-117918/AS. The toll-free number is (800) 336-4700; in the Washington, D.C. area: (703) 487-4650.

## II. GENERAL INFORMATION AND PROPERTIES

| CAS No. | o-DCB | m-DCB | p-DCB |
|---|---|---|---|
| | 95-50-1 | 541-73-1 | 106-46-7 |

Structural Formula



Synonyms

- o-DCB, m-DCB, p-DCB; 1,2-dichlorobenzene, 1,3-dichlorobenzene, 1,4-dichlorobenzene.

Uses (U.S. EPA, 1987)

- o-DCB: Solvent, chemical intermediate, deodorizer
  p-DCB: Deodorizer, insecticide
  m-DCB: None documented

Properties (U.S. EPA, 1987; 1985a)

o-DCB

| | |
|---|---|
| Molecular Formula | $C_6H_4Cl_2$ |
| Molecular Weight | 147.01 |
| Physical State | Colorless liquid |
| Boiling Point | 179°C |
| Melting Point | -17.6°C |
| Density | 1.3 g/mL at 20°C |
| Vapor Pressure | 1.56 mm Hg at 25°C |
| Water Solubility | 145 mg/L |
| Log Olive Oil/Water Partition Coefficient | 3.65 |
| Odor Threshold (water) | 0.01-0.03 mg/L |
| Taste Threshold | -- |
| Conversion Factor (air) | 1 ppm = 6.01 mg/L |

m-DCB

| | |
|---|---|
| Molecular Formula | $C_6H_4Cl_2$ |
| Molecular Weight | 147.01 |
| Physical State | Colorless liquid |
| Boiling Point | 172°C |
| Melting Point | -24.2°C |
| Density | 1.29 g/mL at 20°C |
| Vapor Pressure | 5 mm Hg at 39°C |
| Water Solubility | 1.23 mg/L |
| Log Olive Oil/Water Partition Coefficient | 3.69 |
| Odor Threshold (water) | 0.01-0.03 mg/L |
| Taste Threshold | -- |
| Conversion Factor | -- |

p-DCB

| | |
|---|---|
| Molecular Formula | $C_6H_4Cl_2$ |
| Molecular Weight | 147.01 |
| Physical State | Colorless crystals |
| Boiling Point | 174°C |
| Melting Point | 53°C |
| Density | 1.46 g/mL at 20°C |
| Vapor Pressure | 0.4 mm Hg at 25°C |
| Log Olive Oil/Water Partition Coefficient | 3.65 |
| Water Solubility | 79 mg/L |
| Odor Threshold (water) | 0.01-0.03 mg/L |
| Taste Threshold | -- |
| Conversion Factor (air) | 1 ppm = 6.01 $mg/m^3$ |

Occurrence

- There are no natural sources for the three isomers of dichlorobenzene (DCB).
- Production of the DCB isomers in 1981 was 11 million lbs for the ortho isomer and 15 million for the para isomer. Production of the meta isomer was not reported and is believed to be small.
- Releases of the ortho and meta isomers to the environment are believed to be small. The majority of the para isomer produced is released to the environment during its use as a deodorant and moth repellent. Dichlorobenzenes, while they have a low vapor pressure, are released to the environment largely by evaporation. Dichlorobenzenes in air are expected to degrade within a few days or weeks. Dichlorobenzenes released to surface waters would tend to be removed either by volatilization or adsorption onto soil and sediments. Dichlorobenzenes are biodegraded poorly in the environment. When released to the ground the compounds are expected to bind to soil and only slowly migrate to ground water. Dichlorobenzenes have been reported to bioaccumulate in fish, aquatic invertebrates and algae.

- The DCBs rarely occur as environmental contaminants (U.S. EPA, 1983). Based upon Federal surveys of drinking water, it is estimated that the ortho and para isomers occur at detectable levels in approximately 0.2 and 1.1 percent of all ground water supplies and 0.3 and 0.1 of all surface water supplies, respectively. No levels have been detected greater than 5 ug/L. Federal surveys of drinking waters have not reported finding the meta isomer. No information on the occurrence of DCB in food has been identified. Dichlorobenzenes have been identified as contaminants of air at very low levels (< 40 ppt) in urban and suburban areas. There are insufficient data on the DCBs to identify the major route of environmental exposure.

## III. PHARMACOKINETICS

### Absorption

- No studies have been reported which determine the percentage of a dose of DCB absorbed following oral or inhalation exposure. However, it will be assumed that 100% of an oral dose of any of the isomers of DCB is absorbed and that 60% of an inhalation dose is absorbed when exposure persists for longer than one to three hours (Astrand, 1975; Dallas et al., 1983).

### Distribution

- The ortho- and para- isomers are lipophilic and can be expected to bioaccumulate to some extent, particularly in tissues with high fat content, during prolonged, continuous exposures. Para-DCB has been detected in human adipose tissue and all three isomers have been detected in blood (Dowty et al., 1975; Morita et al., 1975; Morita and Ohi, 1975).

### Metabolism

- After oral administration to rabbits, the DCBs are oxidized principally to phenols. Ortho- and meta-DCB also form catechols (Azouz et al., 1955; Williams, 1959). Although small amounts of the metabolites are excreted as free phenols or catechols, the overwhelming percentage are eliminated as conjugates of glucuronic or sulfuric acids. Ortho- and meta-DCB form mercapturic acids as well, but p-DCB does not (Williams, 1959). The conjugated dichlorophenols appear to be the principal metabolic products of the DCB isomers in humans (Hallowell, 1959; Pagnatto and Walkley, 1965).

### Excretion

- Hawkins et al. (1980) found that, after exposure of female CFY rats to $^{14}C$ p-DCB, more than 90% of the $^{14}C$ was eliminated in urine within five days post-treatment, with the remainder in feces and expired air. During the first two days following treatment, 50 to 60% of the $^{14}C$ was excreted in bile, thus indicating reabsorption in the enterohepatic circulation.

## IV. HEALTH EFFECTS

### Humans

- Cases have been reported in which individuals suffered moderate to severe anemia following exposure to DCBs (concentrations not estimated) (U.S. EPA, 1987). Several instances of skin lesions (e.g., pigmentation and allergic dermatitis) developing after contact also have been reported. Exposure levels were not estimated in these reports.

- In other reported cases, patients complained of vomiting, headaches, irritation of the eyes and upper respiratory tract and profuse rhinitis and periorbital swelling (U.S. EPA, 1987). Anorexia, nausea, vomiting, weight loss, yellow atrophy of the liver and blood dyscrasias also were reported for higher exposure concentrations. Liver damage was sometimes accompanied by porphyria (Hallowell, 1959). Exposure levels were not estimated in these reports.

- Zapata-Gayon (1982) reported headache, dizziness, nausea, and chromosomal breaks in blood samples from men and women exposed to o-DCB (exposures not given) 8 hours per day for 4 days with reduced chromosomal breaks by 6 months after exposure.

### Animals

#### Short-term Exposure

- The DCBs produce sedation and anesthesia in animals after acute oral or parenteral administration (U.S. EPA, 1987). Relatively high doses are needed to produce acute effects. Acute poisoning is characterized by signs of disturbance of the central nervous system including hyperexcitability, restlessness and muscle spasms or tremors. The most frequent cause of death is respiratory depression. Acute and subchronic exposures also may result in kidney and/or liver damage. Liver alterations may be manifested as necrosis/degeneration, perhaps coincident with porphyria.

- Fourteen-day repeated dose gavage studies in mice (30 to 4,000 mg/kg) and rats (60 to 1,000 mg/kg) were conducted with both o- and p-DCB in the prechronic testing phase of the National Toxicology Program (NTP) bioassay on these two substances (Battelle-Columbus, 1978a,b,d,e,f,g,h). In addition to early deaths and lack of body weight gain at the higher doses, animals exhibited histopathological changes indicative of hepatic centrolobular necrosis and degeneration, occasionally with cyto- and karyomegaly, as well as lymphoid depletion of the spleen and thymus. The NOAEL for o-DCB in mice cannot be determined since degeneration and necrosis in liver found at 250 and 500 mg/kg were not assessed at lower doses. In rats given o-DCB, the NOAEL was 250 mg/kg with the LOAEL being 500 mg/kg for decreased body weights in males. For animals given p-DCB, the LOAEL in mice was 250 mg/kg (lowest dose tested) for tissue lesions and in rats the NOAEL was 250 mg/kg and the LOAEL 500 mg/kg (lower body weight in males).

Long-term Exposure

- Gavage doses of o-DCB at 250 and 500 mg/kg given to rats and mice over a thirteen-week schedule of five days/week resulted in hepatic necrosis as well as porphyria (Battelle-Columbus, 1978c,i). Serum GPT levels were increased in mice exhibiting liver histopathology at the highest dose level. Some mice also exhibited myocardial and skeletal muscle mineralization and lymphoid depletion of the thymus and spleen and necrosis of the spleen. Rats also showed pathological changes in their kidneys, characterized by tubular degeneration. No treatment-related effects were observed with doses of 30, 60 and 125 mg/kg.

- Hollingsworth et al. (1958) gave rats a series of 138 doses of o-DCB over a period of 192 days (18.8, 188 or 376 mg/kg/day, five days a week) by gastric intubation. No adverse effects were noted at the lowest dose. With the intermediate dose, slight increases in the weights of the liver and kidney were noted. At the highest dose, there was a moderate increase in the weight of the spleen and swelling and cloudy appearance of the liver.

- Hollingsworth et al. (1958) also assessed the effects of multiple inhalation exposures to o-DCB in rats, guinea pigs, mice, rabbits and monkeys. The animals were exposed seven hours a day, five days a week, for six to seven months. No adverse effects were observed in rats, guinea pigs or mice exposed to 49 ppm (0.29 mg/L), or in rats, guinea pigs, rabbits and monkeys exposed to 93 ppm (0.56 mg/L).

- Twenty oral doses of 10, 100 or 500 mg/kg p-DCB given five days/week to rats produced marked hepatic effects including cloudiness, swelling and centrilobular necrosis at only the highest dose (Hollingsworth et al., 1958). No adverse effects were observed at the other doses.

- Thirteen-week exposures to p-DCB by gavage resulted in histopathological alterations in the liver similar to those observed with o-DCB, but at somewhat higher doses (675 and 800 mg/kg in the mouse, 300 and 600 mg/kg in the rat) (Battelle-Columbus, 1978a,b, 1980a,b). Hepatic necrosis, degeneration and porphyria were found in both species. The spleen and thymus also exhibited histopathological changes similar to those observed with o-DCB. In mice and rats, hematopoietic hypoplasia of the bone marrow occurred in survivors at the highest dose (1,500 mg/kg/day). Rats at the two highest dose levels (1,000 and 1,500 mg/kg) also exhibited epithelial necrosis of the nasal turbinates and small intestine as well as villar bridging of the mucosa of the latter tissue. Again, the rats exhibited multifocal degeneration or necrosis of the cortical tubular epithelium of the kidney. A NOAEL of 150 mg/kg/day for rats and 337.5 mg/kg for mice was identified.

- Oral doses of 188 or 376 mg p-DCB/kg given five days a week, for 192 days (138 doses) to rats produced an increase in the weights of the liver and kidneys (Hollingsworth et al., 1956). At 376 mg/kg, increased splenic weight and slight cirrhosis and focal necrosis of the liver were observed. No adverse effects were seen with the 18.8 mg/kg dose.

- Inhalation studies also were carried out by Hollingsworth et al. (1956) with p-DCB in rats, rabbits, mice and monkeys. The concentrations used were 96, 158, 173, 314 and 798 ppm (0.58, 0.95, 1.04, 2.05 and 4.8 mg/L, respectively). Exposures were conducted seven hours/day, five days/week for six to seven months. Adverse effects observed included liver and kidney lesions with increased organ weights, pulmonary edema and congestion, splenic weight changes and reversible, non-specific eye changes. The NOAELs were 96 ppm in rats and 158 ppm in the other species.

- Because available studies with lifetime exposures were conducted to assess carcinogenicity, they are discussed in the Carcinogenicity section.

Reproductive Effects

- Data on reproductive effects were not found in available literature.

Developmental Effects

- Several teratogenicity studies have been conducted on two of the three isomers of DCB. Hayes et al. (1985) observed no teratogenic or fetotoxic effects in rat or rabbit fetuses whose dams were exposed by inhalation to doses of o-DCB at levels up to 400 ppm. Similarly, no fetotoxic or teratogenic effects were noted in rabbits subjected to exposures of p-DCB at levels up to 500 ppm. In addition, the results of a study by Hodge et al. (1977, summarized in Loeser and Litchfield, 1983), support the conclusions of the Hayes et al. (1985) study in showing that maternal exposure to atmospheric levels of p-DCB up to 500 ppm on days 6 through 15 of pregnancy in the rat does not result in any embryotoxic, fetotoxic or teratogenic effects in the offspring.

Mutagenicity

- Para-dichlorobenzene induces abnormal mitotic division in higher plants. Observed effects include shortening and thickening of chromosomes, precocious separation of chromatids, tetraploid cells, binucleate cells and chromosome bridges (c-mitosis) (Sharma and Battacharya, 1956; Sharma and Sarkar, 1957; Srivastava, 1966; Gupta, 1972). Ortho-DCB was shown to produce abnormal mitotic division in the onion Allium cepa (Ostergren and Levan, 1943).

- Ortho- and para-dichlorobenzene were not mutagenic when tested in a culture of histidine-requiring mutants of Salmonella typhimurium or in the E. coli WP2 system (Anderson et al., 1972; Anderson, 1976; Simmon et al., 1979; Shimizu et al., 1983; NTP, 1985; NTP, 1986). However, all three isomers increased the frequency of back mutation of the methionine-requiring locus in the fungus Aspergillus nidulans (Prasad and Pramer, 1968; Prasad, 1970). In addition, the meta isomer was shown to increase mitotic recombination in the Saccharomyces cerevisiae C3 yeast system (Simmon et al., 1979). The results with the para isomer were ambiguous. These investigators also showed that

both o- and m-DCB interacted with and damaged bacterial DNA in the E. coli W3110 polA+/p3478 polA- differential toxicity assay system. Treatment with p-DCB did not induce forward mutations in mouse lymphoma cells (NTP, 1986), sister-chromatid exchange in Chinese hamster ovary cells (NTP, 1986), and unscheduled DNA synthesis in human lymphocytes (Perocco et al., 1983).

- DCB has not been found to be mutagenic in animals. Guerin et al. (1971) showed that DCB (unspecified isomer) did not produce a significantly different number of mitoses in rat lung cell cultures. Cytogenetic studies with rat bone marrow cells and a dominant lethal study in CD-1 mice following exposure to p-DCB were all negative (Anderson and Hodge, 1976; Anderson and Richardson, 1976; NTP, 1986).

Carcinogenicity

- Hollingsworth et al. (1956, 1958) exposed several species of animals to various oral and inhalation exposures of ortho- and para-dichlorobenzene for six to seven months. No evidence of carcinogenicity was observed; however, the exposure duration was too short to allow conclusions on carcinogenicity to be drawn.

- An assessment of the data from an NTP bioassay using o-DCB administered by gavage indicates that, under the conditions of the study, this substance is not carcinogenic in Fischer 344 rats or B6C3F$_1$ mice (NTP, 1985). The NTP Board of Scientific Counselors added that no non-neoplastic lesions were noted in either the mice or the rats, suggesting that the maximum tolerated dose was not achieved. Both rats and mice (50/sex/dose) were given o-DCB in corn oil by gavage 5 days/week for 103 weeks at doses of 0, 60 or 120 mg/kg. No effect on survival, body weight, and pathology was noted except for lower ($p < 0.001$) survival in high-dose male rats and increased tubular regeneration in kidney of high-dose male mice.

- In an NTP (1986) bioassay on p-DCB in F344 rats and B6C3F$_1$ mice, treatment-related neoplastic effects include renal adenocarcinomas in male rats (1/50, controls; 3/50, low dose, $p > 0.05$; 7/50, high dose, $p < 0.05$) and carcinomas and adenomas in liver of high-dose male and female mice ($P < 0.001$). Rats and mice (50/sex/group) were given p-DCB in corn oil by gavage 5 days/week for 103 weeks at 0, 150 or 300 mg/kg (male rats) and 0, 300 or 600 mg/kg (remaining groups). Other treatment-related effects include kidney lesions in male and female rats at both doses, kidney and liver lesions in male and female mice at both doses, and reduced survival ($p < 0.05$) in high-dose male rats.

- A long-term (76 weeks exposure, 36 weeks further observation) inhalation study revealed no increase in tumor incidence or type after exposure to p-DCB in Alderley Park Wistar rats (Riley et al., 1980, summarized in Loeser and Litchfield, 1983). At the high exposure level (500 ppm), observed effects included increases in liver, kidney, heart and lung weights (both sexes) and an increase in urinary protein and coproporphyrin output (males). The low exposure level of 75 ppm was a NOAEL. The 500 and 75 ppm levels equal 3,005 and 451 mg/m3, respectively.

## V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for One-day, Ten-day, Longer-term (approximately 7 years) and Lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(NOAEL \text{ or } LOAEL) \times (BW)}{(UF) \times (\_\_\_ \text{ L/day})} = \_\_\_ \text{ mg/L } (\_\_\_ \text{ ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect-Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100 or 1,000), in accordance with NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

### o-Dichlorobenzene (and/or m-Dichlorobenzene)

#### One-day and Ten-day Health Advisories

No satisfactory dose-response data are available from which to derive a One-day HA or Ten-day HA for the 10-kg child. It is recommended, that for this duration of exposure, the Longer-term HA for the 10-kg child (8.93 mg/L) be applied (see below).

#### Longer-term Health Advisory

Subchronic treatment studies with o-DCB in rats and mice were conducted in which daily doses were administered in corn oil by gavage at dose levels of 30, 60, 125, 250 and 500 mg/kg/day five days/week for 13 weeks (Battelle Columbus, 1978c,i). The NOAEL in these studies was 125 mg/kg. Renal and hepatic lesions, lower body weights and increased uro- and coproporphyrin levels were found with higher doses.

The Longer-term HA for a 10-kg child is calculated as follows:

$$\text{Longer-term HA} = \frac{(125 \text{ mg/kg/day}) (10 \text{ kg}) (5)}{(100) (1 \text{ L/day}) \quad (7)} = 8.93 \text{ mg/L } (8{,}930 \text{ ug/L})$$

where:

125 mg/kg/day = NOAEL based on absence of renal and hepatic effects in rats and mice exposed to o-DCB for 13 weeks.

10 kg = assumed body weight of a child.

5/7 = conversion of 5 day/week dosing regimen to 7 day/week exposure pattern.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

For a 70-kg adult consuming 2 L of water per day, the Longer-term HA is calculated as follows:

$$\text{Longer-term HA} = \frac{(125\ \text{mg/kg/day})\ (70\ \text{kg})\ (5)}{(100)\ (2\ \text{L/day})\ \ (7)} = 31.25\ \text{mg/L}\ (31{,}250\ \text{ug/L})$$

125 mg/kg/day = NOAEL based on absence of renal and hepatic effects in rats and mice exposed to o-DCB for 13 weeks.

70 kg = assumed body weight of an adult.

5/7 = conversion of 5 day/week dosing regimen to 7 day/week exposure pattern.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

2 L/day = assumed daily water consumption of an adult.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed for synthetic organic chemicals and a value of 10% is assumed for inorganic chemicals. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986a), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

The fact that the HAs generated from the chronic studies in the NTP bioassay with a NOAEL of 120 mg/kg/day would be larger than those derived from the subchronic studies preceding them with a NOAEL of 125 mg/kg/day would suggest that the extra 10-fold uncertainty factor used with the subchronic data to estimate a Lifetime HA from subchronic data may not be necessary for this compound. However, the chronic studies offer a narrower evaluation of toxicity in that urinalysis, clinical chemistry and hematology were not included in the chronic study protocols. In view of this consideration, the extra 10-fold uncertainty factor may be appropriate.

The results of Hollingsworth et al. (1958) suggest a safe daily level of 0.94 mg/day to be used in the calculation of a lifetime HA, while those of the subchronic studies preceding the NTP bioassay suggest a level of 6.25 mg/day. Each of these levels was derived from a NOAEL (18.8 mg/kg and 125 mg/kg, respectively). Since the highest NOAEL should be used to derive a Lifetime HA, it is more appropriate to use the NOAEL established in the NTP subchronic studies than the NOAEL from the Hollingsworth study. Furthermore, the minimal effect dose identified in the Hollingsworth study (188 mg/kg) is somewhat higher than the NOAEL established in the NTP subchronic studies.

The Lifetime HA is, therefore, calculated as follows:

Step 1: Determination of the Reference Dose (RfD)

$$RfD = \frac{(125\ mg/kg/day)\ (5)}{(1,000)\quad (7)} = 0.089\ mg/kg/day\ (89\ ug/kg/day)$$

where:

125 mg/kg/day = NOAEL used for Longer-term HA.

1,000 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study of less-than-lifetime duration.

5/7 = conversion of 5 day/week dosing to 7 day/week.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$DWEL = \frac{(0.089\ mg/kg/day)\ (70\ kg)}{(2\ L/day)} = 3.13\ mg/L\ (3,125\ ug/L)$$

where:

0.089 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

Lifetime HA = 3.13 mg/L x 20% = 0.62 mg/L (620 ug/L)

where:

3.13 mg/L = DWEL.

20% = assumed relative source contribution from water.

m-Dichlorobenzene

There are no toxicity studies on m-DCB on which to base Health Advisories; however, because certain properties of o-DCB and m-DCB are similar, the HAs for o-DCB are recommended for m-DCB (U.S. EPA, 1987).

p-Dichlorobenzene

One-day and Ten-day Health Advisories

No satisfactory dose-response data are available from which to derive a One-day HA or a Ten-day HA for p-DCB for the 10-kg child. It is recommended that for this duration of exposure, the Longer-term HA for the 10-kg child (10.7 mg/L) be applied (see below).

Longer-term Health Advisory

The 90-day treatment study with p-DCB by Battelle-Columbus (1979a) is selected for calculation of a Longer-term HA; results in rats were used since they indicated a lower NOAEL compared to that in mice (Battelle-Columbus, 1979b). In addition, a 90-day study is considered to provide a stronger evaluation of toxicity than 14-day treatment studies which preceded the 90-day studies. The rats were given p-DCB in corn oil by gavage, 5 days/week, for 13 weeks. The NOAEL was 150 mg/kg/day since renal lesions were observed in males at higher doses.

The Longer-term HA for the 10-kg child is calculated as follows:

$$\text{Longer-term HA} = \frac{(150 \text{ mg/kg/day})\ (10 \text{ kg})\ (5)}{(100)\ (1 \text{ L/day})\ \ (7)} = 10.7 \text{ mg/L } (10{,}700 \text{ ug/L})$$

where:

150 mg/kg/day = NOAEL, based on absence of renal lesions.

10 kg = assumed body weight of a child.

5/7 = conversion of 5 day/week dosing regimen to 7 day/week exposure pattern.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

For a 70-kg adult, the Longer-term HA is calculated as follows:

$$\text{Longer-term HA} = \frac{(150 \text{ mg/kg/day})\ (70 \text{ kg})\ (5)}{(100)\ (2 \text{ L/day})\ \ (7)} = 37.5 \text{ mg/L } (37{,}500 \text{ ug/L})$$

where:

150 mg/kg/day = NOAEL, based on absence of renal lesions.

70 kg = assumed body weight of an adult.

5/7 = conversion of 5 day/week dosing regimen to 7 day/week exposure pattern.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

2 L/day = assumed daily water consumption of an adult.

Lifetime Health Advisory

p-Dichlorobenzene

The EPA has developed for comparison with cancer-based criteria, a presumed safe daily intake level based on non-carcinogenic effects as indicated in U.S. EPA (1987). For consistency, the rationale used by EPA for the calculation of this value by U.S. EPA (1987) is used here for the DWEL calculation. The rationale as presented in U.S. EPA (1987) is as follows:

The results of the Hollingsworth et al. (1956) study and the subchronic studies preceding the NTP bioassay, as well as the acute toxicity studies described earlier, indicate that the rat is somewhat more sensitive to p-DCB toxicity than is the mouse. Therefore, when estimating potential risk to the human, the data from the experiments in the rat should be used in deriving a Lifetime HA.

The NOAEL derived from the Hollingsworth study was 18.8 mg/kg; the NOAEL from the NTP subchronic study in the rat was 150 mg/kg. Since the highest NOAEL should be used to calculate a daily level of intake, the NOAEL established in the NTP subchronic study will be used. In addition, it should be noted that the minimal effect level identified in the Hollingsworth study (188 mg/kg) was somewhat higher than the NOAEL established in the NTP subchronic study.

As with o-DCB (and m-DCB), any Lifetime Health Advisories derived from the NTP chronic studies might be higher than those derived from the subchronic studies preceding them because the 10-fold uncertainty factor applied to accommodate for the difference in duration of exposure may be unnecessarily large. However, as mentioned for o-DCB, the lack of certain parameters in the chronic study (urinalysis, clinical chemistry and hematology) may make the use of a 10-fold uncertainty factor appropriate. Also, the finding of renal lesions with 150 mg/kg/day in the NTP (1986) chronic study in rats further supports use of an extra 10-fold uncertainty factor.

The Lifetime HA is, therefore, calculated as follows:

Step 1: Determination of the Reference Dose (RfD)

$$RfD = \frac{(150\ mg/kg/day)\ (5)}{(1,000)\quad (7)} = 0.1\ mg/kg/day\ (100\ ug/kg/day)$$

where:

150 mg/kg/day = NOAEL used for Longer-term HA.

1,000 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study of less-than-lifetime duration.

5/7 = conversion of 5 day/week dosing to 7 day/week.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$DWEL = \frac{(0.1\ mg/kg/day)\ (70\ kg)}{(2\ L/day)} = 3.75\ mg/L\ (3,750\ ug/L)$$

where:

0.1 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

$$Lifetime\ HA = \frac{(3.75\ mg/L)\ (20\%)}{10} = 0.075\ mg/L\ (75\ ug/L)$$

where:

3.75 mg/L = DWEL.

20% = assumed relative source contribution from water.

10 = additional uncertainty factor for Group C carcinogens per Office of Drinking Water policy.

Evaluation of Carcinogenic Potential

- Assessment of the NTP bioassay on o-DCB suggests that it was not carcinogenic under the conditions of the experiment.
- No adequate data are available to assess the potential cancer risk associated with exposure to m-DCB.

- The IARC (1982) classified both p-DCB and o-DCB as Group 3 chemicals with inadequate evidence for carcinogenicity in animals and humans.

- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986a), o-DCB and m-DCB may be classified in Group D: Not classified. This category is for agents with inadequate animal evidence of carcinogenicity.

- Because of positive evidence in two animal species, p-DCB may be placed in category B2 (sufficient animal evidence, inadequate human evidence) by these guidelines. However, consideration of the overall weight of evidence could suggest the alternative view that p-DCB be placed in Group C (limited animal evidence) by these guidelines, with respect to uncertainties with high doses and corn oil gavage and diminished toxicological significance of the mouse liver tumor results. The EPA has concluded that the overall weight of evidence favors classification of p-DCB in Group C (U.S. EPA, 1987).

- Because p-DCB is considered a Group C agent, the DWEL would be divided by an extra uncertainty factor of 10 to yield 0.375 mg/L.

- Provisional cancer potency estimates for p-DCB were derived using the multistage model and the liver tumor data on male mice in the chronic feeding study by NTP (1986).

- The 95% upper-limit carcinogenic potency factor for humans, $q_1^*$, is $2 \times 10^{-2}$ $(mg/kg/day)^{-1}$ by the multistage model (U.S. EPA, 1986b). For a 70 kg human drinking 2 L water/day, the water concentration should be 17.5 ug/L in order to keep the upper-limit individual lifetime cancer risk at $10^{-5}$. Water concentrations corresponding to excess cancer risk of $10^{-4}$ and $10^{-6}$ are, therefore, 175 and 1.8 ug/L, respectively. Maximum likelihood estimates by the multistage model associate risks of $10^{-5}$ and $10^{-6}$ with exposures to 20.7 and 6.3 mg/L, respectively. There are not enough distinct data points to allow fits to other models tried (Weibull, logit, probit). While recognized as statistically alternative approaches, the range of risks described by using any of these modeling approaches has little biological significance unless data can be used to support the selection of one model over another. In the interest of consistency of approach and in providing an upper bound on the potential cancer risk, the EPA has recommended use of the linearized multistage approach.

## VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- The OSHA standard for 1,2-dichlorobenzene is 50 ppm (300 $mg/m^3$) (U.S. EPA, 1985a).

- The 1982 ACGIH TLV is 50 ppm (U.S. EPA, 1985a).

- The OSHA standard for 1,4-dichlorobenzene is 75 ppm (450 $mg/m^3$) (U.S. EPA, 1985a).

- The dichlorobenzene isomers are designated as hazardous wastes under the Resource Conservation and Recovery Act (RCRA) (U.S. EPA, 1985a).

- Under the Federal Water Pollution Control Act, 1,2-di- and 1,4-dichlorobenzenes are hazardous substances with reportable quantities of 100 lbs.

- The ambient water quality criterion for dichlorobenzenes is 400 ug/L, using a NOAEL of 13.4 mg/kg/day and an uncertainty factor of 1,000 (U.S. EPA, 1980).

- The WHO (1984) recommended an acceptable drinking water level of 1 ug/L for 1,2- and 1,4-dichlorobenzenes based on odor threshold.

- The NAS (1983) calculated a chronic SNARL of 0.3 mg/L for o-DCB, using a NOAEL of 60 mg/kg, 20% relative source contribution, and a 1,000-fold uncertainty factor.

- The NAS (1977) calculated a chronic SNARL of 0.094 mg/L for p-DCB, using a NOAEL of 13.4 mg/kg/day, a relative source contribution of 20%, and an uncertainty factor of 1,000.

- The proposed RMCL for o-DCB is 0.62 mg/L (U.S. EPA, 1985b).

- The U.S. EPA Office of Drinking Water issued a final RMCL of 0.75 mg/L, a proposed MCL of 0.75 mg/L, and a practical quantitation level of 5 ug/L for p-DCB (U.S. EPA, 1985c). However, p-DCB is being considered for reproposal as a result of the recent positive NTP (1986) carcinogenicity bioassay.

## VII. ANALYTICAL METHODS

- Analysis of dichlorobenzene(s) is by a purge-and-trap gas chromatographic procedure used for the determination of volatile organohalides in drinking water (U.S. EPA, 1985d). This method calls for the bubbling of an inert gas through the sample and trapping dichlorobenzene(s) on an adsorbant material. The adsorbant material is heated to drive off the dichlorobenzene(s) onto a gas chromatographic column. The gas chromatograph is temperature programmed to separate the method analytes which are then detected by a halogen specific detector. This method is applicable to the measurement of dichlorobenzene(s) over a concentration range of 0.05 to 1500 ug/L. Confirmatory analysis for dichlorobenzene(s) is by mass spectrometry (U.S. EPA, 1985e). The detection limit for confirmation by mass spectrometry is 0.3 ug/L.

## VIII. TREATMENT TECHNOLOGIES

- Granular activated carbon (GAC) adsorption and aeration for the removal of ortho-, meta- and para-dichlorobenzene from water are available and have been reported to be effective. Because ortho-, meta- and para-dichlorobenzene are chemically similar, they can be considered together (U.S. EPA, 1985f).

- McCarty et al. (1979b) conducted a study at a 15-MGD advanced waste treatment (AWT) plant which examined organics removal in air stripping towers designed for ammonia removal. That study showed that 83 to 97 percent of trace quantities (ug/L range) of o-DCB, m-DCB and p-DCB were removed.

- In a laboratory study where water containing an average of 151 ug/L of o-DCB, 229 ug/L of m-DCB and 225 ug/L of p-DCB was passed through a diffused-air aerator using a 15:1 air to water ratio, there was a 74% reduction in the o-DCB concentration, a 79% reduction of m-DCB and a 77% reduction in the p-DCB (Love et al., 1983). In another study of well water contaminated with 3.0 ug/L o-DCB, 90% or more of the compound was removed with air to water ratios of 47:1.

- Carbon adsorption also can be used to remove o-DCB, m-DCB and p-DCB from contaminated water. According to Dobbs and Cohen (1980) at equilibrium concentrations of 1 mg/L and 10 mg/L, activated carbon had adsorptive capacities of 129 mg and 350 mg of o-DCB per gram of carbon, respectively. Their data for p-DCB show carbon capacities of 121 mg/gram of carbon and 470 mg/gram of carbon, respectively, at the identical equilibrium concentrations. Adsorption capacities for m-DCB are slightly less than those for o-DCB and p-DCB (Love et al., 1983).

- Data from a GAC system containing Filtrasorb® 300 at an AWT Plant demonstrated significant removals of o-DCB and p-DCB at trace concentrations (McCarty et al., 1979a).

- A column study by EPA/ESE (ESE, 1981) examined removal of benzene, monochlorobenzene, o-DCB and p-DCB from a wastewater stream by regenerated GAC. With influent concentrations of each in the mg/L range, o-DCB and p-DCB did not break through during the study. Estimated carbon usage rates for each could be expected to be less than those obtained for benzene (10 lb/1,000 gallons). Although experimental data from drinking water and wastewater experimentation are markedly different, some comparisons can be made. Another ESE field study (1978) at North Miami Beach using powdered activated carbon addition to potable water demonstrated up to 97 percent removal of dichlorobenzenes by 52 mg/L (434 lb/$10^6$ gallons) of PAC. This concentration of PAC is much greater than that normally used.

## IX. REFERENCES

Anderson, D. 1976. Paradichlorobenzene: Estimation of its mutagenic potential in the Salmonella typhimurium plate incorporation mutagenicity assay. ICI Report No. CTL/P/298. November. (Unpublished)

Anderson, D., and M.C.E. Hodge. 1976. Paradichlorobenzene: Dominant lethal study in the mouse. ICI Report No. CTL/P/296. November. (Unpublished)

Anderson, D., and C.R. Richardson. 1976. Paradichlorobenzene: Cytogenic study in the rat. ICI Report No. CTL/P/293. November. (Unpublished)

Anderson, K.J., E.G. Leignty and M.T. Takahashi. 1972. Evaluation of herbicides for possible mutagenic properties. J. Agr. Food Chem. 20:649-656.

Astrand, I. 1975. Uptake of solvents in the blood and tissues of man. Scand. J. Work Environ. Hlth. 1:199-208.

Azouz, W.M., D.V. Parke, and R.T. Williams. 1953. Studies in detoxication. 51: The determination of catechols in urine, and the formation of catechols in rabbits receiving halogenobenzenes and other compounds, dihydroxylation in vivo. Biochem. J. 55(1):146-151.

Azouz, W.M., D.V. Parke, and R.T. Williams. 1955. Studies in detoxication. 62: The metabolism of halogenobenzenes. Ortho- and Paradichlorobenzenes. Biochem. J. 59(3):410-415.

Battelle's Columbus Laboratories. 1978a. Repeated dose toxicity study: Ortho-dichlorobenzene (C54944), B6C3F1 mice. Unpublished Report. Subcontract No. 76-34-106002. Feb. 23, 1978.

Battelle's Columbus Laboratories. 1978b. Re-run repeated dose toxicity study: Ortho-dichlorobenzene (C54944), B6C3F1 mice. Unpublished Report. Subcontract No. 76-34-106002. May 26, 1978.

Battelle's Columbus Laboratories. 1978c. Subchronic toxicity study: Ortho-dichlorobenzene (C54944), B6C3F1 mice. Unpublished Report. Subcontract No. 76-34-106002. Dec. 21, 1978.

Battelle's Columbus Laboratories. 1978d. Repeated dose toxicity study: Ortho-dichlorobenzene (C54944), Fischer 344 rats. Unpublished Report. Subcontract No. 76-34-106002. Feb. 23, 1978.

Battelle's Columbus Laboratories. 1978e. Repeated dose toxicity study: Para-dichlorobenzene (C54955), B6C3F1 mice. Unpublished Report. Subcontract No. 76-34-106002. Feb. 24, 1978.

Battelle's Columbus Laboratories. 1978f. Repeated dose toxicity study: Para-dichlorobenzene (C54955), Fischer 344 rats. Unpublished Report. Subcontract No. 76-34-106002. Feb. 24, 1978.

Battelle's Columbus Laboratories. 1978g. Re-run repeated dose toxicity study: Para-dichlorobenzene (C54955), Fischer 344 rats. Unpublished Report. Subcontract No. 76-34-106002. June 7, 1978.

Battelle's Columbus Laboratories. 1978h. Re-run repeated dose toxicity study: Para-dichlorobenzene (C54955), B6C3F1 mice. Unpublished Report. Subcontract No. 76-34-106002. June 14, 1978.

Battelle's Columbus Laboratories. 1978i. Subchronic study: Ortho-dichlorobenzene (C54944), Fischer 344 rats. Unpublished Report. Subcontract No. 76-34-106002. Dec. 21, 1978.

Battelle's Columbus Laboratories. 1979a. Subchronic toxicity study: Para-dichlorobenzene (C54955), B6C3F1 mice. Unpublished Report. Subcontract No. 76-34-106002. March 20, 1979.

Battelle's Columbus Laboratories. 1979b. Subchronic toxicity study: Para-dichlorobenzene (C54955), Fischer 344 rats. Unpublished Report. Subcontract No. 76-34-106002. Mar. 20, 1979.

Battelle's Columbus Laboratories. 1980a. Re-run subchronic toxicity study: Para-dichlorobenzene (C54955), B6C3F1 mice. Unpublished Report. Subcontract No. 76-34-106002. Feb. 12, 1980.

Battelle's Columbus Laboratories. 1980b. Re-run subchronic toxicity study: Para-dichlorobenzene (C54955), Fischer 344 rats. Unpublished Report. Subcontract No. 76-34-106002. Feb. 12, 1980.

Dallas, C.E., F.W. Weir, S. Feldman, L. Putcha and J.V. Bruckner. 1983. The uptake and distribution of 1,1-dichloroethylene in rats during inhalation exposure. Toxicol. Appl. Pharmacol. 68:140-151.

Dobbs, R.J., and J.M. Cohen. 1980. Carbon isotherms for toxic organics. United States Environmental Protection Agency. Cincinnati, Ohio.

Dowty, B., D. Carlisle, J. Laesleter and J. Storer. 1975. Halogenated hydrocarbons in New Orleans drinking water and blood plasma. Science. 187:75-77.

ESE. 1978. Environmental Science and Engineering. Final data report for the Sunny Isle Water Plant. North Miami Beach, Florida. EPA Contract.

ESE. 1981. Environmental Science and Engineering. Final report on pilot operations on simulated wastewater from the production of chlorinated benzenes. EPA Contract No. 68 03 2610.

Girard, R., P. Tolot, P. Martin and J. Bourret. 1969. Serious blood disorders and exposure to chlorine derivatives of benzene (a report of seven cases). J. Med. Lyon. 50(1164):771-773.

Glaze, W.H., G.R. Peyton, F.Y. Huang, J.L. Burleson and P.C. Jones. 1980. Oxidation of water supply refractory species by ozone with ultraviolet radiation. United States Environmental Protection Agency, Cincinnati, OH.

Guerin, M., P. Lazar and I. Chouroulinkov. 1971. Inhibitory action of chemical carcinogens on mitosis of rat lung cell cultures. 2. Comparative study of carcinogenic and non-carcinogenic substances. C.R. Seances Co. Biol. Filiales. 165:2255-2258.

Gupta, K.C. 1972. Effects of some antimitotics on the cytology of fenugreek roots in vivo and in vitro. Cytobios. 5(19):179-187.

Hallowell, M. 1959. Acute haemolytic anaemia following the ingestion of paradichlorobenzene. Arch. Dis. Child. 34:74-75.

Hawkins, D.R., L.F. Chasseaud, R.N. Woodhouse and D.G. Cresswell. 1980. The distribution, excretion and biotransformation of p-dichloro-[$^{14}$]-benzene in rats after repeated inhalation, oral and subcutaneous doses. Xenobiotica. 10:81-95.

Hayes, W.C., T.R. Hanley, Jr., T.S. Gushow, K.A. Johnson and J.A. John. 1985. Teratogenic potential of inhaled dichlorobenzenes in rats and rabbits. Fund. Appl. Toxicol. 5:190-202.

Hodge, M.C.E., S. Palmer, J. Wilson and I.P. Bennett. 1977. Paradichlorobenzene: Teratogenicity study in rats. ICI Report No. CTL/P/340. July 27, 1976. (Unpublished)

Hollingsworth, R.L., V.K. Rowe, F. Oyen, H.R. Hoyle and H.C. Spencer. 1956. Toxicity of paradichlorobenzene: Determination on experimental animals and human subjects. AMA Arch. Ind. Hlth. 14:138-147.

Hollingsworth, R.L., V.K. Rowe, F. Oyen, T.R. Torkelson and E.M. Adams. 1958. Toxicity of o-dichlorobenzene: Studies on animals and industrial experience. AMA Arch. Ind. Hlth. 17(1):180-187.

IARC. 1982. International Agency for Research on Cancer. IARC Monographs on the evaluation of the carcinogenic use of chemicals to humans. Chemical industrial processes and industries associated with cancer in humans. Suppl. 4. Lyon, France. pp. 108-109.

Loeser, E., and M.H. Litchfield. 1983. Review of recent toxicology studies on p-dichlorobenzene. Food Chem. Toxicol. 21:825-832.

Love, G.T., R.J. Miltner, R.G. Eilers and C.A. Fronk-Leist. 1983. Treatment of volatile organic compounds in drinking water. United States Environmental Protection Agency, Municipal Environmental Research Laboratory. EPA-600/8-83-019.

McCarty, P.L., D. Argo and M. Reinhard. 1979a. Operational experiences with activated carbon adsorbers at Water Factory 21. J. AWWA. 11:;683-689.

McCarty, P.L., K.K. Sutherland, J. Graydon and M. Reinhard. 1979b. Volatile organic contaminants removal by air stripping. Presented at the Seminar on Controlling Organics in Drinking Water, American Water Works Annual Conference, San Francisco, CA.

Morita, M., and G. Ohi. 1975. Paradichlorobenzene in human tissue and atmosphere in Tokyo metropolitan area. Environ. Pollut. 8:267-274.

Morita, M., S. Mimura, G. Ohi, H. Yagyu and T. Nishizawa. 1975. A systematic determination of chlorinated benzenes in human adipose tissue. Environ. Pollut. 9:175-179.

NAS. 1977. National Academy of Sciences. Drinking Water and Health. Vol. 1. National Academy Press. Washington, D.C.

NAS. 1983. National Academy of Sciences. Drinking Water and Health. Vol. 5. National Academy Press. Washington, D.C.

NTP. 1985. National Toxicology Program. Toxicology and carcinogenesis studies of 1,2-dichlorobenzene (CAS No. 95-50-1) in F344/N rats and B6C3F$_1$ mice (gavage study). NTP TR 235. NIH Publication No. 86-2511.

NTP. 1986. National Toxicology Program. Toxicology and carcinogenesis studies of 1,4-dichlorobenzene (CAS No. 106-46-7) in F344/N rats and B6C3F$_1$ mice (gavage studies). Galley draft. NTP TR 319. NIH Publication No. 86-2575.

Ostergren, G., and A. Levan. 1943. The connection between c-mitotic activity and water solubility in some monocyclic compounds. Hereditas. 29:496-498.

Pagnatto, L.D., and J.E. Walkley. 1965. Urinary dichlorophenol as an index of paradichlorobenzene exposure. Amer. Ind. Hyg. Assoc. J. 26:137-142.

Perocco, P., B. Silvana, and W. Alberghini. 1983. Toxic activity of seventeen industrial solvents and halogenated compounds on human lymphocytes cultured in vitro. Toxicol. Lett. 16:69-75.

Prasad, I., and D. Pramer. 1968. Mutagenic activity of some chloroanilines and chlorobenzenes. Genetics. 20:212-213.

Prasad, I. 1970. Mutagenic effects of the herbicide 3,4-dichloropropionanilide and its degradation products. Can. J. Microbiol. 16:369-372.

Riley, R.A., I.S. Chart, A. Doss, C.W. Gore, D. Patton and T.M. Weight. 1980. Para-dichlorobenzene: Long-term inhalation study in the rat. ICI Report No. CTL/P/447. August, 1980. (Unpublished)

Sharma, A.K., and N.K. Battacharya. 1956. Chromosome breakage through para-dichlorobenzene treatment. Cytologia. 21:353-360.

Sharma, A.K., and S.K. Sarkar. 1957. A study on the comparative effect of chemicals on chromosomes of roots, pollen mother cells and pollen grains. Proc. Ind. Acad. Sci. B. XLV(xxx):288-293.

Shimizu, M., Y. Yasui, and N. Matsumoto. 1983. Structural specifity of aromatic compounds with special reference to mutagenic activity in Salmonella typhimurium -- a series of chloro- or fluoro-nitrobenzene derivatives. Mutat. Res. 116:217-238.

Simmon, V.F., E.S. Riccio and M.V. Peirce. 1979. In vitro microbiological genotoxicity tests of chlorobenzene, m-dichlorobenzene, o-dichlorobenzene, and p-dichlorobenzene. Unpublished report by SRI International for U.S. EPA, Contract No. 68-02-2947. Final Report, May 1979.

Srivastava, L.M. 1966. Induction of mitotic abnormalities in certain genera of tribe vicieae by paradichlorobenzene. Cytologia. 31:166-171.

U.S. EPA. 1979. U.S. Environmental Protection Agency. Water Related Environmental Fate of 129 Priority Pollutants. Office of Water Planning and Standards, EPA-440/4-79-029.

U.S. EPA. 1980. U.S. Environmental Protection Agency. Ambient water quality criteria for dichlorobenzenes. Environmental Criteria and Assessment Office for the Office of Water Regulations and Standards. EPA 440/5-80-039.

U.S. EPA. 1983. U.S. Environmental Protection Agency. Dichlorobenzene occurrence in drinking water, food, and air. Office of Drinking Water.

U.S. EPA. 1985a. U.S. Environmental Protection Agency. Health assessment document for chlorinated benzenes. Final Report. Office of Health and Environmental Assessment. EPA/60018-84015F. January.

U.S. EPA. 1985b. U.S. Environmental Protection Agency. National primary drinking water regulations; Synthetic organic chemicals, inorganic chemicals and microorganisms; Proposed rule. Federal Register. 50(219):46934-47022. November 13.

U.S. EPA. 1985c. U.S. Environmental Protection Agency. National primary drinking water regulations: Volatioe synthetic organic chemicals; Final and proposed rule. Federal Register. 50(219):46880-46933. November 13.

U.S. EPA. 1985d. U.S. Environmental Protection Agency. Method 502.1. Volatile halogenated organic compounds in water by purge and trap gas chromatography. Environmental Monitoring and Support Laboratory, Cincinnati, Ohio 45268, June.

U.S. EPA. 1985e. U.S Environmental Protection Agency. Method 524.1. Volatile organic compounds in water by purge and trap gas chromatography/ mass Spectrometry. Environmental Monitoring and Support Laboratory, Cincinnati, Ohio 45268, June.

U.S. EPA. 1985f. U.S. Environmental Protection Agency. Draft. Technologies and costs for the removal of synthetic organic chemicals from potable water supplies. Science and Technology Branch, Criteria and Standards Division, Office of Drinking Water, Washington, D.C.

U.S. EPA. 1986a. U.S. Environmental Protection Agency. Guidelines for carcinogenic risk assessment. Federal Register. 51(185):33992-34003. September 24.

U.S. EPA. 1986b. U.S. Environmental Protection Agency. Risk estimates for p-dichlorobenzene. U.S. EPA Office of Toxic Substances.

U.S. EPA. 1987. U.S. Environmental Protection Agency. Final draft criteria document for ortho-dichlorobenzene, meta-dichlorobenzene, para-dichlorobenzene. Criteria and Standards Division. Office of Drinking Water.

Williams, R.T. 1959. The metabolism of halogenated aromatic hydrocarbons. In: Detoxication mechanisms, 2nd ed. John Wiley and Sons, New York, pp. 237-258.

WHO. 1984. World Health Organization. Guidelines for drinking water quality. Recommendations--Volume 1. Geneva.

Zapata-Gayon, C., N. Zapata-Gayon, and A. Gonzalez-Angulo. 1982. Clastogenic chromosomal aberrations in 26 individuals accidentally exposed to orthodichlorobenzene vapors in the National Medical Center in Mexico City. Arch. Environ. Health 37:231-235.

March 31, 1987

# 1,2-DICHLOROETHANE

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

## I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

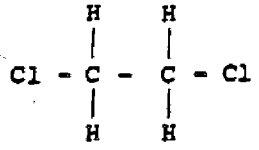
Health Advisories are developed for One-day, Ten-day, Longer-term (approximately 7 years, or 10% of an individual's lifetime) and Lifetime exposures based on data describing noncarcinogenic end points of toxicity. Health Advisories do not quantitatively incorporate any potential carcinogenic risk from such exposure. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

This Health Advisory is based on information presented in the Health Assessment Document for 1,2-Dichloroethane (Ethylene Dichloride) (U.S. EPA, 1985a). Individuals desiring further information on the toxicological data should use this document. Information on the Quantification of Toxicological Effects (QTE) section is contained in the QTE Document (PB#86-118080). Both documents are available for review at each EPA Regional Office of Drinking Water counterpart (e.g., Water Supply Branch or Drinking Water Branch), or for a fee from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Road, Springfield, VA 22161. The toll-free number is (800) 336-4700; in the Washington, D.C. area: (703) 487-4650.

## II. GENERAL INFORMATION AND PROPERTIES

CAS No. 107-06-2

Structural Formula



1,2-Dichloroethane

Synonyms

- Ethylene dichloride, EDC, 1,2-DCE

Uses (U.S. EPA, 1985a)

- The major use for EDC is in the production of vinyl chloride. In addition, it is used as a starting material for the production of other solvents, as an additive (lead scavenger) in gasolines and is widely exported. Some of its minor uses include its use as a solvent in metal degreasing and textile and PVC cleaning, in paints, coatings and adhesives, as a grain fumigant, a varnish and finish remover, in soaps and scouring compound, as a wetting and penetrating agent, in ore flotation and as a chemical intermediate.

Properties (EPA, 1985a; Amoore and Hautala, 1983)

| | |
|---|---|
| Chemical Formula | $C_2H_2Cl_2$ |
| Molecular Weight | 98.96 |
| Physical State | Clear, colorless, volatile, oily liquid |
| Boiling Point | 83.7°C |
| Melting Point | -35.3°C |
| Density (20°C) | 1.2529 g/mL |
| Vapor Pressure | 64 torr (20°C) |
| Water Solubility (20°C) | 8820 mg/L |
| Log Octanol/Water Partition Coefficient | 1.48 |
| Organoleptic Threshold (water) | 29 mg/L |
| Odor Threshold (air) | 3 ppm |
| Conversion Factor | 1 ppm = 4.05 $mg/m^3$ |

Occurrence

- Dichloroethane is a synthetic chemical with no natural sources.

- Production of dichloroethane was approximately 12 billion pounds in 1983 (U.S. ITC, 1984). However, the vast bulk of dichloroethane is used as a feed stock for the production of other chlorinated compounds and it is not readily released to the environment. Releases of dichloroethane largely result from the approximately 3 million pounds used as solvents and metal cleaners.

- Releases of dichloroethane are largely to air, with smaller amounts released to surface and ground waters. Because metal working operations are performed nationwide, dichloroethane releases occur in all industrialized areas.

- Dichloroethane released to the air slowly degrades over a few months. Photooxidation is thought to be the predominant environmental process determining the fate of 1,2-dichloroethane (U.S. EPA, 1979). Dichloroethane released to surface waters migrates to the atmosphere in a few days or weeks where it also degrades. Dichloroethane released to the land does not sorb onto soil but migrates readily to ground water where it is expected to remain for months to years.

- Due to dichloroethane's limited releases, it is a relatively rare environmental contaminant. Dichloroethane has been detected in both ground and surface waters but, unlike other volatile organic compounds, higher levels were reported in surface waters than in ground waters. The Agency estimates that 0.3% of all ground water supplies contain concentrations of dichloroethane ranging from 0.5 to 5 ug/L. Surface waters contain higher levels, with 3% of all wells estimated to have from 0.5 to 20 ug/L. Dichloroethane commonly occurs in air in urban and suburban areas at concentrations of less than 0.2 ppb. No information on the levels of dichloroethane in food have been reported.

- For the majority of the U.S. population, the greatest source of dichloroethane exposure is from air. Drinking water is the greatest source only for populations with drinking water levels greater than 6 ug/L.

## III. PHARMACOKINETICS

Absorption

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

- The proportions of a dose of 1,2-dichloroethane absorbed through the skin and gastrointestinal tract are unknown. The nature of its other chemical and physical properties would suggest that this substance would be absorbed completely when ingested.

Distribution

- Forty-eight hours after the administration of a single oral dose of 150 mg/kg of 1,2-dichloroethane to rats, the liver and kidneys were reported to have the highest concentration of the chemical. Successively lower concentrations occurred in the forestomach, stomach and spleen (Reitz et al., 1980).

- 1,2-Dichloroethane readily passes the blood/brain barrier. Distribution is also known to occur into milk (Urosova, 1953).

Metabolism

- Following intraperitoneal administration to mice, 1,2-dichloroethane is metabolized to 2-chloroethanol, converted to alcohol and aldehyde dehydrogenases, to monochloroacetic acid, and further dehalogenated by enzyme interaction of monochloroacetate with glutathione or cysteine to yield 5-carboxymethylcysteine and thiodiacetic acid (Yllner, 1971a,b).

- Urinary metabolites of 1,2-dichloroethane intraperitoneally administered to mice include chloroacetic acid, 2-chloroethanol, 5-carboxymethyl cysteine, conjugated 5-carboxymethyl cysteine, thiodiacetic acid and 5,5-ethylene-bis-cysteine (Yllner, 1971a,b).

- Following oral administration of 1,2-dichloroethane (750 mg/kg) or 2-chloroethanol (80 mg/kg) to rats, the blood level of 2-chloroethanol at four hours was 67.8 or 15.8 ug/mL, respectively (Kokarovtseva and Kiseleva, 1978). These levels declined in accordance with first-order kinetics with a half-life of about nine hours. The relatively low blood concentrations found were postulated to be due to initial sequestration of 1,2-dichloroethane in adipose and other tissues with gradual diffusion redistribution as liver metabolism of 1,2-dichloroethane to chloroethanol and chloroethanol to chloroacetic acid proceeded.

Excretion

- Mice intraperitoneally injected with a dose of 0.05 to 0.17 g/kg of 1,2-dichloroethane excreted 11 to 46% of the dose, unchanged, via the lungs; 5 to 13% of the dose was metabolized to carbon dioxide and water; 50 to 73% of the dose was excreted as urinary metabolites (Yllner, 1971a).

- Within 48 hours after dosing, 96% of the radioactivity of a single oral dose of 150 mg/kg was eliminated from the body by rats (Reitz et al., 1980).

## IV. HEALTH EFFECTS

### Humans

- Clinical symptoms of acute 1,2-dichloroethane poisoning by ingestion usually appear within two hours after exposure and typically include headache, dizziness, general weakness, nausea, vomiting of blood and bile, dilated pupils, heart pains and constriction, pain in the epigastric region, diarrhea and unconsciousness. Pulmonary edema and increasing cyanosis also may occur. These symptoms may disappear if exposure is sufficiently brief (Wirtschafter and Schwartz, 1939; McNally and Fostvedt, 1941).

- A 14-year-old male who drank 15 ml (340 mg/kg) of 1,2-dichloroethane died six days later despite supportive treatment (Yodaiken and Babcock, 1973). During treatment, serum enzyme and calcium levels increased, blood glucose decreased and blood clotting time increased. Autopsy findings revealed extensive liver necrosis and epithelial cell damage in the entire cortico-tubular structure of the kidneys accompanied by degeneration in the proximal tubules.

- While not all instances of 1,2-dichloroethane ingestion are fatal, death has resulted in the majority of reported cases. Death is most often attributed to circulatory and respiratory failure (Budanova, 1965; Yodaiken and Babcock, 1973; Luzhnikov et al., 1974, 1976; and Zhizhonkov, 1976).

- A number of neurological effects following ingestion of 20 to 200 ml of 1,2-dichloroethane have been reported (Akimov et al., 1976, 1978). The most common of these involved disturbances in consciousness, mental disorders and cerebellar and extrapyramidal disorders.

### Animals

#### Short-term Exposure

- Information on the acute oral toxicity of 1,2-dichloroethane indicates the following: rat $LD_{50}$ - 680 mg/kg; rabbit $LD_{50}$ - 860 mg/kg; (NIOSH, 1977).

- The principal acute effect of 1,2-dichloroethane in mammals is central nervous system depression with unconsciousness and coma resulting from exposure to high concentrations (Spencer et al., 1951; Irish, 1963). Visible signs of 1,2-dichloroethane poisoning include restlessness, intolerance to handling, extreme weakness, intoxication, dizziness, muscle incoordination, irregular respiration and loss of consciousness. Deaths occurring within a few hours after recovery from narcosis are usually the result of shock or cardiovascular collapse; deaths delayed by several days most often result from renal damage.

Reproductive Effects

- No reproductive effects, as measured by fertility, gestation, viability or lactation indices, pup survival and weight gain, were indicated in a multigeneration reproduction study using male and female ICR Swiss mice receiving 0, 5, 15 or 50 mg/kg/day in drinking water. No effect on the adult generations was evident after 25 weeks of dosing as measured by body weight, fluid intake or gross pathology (Lane et al., 1982).

Developmental Effects

- In a study in which male and female mice were exposed to 1,2-dichloroethane in drinking water at doses of 0, 5, 15 or 50 mg/kg/day, no statistically significant dose-related developmental effects were observed, as indicated by incidence of fetal visceral or skeletal anomalies (Lane et al., 1982).

Mutagenicity

- 1,2-Dichloroethane has been shown to be weakly mutagenic in Salmonella typhimurium strains TA 1530, 1535 and 1538 and in DNA polymerase-deficient Escherichia coli (Brem et al., 1974).

- 1,2-Dichloroethane has been found to be highly mutagenic in Salmonella typhimurium strains TA 1530 and 1535 with S-9 activation (Rannug and Beije, 1979).

- 1,2-Dichloroethane has been shown to induce sex-linked recessive lethals in Drosophila melanogaster (Rapport, 1960; Shakarnis, 1969).

- 1,2-Dichloroethane was not mutagenic in Salmonella microsome assay system (McCann et al., 1975).

Carcinogenicity

- In an NCI (1978) bioassay, 1,2-dichloroethane was administered by gavage at levels of 47 or 95 mg/kg body weight to Osborne-Mendel rats five times per week for 78 weeks. Statistically significant increases in the incidence of squamous cell carcinomas of the forestomach and hemangiosarcomas of the circulatory system were observed in male rats($p < 0.04$). Female rats had a statistically significant increased incidence of adenocarcinoma of the mammary glands ($p < 0.002$).

- In the same NCI (1978) bioassay, $B6C3F_1$ mice received 1,2-dichloroethane by gavage five times per week for 78 weeks; males were dosed at levels of 97 or 195 mg/kg body weight and females at 149 or 299 mg/kg body weight. Statistically significant increases in the incidence of mammary adenocarcinoma ($p < 0.04$) and endometrial stromal polyps or sarcomas ($p < 0.016$) were seen in female mice. The incidence of alveolar/bronchiolar adenomas was increased in both sexes ($p < 0.028$).

## V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for One-day, Ten-day, Longer-term (approximately 7 years) and Lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(NOAEL \text{ or } LOAEL) \times (BW)}{(UF) \times (\_\_\_ L/day)} = \_\_\_ mg/L \ (\_\_\_ ug/L)$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect-Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100 or 1,000), in accordance with NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

### One-day and Ten-day Health Advisories

Appropriate data for the derivation of One-day and Ten-day HAs were not located. It is recommended that the Longer-term HA of 0.74 mg/L for the 10 kg child be used as a conservative estimate for One-day and Ten-day exposures.

### Longer-term Health Advisory

A combination of three inhalational studies in which various animal species were exposed to 1,2-dichloroethane for up to eight months are considered appropriate to use in calculating a Longer-term HA. In these studies, exposures of rats and guinea pigs to air containing 100 ppm 1,2-dichloroethane for 6 to 7 hours/day, 5 days/week resulted in no mortality and no adverse effects as determined by general appearance, behavior, growth, organ function or blood chemistry. However, similar exposures of rats, guinea pigs, rabbits, and monkeys to air containing 400 or 500 ppm 1,2-dichloroethane resulted in high mortality and varying pathological findings including pulmonary congestion, diffused myocarditis, slight to moderate fatty degeneration of the liver, kidney, adrenal, and heart, and increased plasma prothrombin time (Heppel et al., 1946; Spencer et al., 1951; Hofmann et al., 1971).

The Longer-term HA is calculated as follows:

Step 1: Determination of Total Absorbed Dose (TAD)

$$TAD = \frac{(405 \text{ mg/m}^3) \ (1 \text{ m}^3/\text{hr}) \ (6 \text{ hr}) \ (0.3) \ (5/7)}{70 \text{ kg}} = \frac{521 \text{ mg/day}}{70 \text{ kg}} = 7.4 \text{ mg/kg/day}$$

where:

405 $mg/m^3$ = NOAEL of 100 ppm (1 ppm = 4.05 $mg/m^3$) for adverse effects in rats and guinea pigs.

1 $m^3/hr$ = respiratory rate of adult human (pulmonary rate/body weight ratio assumed to be the same for humans and test animals).

6 hr = exposure duration per day.

0.3 = fraction of test substance assumed to be absorbed.

5/7 = conversion of 5-day dosing regimen to full 7-day week.

70 kg = assumed body weight of an adult.

Step 2: Determination of the Longer-term HA

For a 10-kg child:

$$\text{Longer-term HA} = \frac{(7.4 \text{ mg/kg/day})\ (10 \text{ kg})}{(100)\ (1 \text{ L/day})} = 0.74 \text{ mg/L } (740 \text{ ug/L})$$

For a 70-kg adult:

$$\text{Longer-term HA} = \frac{(7.4 \text{ mg/kg/day})\ (70 \text{ kg})}{(100)\ (2 \text{ L/day})} = 2.6 \text{ mg/L } (2600 \text{ ug/L})$$

where:

7.4 mg/kg/day = total absorbed dose (TAD).

10 kg = assumed body weight of a child.

1 L/day = assumed daily water consumption of a child.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from

the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed for synthetic organic chemicals and a value of 10% is assumed for inorganic chemicals. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

No appropriate data are available for determining a reference dose and drinking water equivalent level (DWEL) for 1,2-dichloroethane. A Lifetime Health Advisory is not estimated for this chemical.

Evaluation of Carcinogenic Potential

- 1,2-Dichloroethane was shown to be carcinogenic in rats and mice following gavage exposure in the NCI bioassay (NCI, 1978).
- IARC has not classified 1,2-dichloroethane (IARC, 1982).
- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986), 1,2-dichloroethane may be classified in Group B2: Probable Human Carcinogen. This category is for agents for which there is inadequate evidence from human studies and sufficient evidence from animal studies.
- The most recent calculations by EPA's Carcinogen Assessment Group (CAG) indicates the cancer risk estimate for 1,2-dichloroethane corresponding to a $10^{-5}$ risk level is 3.8 ug/L, using the multistage model (95% confidence limit) (U.S. EPA, 1985d).
- The linear multistage model is only one method of estimating carcinogenic risk. Using the 95% upper-bound estimate of risk at 1 mg/kg/day for hemangiosarcomas in male rats, the following comparisons can be made: Multistage, $6.0 \times 10^{-2}$; Probit, $2.81 \times 10^{-1}$; Weibull, $2.7 \times 10^{-1}$ (U.S. EPA, 1985a). Each model is based on differing assumptions. No current understanding of the biological mechanisms of carcinogenesis is able to predict which of these models is more accurate than another.
- While recognized as statistically alternative approaches, the range of risks described by using any of these modelling approaches has little biological significance unless data can be used to support the selection of one model over another. In the interest of consistency of approach and in providing an upper bound on the potential cancer risk, the Agency has recommended use of the linearized multistage approach.

## VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- U.S. EPA (1985d) has promulgated a final Recommended Maximum Contaminant Level (RMCL) of zero for 1,2-dichloroethane in drinking water based upon its carcinogenic potential and has proposed a Maximum Contaminant Level (MCL) of 0.005 mg/L.

- Due to the lack of appropriate data, the National Academy of Sciences did not calculate a chronic Suggested-No-Adverse-Response-Level (SNARL) for 1,2-dichloroethane (NAS, 1980).

- ACGIH (1984) has recommended a threshold limit value (TLV) of 10 ppm ($\sim$ 40 mg/m$^3$) and a short-term exposure level (STEL) of 15 ppm ($\sim$ 60 mg/m$^3$) due to its hepatotoxic effects.

## VII. ANALYTICAL METHODS

- Analysis of 1,2-dichloroethane is by a purge-and-trap gas chromatographic procedure used for the determination of volatile organohalides in drinking water (U.S. EPA, 1985b). This method calls for the bubbling of an inert gas through the sample and trapping 1,2-dichloroethane on the adsorbant material. The adsorbant material is heated to drive off the 1,2-dichloroethane onto a gas chromatographic column. The gas chromatograph is temperature programmed to separate the method analytes which are then detected by a halogen specific detector. This method is applicable to the measurement of 1,2-dichloroethane over a concentration range of 0.2 to 1,500 ug/L. Confirmatory analysis for 1,2-dichloroethane is by mass spectrometry (U.S. EPA, 1985c). The detection limit for confirmation by mass spectrometry is 0.3 ug/L.

## VIII. TREATMENT TECHNOLOGIES

- Treatment technologies which will remove 1,2-dichloroethane from water include granular activated carbon (GAC) adsorption, aeration and boiling.

- Dobbs and Cohen (1980) developed adsorption isotherms for several organic chemicals including 1,2-dichloroethane. It was reported that Fibrasorb® 300 carbon exhibited adsorptive capacities of 3.5 mg and 0.5 mg 1,2-dichloroethane/gm carbon at equilibrium concentrations of 1,000 and 100 mg/L, respectively. Also, Love (1983) reported that Witcarb® 950 carbon exhibited adsorptive capacities of 1.9 mg and 0.6 mg 1,2-dichloroethane/gm carbon at equilibrium concentrations of 100 and 10 mg/L, respectively. USEPA-DWRD installed pilot-scale adsorption columns in New Jersey to treat contaminated groundwater (Love and Eilers, 1982). A Witcarb® 950 carbon column removed 1,2-dichloroethane from a concentration as high as 8 mg/L to 0.1 mg/L. Breakthrough occurred at 1,700 bed volumes (BV) with an empty bed contact time (EBCT) of 18 minutes. Similar studies in Louisiana showed removal of 1,2-dichloroethane from a concentration of 8 mg/L

to less than 0.1 mg/L after 39 days of continuous operation by a full-scale GAC column containing Nuchar® WF-G activated carbon (Love, 1983).

- 1,2-Dichloroethane is amenable to aeration on the basis of its Henry's Law Constant of 61 atm (Kavanaugh and Trussell, 1980). In a pilot-scale diffused air aeration column, removal efficiency of 42% of 1,2-dichloroethane was achieved at an air-to-water ratio of 4:1 (Love and Eilers, 1982). In a pilot-scale packed tower aeration study removal efficiencies of 85 to 98.5% for 1,2-dichloroethane were achieved on air-to-water ratios of 5-45, respectively (ESE, 1985).

- Boiling also is effective in eliminating 1,2-dichloroethane from water on a short-term, emergency basis. Studies have shown that 5 to 10 minutes of vigorous boiling will remove 88 to 98% of 1,2-dichloroethane originally present (Love, 1983).

- Air stripping is an effective, simple and relatively inexpensive process for removing 1,2-dichloroethane and other volatile organics from water. However, use of this process then transfers the contaminant directly to the air stream. When considering use of air stripping as a treatment process, it is suggested that careful consideration be given to the overall environmental occurrence, fate, route of exposure and various other hazards associated with the chemical.

## IX. REFERENCES

ACGIH. 1984. American Conference of Governmental Industrial Hygienists. Documentation of threshold limit values. 4th ed. 1980-1984 supplement. pp. 181-182.

Akimov, G.A. et al., 1976. Changes in the nervous system in acute dichloroethane poisoning. Voenno-meditisinskiy Zhurnal. 5:35-37.

Akimov, G.A. et al., 1978. Neurological disorders in acute dichloroethane poisoning. Zh. Nevropatol. Psikhiatr. 78(5):687-692.

Amoore, J.E., and E. Hautala. 1983. Odor as an aid to chemical safety: Odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. J. T. Appl. Tox. 3:272-290.

Brem, H., A. Stein and H. Rosenkrantz. 1974. The mutagenicity and DNA-modifying effect of haloalkanes. Cancer Res. 34:2576-2579.

Budanova, L.F. 1965. On the clinical picture specific to acute peroral dichloroethane poisoning. Ter Arkh. 37(3):110-112.

Dobbs, R.A., and J.M. Cohen. 1980. Carbon adsorption isotherms for toxic organics. Office of Research and Development, MERL, Wastewater Treatment Division, Cincinnati, Ohio. EPA 600/8-80-023.

ESE. 1985. Environmental Science and Engineering. Draft technologies and costs for the removal of volatile organic chemicals from potable water supplies. No. 84-912-0300. Prepared for U.S. EPA, Science and Technology Branch, CSD, ODW, Washington, D.C.

Heppel, L.A., P.A. Neal, T.L. Perrin, K.M. Endicott and V.T. Porterfield. 1946. The toxicology of 1,2-dichloroethane (ethylene dichloride). J. Ind. Hyg. Tox. 28:4, 113-120.

Hofmann, H. Th., H. Birnsteil and P. Jobst. 1971. Zur inhalationtoxicitat von 1,1- and 1,2-dichloroathan. Arch. Toxikol. 27:248-265.

IARC. 1982. International Agency For Research on Cancer. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. IARC Monographs Supplement 4.

Irish, D.D. 1963. Aliphatic halogenated hydrocarbons. In: Industrial Hygiene and Toxicology, 2nd Ed., Vol. II. Interscience Publishers, New York, pp. 1280-1284.

Kavanaugh, M.C., and R.R. Trussell. 1980. Design of aeration towers to strip volatile contaminants from drinking water. JAWWA.

Kokarovtseva, M.G., and N.I. Kiseleva. 1978. Chloroethanol (ethylene chlorohydrin) - a toxic metabolite of 1,2-dichloroethane. Farmakologiya i Toksikologiya, 1978, No. 1. 118-121.

Lane, R.W., B.L. Riddle and J.F. Borzelleca. 1982. Effects of 1,2-dichloroethane and 1,1,1-trichloroethane in drinking water on reproduction and development in mice. Toxicol. Appl. Pharmacol. 63:409-421.

Love, O.T., Jr., and R.G. Eilers. 1982. Treatment of drinking water containing trichloroethylene and related industrial solvents. JAWWA.

Love, O.T., Jr. 1983. Treatment of volatile organic compounds in drinking water. NTIS, U.S. Department of Commerce.

Luzhnikov, E.A., A.A. Andryukin, A.S. Savina, V.N. Aleksandrovskiy, V.G. Anan-chenko, L.G. Vysochina, V.S. Morosov, T.V. Novikovskaya, Y.N. Ostansako and A.N. Fandey. 1974. The pathogenesis of acute poisonings by dichloroethane. Terapevticheskiy Arkhiv. 46(2):131-135.

Luzhnikov, E.A., L.I. Petrova, A.S. Savina, A.G. Kostomarova, K.K. Iliyashenko and O.M. Shekhaeva. 1976. Exotocic shock. Sov. Med. 9:19-24.

McCann, J., V. Simmon, D. Streitweisser and B.N. Ames. 1975. Mutagenicity of chloroacetaldehyde, a possible metabolic product of 1,2-dichloroethane (ethylene dichloride), chloroethanol (ethylene chlorohydrin), vinyl chloride and cyclophosphomide. Proc. Natl. Acad. Sci. U.S.A. 72:3190-3193.

McNally, W.D., and G. Fostvedt. 1941. Ethylene dichloride poisoning. Ind. Med. 10:373.

NAS. 1980. National Academy of Sciences. Drinking Water and Health. Volume 3. National Academy Press. Washington, D.C.

NCI. 1978. National Cancer Institute. Bioassay of 1,2-dichloroethane for possible carcinogenicity. NCI. NIH. U.S. DHEW. Washington, D.C. NCI-CG-TR-55.

NIOSH. 1977. National Institute for Occupational Safety and Health. Registry of Toxic Effects of Chemical Substances. U.S. Dept. of HEW, USPHS, CDC. Washington, D.C. p. 388.

Rannug, U., and B. Beije. 1979. The mutagenic effect of 1,2-dichloroethane on Salmonella typhimurium. II. Activation by the isolated perfused rat liver. Chem.-Biol. Interactions. 24(1979):265-285.

Rapport, I.A. 1960. The reaction of genic proteins with 1,2-dichloroethane. Dokl. Biol. Sci. 134:745.

Reitz, R.H., T.R. Fox, J.Y. Domoradzki, J.F. Quast, P. Langvardt and P.G. Watanabe. 1980. Pharmacokinetics and macromolecular interactions of ethylene dichloride: Comparison of oral and molecular exposures. In: Ethylene dichloride: A potential health risk? Banbury report 5. Ames, B., P. Infante, R. Reitz, eds. Cold Spring Harbor, N.Y.: Cold Spring Harbor Laboratory. Pp. 135-144.

Shakarnis, V. 1969. Induction of X chromosome nondisjunctions and recessive sex linked lethal mutations in females of Drosophila melanogaster by 1,2-dichloroethane. Sov. Genet. 5(12):89-95.

Spencer, H.C., V.K. Rowe, E.M. Adams, D.D. McCollister and D.D. Irish. 1951. Vapor toxicity of ethylene dichloride determined by experiments on laboratory animals. Ind. Hyg. Occup. Med. 4:482-493.

Urosova, T.P. 1953. The possible presence of dichloroethane in human milk with exposure in industrial conditions. Gigiena i. Sanitariy. 18:36-37.

U.S. EPA. 1979. U.S. Environmental Protection Agency. Water related environmental fate of 129 priority pollutants. Office of Water Planning and Standards, EPA-440/4-79-029.

U.S. EPA. 1985a. U.S. Environmental Protection Agency. Health Assessment Document for 1,2-Dichloroethane. Office of Health and Environmental Assessment.

U.S. EPA. 1985b. U.S. Environmental Protection Agency. Method 502.1. Volatile halogenated organic compounds in water by purge and trap gas chromatography. Environmental Monitoring and Support Laboratory, Cincinnati, Ohio 45268.

U.S. EPA. 1985c. U.S. Environmental Protection Agency. Method 524.1. Volatile organic compounds in water by purge and trap gas chromatography/ mass spectrometry. Environmental Monitoring and Support Laboratory, Cincinnati, Ohio 45268.

U.S. EPA. 1985d. U.S. Environmental Protection Agency. National Primary Drinking Water Regulations; Volatile Synthetic Organic Chemicals. Final Rule and Proposed Rule. Federal Register. 50(219):46880-46933. November 13.

U.S. EPA. 1986. U.S. Environmental Protection Agency. Guidelines for carcinogen risk assessment. Fed. Reg. 51(185):33992-34003. September 24.

U.S. ITC. 1984. U.S. International Trade Commission. Synthetic Organic Chemicals United States Production. USITC Publication 1422. Washington, D.C. 20436.

Wirtschafter, Z.T., and E.D. Schwartz. 1939. Acute ethylene dichloride poisoning. Jour. Ind. Hyg. Toxicol. 21:126.

Yllner, S. 1971a. Metabolism of 1,2-dichloroethane-$^{14}C$ in the mouse. Acta Pharmacol. et. Toxicol. 30:69-80.

Yllner, S. 1971b. Metabolism of chloroacetate-$^{14}C$ in the mouse. Acta Pharmacol. et. Toxicol. 30:257-265.

Yodaiken, R.E., and J.R. Babcock. 1973. 1,2-Dichloroethane poisoning. Arch. Environ. Health. 26:281-184.

Zhizhonkov, N.Y. 1976. Acute dichloroethane poisoning. Vrach Delo. 6:127-128.

March 31, 1987

# 1,1-DICHLOROETHYLENE

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

## I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

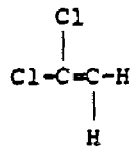
Health Advisories are developed for One-day, Ten-day, Longer-term (approximately 7 years, or 10% of an individual's lifetime) and Lifetime exposures based on data describing noncarcinogenic end points of toxicity. Health Advisories do not quantitatively incorporate any potential carcinogenic risk from such exposure. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

This Health Advisory is based on information presented in the Office of Drinking Water's Health Effects Criteria Document (CD) for the dichloroethylenes (U.S. EPA, 1984a). The HA and CD formats are similar for easy reference. Individuals desiring further information on the toxicological data base or rationale for risk characterization should consult the CD. The CD is available for review at each EPA Regional Office of Drinking Water counterpart (e.g., Water Supply Branch or Drinking Water Branch), or for a fee from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Rd., Springfield, VA 22161, PB #86-117785/AS. The toll-free number is (800) 336-4700; in the Washington, D.C. area: (703) 487-4650.

## II. GENERAL INFORMATION AND PROPERTIES

CAS No. 75-35-4

Chemical structure



Synonyms

- Vinylidene chloride, 1,1-DCE, dichloroethene

Uses

- 1,1-Dichloroethylene has been used as a chemical intermediate and in the manufacture of polyvinylidene copolymers.

Properties (Irish, 1963; Windholz et al., 1976)

| | |
|---|---|
| Chemical Formula | $C_2H_2Cl_2$ |
| Molecular Weight | 96.95 |
| Physical State (room temp.) | clear, colorless liquid |
| Boiling Point | 31.5 °C |
| Melting Point | -122.2 °C |
| Density | -- |
| Vapor Pressure | 591 torr (20°C) |
| Specific Gravity | 1.3 |
| Water Solubility | 250 mg/L (20°C) |
| Log Octanol/Water Partition Coefficient | 5.37 |
| Taste Threshold (water) | -- |
| Odor Threshold (water) | -- |
| Odor Threshold (air) | 2000-5500 $mg/m^3$ |
| Conversion Factor | -- |

Occurrence

- 1,1-Dichloroethylene (1,1-DCE) is a synthetic chemical with no known natural sources (U.S. EPA, 1983).

- Approximately 200 million pounds of 1,1-DCE were produced in 1980. The major use of 1,1-DCE is as a co-monomer in the production of a number of polymers. Polymers of 1,1-DCE and vinyl chloride are used as food wrap (CEH, 1983).

- The major releases of 1,1-DCE to the environment are during its production and its use in the manufacture of polymers. Due to its volatile nature, the majority of releases are expected to be to air. Small amounts of 1,1-DCE may be released to water and land in industrial effluents and from the disposal of solid wastes (U.S. EPA, 1983). 1,1-Dichloroethylene may be a degradation product of trichloroethylene and perchloroethylene. While laboratory studies are currently inconclusive, 1,1-DCE has been found to co-occur in ground water with trichloroethylene and tetrachloroethylene and their other degradation products, cis- and trans-1,2-dichloroethylene and vinyl chloride.

- There is relatively little information on the behavior of 1,1-DCE in the environment. However, the behavior of this chemical has been estimated based upon the information on similar chlorinated compounds (U.S. EPA, 1979). 1,1-Dichloroethylene released to the atmosphere is expected to chemically degrade in hours; when released to surface waters, it is expected to volatilize rapidly. 1,1-DCE is chemically stable in water and mobile in soils and is expected to migrate with ground water. 1,1-Dichloroethylene is not believed to bioaccumulate in plants or animals.

- Available data suggest that 1,1-DCE is not a common contaminant of drinking water. It has not been reported to occur at levels higher than 0.1 ug/L in surface water. However, 1,1-DCE has been reported to occur at levels up to 40 ug/L in wells contaminated with other chlorinated solvents.

- No information is available on the occurrence of 1,1-DCE in food. While 1,1-DCE is used in the manufacture of food wrap, residual levels are expected to be very low because of its high volatility. Due to limited release and rapid degradation, little or no contamination of food by 1,1-DCE is expected.

- 1,1-Dichloroethylene contamination of air has been reported to occur in urban and suburban areas in the low ppt range. Levels in the ppb range have been reported in the areas where 1,1-DCE and its polymers are manufactured (U.S. EPA, 1983).

## III. PHARMACOKINETICS

### Absorption

- 1,1-Dichloroethylene is completely absorbed after gavage, since 96 to 100% of a single dose is excreted within 72 hours (Jones and Hathway, 1978a; McKenna et al., 1978b).

Distribution

- Distribution in rats following a single oral dose of 25 mg of 1,1-DCE/kg resulted in high concentrations in the liver and kidneys after 30 minutes with more general distribution throughout other soft tissues after 1 hour (Jones and Hathway, 1978a).

- Single oral doses of $^{14}C$-1,1-DCE, at 1 or 50 mg/kg, were administered to rats (McKenna et al., 1978a,b). At 72 hours after dosing, the greatest percentage of radioactivity was found in the liver.

Metabolism

- The metabolic end products of chlorinated ethylenes are predominately alcohols and carboxylic acids. The known metabolites of 1,1-DCE are chloroacetic acid, chloroacetyl chloride and dichloroacetaldehyde (Liebler and Guengerich, 1983; Liebler et al., 1984). Toxic intermediates that are formed may interact with tissue macromolecules.

Excretion

- The rate of excretion is relatively rapid, since most of a dose is eliminated within the first 24-72 hours after administration (Jaeger et al., 1977). At low doses, a greater percentage of the metabolites are eliminated via renal and biliary excretion. Carbon dioxide formed during metabolism is expired through the lungs.

- As maximal metabolic capacity is approached at the higher dose levels, proportionally less of the compound is removed from the blood as it passes through the liver. As a result, increasing amounts of unchanged 1,1-DCE are eliminated via the lungs (McKenna et al. 1977).

## IV. HEALTH EFFECTS

Humans

- At high concentrations ($\geq$ 4000 ppm; 15,880 mg/m$^3$), inhalation of 1,1-DCE results in rapid onset of CNS depression, with unconsciousness following if exposure is continued (Irish, 1963).

- Reports of effects on workers exposed to this chemical in combination with other vinyl compounds include liver function abnormalities, headaches, vision problems, weakness, fatigue and neurological sensory disturbances (NIOSH, 1979).

Animals

Short-term Exposure

- Reported oral $LD_{50}$s in adult rats range from 200 to 1800 mg/kg (NIOSH, 1978; Ponomarkov and Tomatis, 1980). Young or fasted rats are more sensitive to the acute effects of 1,1-DCE, with $LD_{50}$s of approximately 50 mg/kg (Andersen and Jenkins, 1977).

- The oral $LD_{50}$s in the mouse and the dog were reported to be 200 mg/kg (Jones and Hathway, 1978b) and 5750 mg/kg (NIOSH, 1978), respectively.

- The most sensitive end-point of 1,1-DCE toxicity is liver damage, ranging from fatty infiltration to necrosis (Reynolds et al., 1975; Chieco et al., 1982). In rats, after doses of 50 to 700 mg of 1,1-DCE/kg, the liver toxicity of 1,1-DCE followed a complex dose-response pattern, with a threshold level, a rapid increase in effect and an extended plateau where increasing doses caused slight increases in effect (Andersen and Jenkins, 1977).

- After a 90 day continuous exposure to 1,1-DCE (189 $mg/m^3$) liver and kidney lesions have been demonstrated (Prendergast et al., 1967).

- Since glutathione depletion increases toxicity (Jaeger et al., 1974; Andersen et al., 1980), the acute toxicity of the chemical is probably the result of a toxic metabolite.

Long-term Exposure

- As with acute exposure, the liver appears to be the principal target of 1,1-DCE toxicity following extended periods of exposure. Chronic exposure of rats to 0 to 200 ppm (0 to 26 mg/kg) in drinking water resulted in fatty changes and hypertrophy of liver cells in females and males at the highest dose (Rampy et al., 1977; Quast et al., 1983).

Reproductive Effects

- In a three-generation rat reproductive study, Nitschke et al. (1983) reported that, at concentrations of 0, 50, 100 or 200 ppm (0 to 26 mg/kg) in the drinking water, 1,1-DCE did not affect rat reproductive capacity.

Developmental Effects

- At levels producing no maternal toxicity (inhalation; 20 ppm in rats and 80 ppm in rabbits and ingestion; 200 ppm in rats) 1,1-DCE did not produce teratogenic effects in rats or rabbits following exposure of dams during organogenesis (Murray et al., 1979).

Mutagenicity

- With S-9 activation, 1,1-DCE was mutagenic in the Ames Salmonella test at concentrations of $3.3 \times 10^{-4}$ to $3.3 \times 10^{-2}$ M (Bartsch et al., 1975) or when exposed to an atmosphere containing 5% 1,1-DCE for 3 hours (Simmon et al., 1977). The chemical had no mutagenic activity in the absence of the S-9 fraction.

- 1,1-Dichloroethylene was mutagenic to E. coli $K_{12}$ at a concentration of 2.5 mM with, but not without, microsomal activation (Greim et al., 1975).

- In mammalian assay systems, a mutagenic effect was not observed. Using the dominant lethal assay, it was reported that exposure to 1,1-DCE at 55 ppm for 6 hr/day for 11 weeks (Short et al., 1977) or to 10 to 50 ppm for 6 hr/day for 5 days (Anderson et al., 1977) did not produce germinal mutation. In addition, using V79 Chinese hamster ovary cells, exposed to 1,1-DCE at concentrations of 2 or 10%, Drevon and Kuroki (1979) did not observe any adverse effects.

- 1,1-Dichloroethylene binds with DNA to a slight degree in the liver and kidneys of both rats and mice after inhalation exposure to 10 or 50 ppm for 6 hours. However, massive tissue damage also occurred. In mice, the kidneys seem to be a more sensitive indicator of tissue damage than the liver (Reitz et al., 1980).

- The International Agency for Research on Cancer (IARC) concluded that there is sufficient evidence to state that 1,1-DCE is mutagenic (IARC, 1982).

- For a recent review of this area, the reader is referred to the article by Jacobson-Kram (1986).

Carcinogenicity

- The results of most studies of the carcinogenic potential of this substance fail to support a significant, treatment-related increase in tumor incidence (U.S. EPA, 1984a). No oral study has resulted in a significant tumor response (NTP, 1982; Quast et al., 1983). Some, but not all, of the inhalation studies have reported significant tumor increases (e.g., mammary tumors in female rats and mice and kidney adenocarcinomas in mice) (Maltoni et al., 1985).

- 1,1-Dichloroethylene was inactive as a whole mouse skin carcinogen when administered subcutaneously (Van Duuren et al., 1979). It was active as a skin tumor initiator following several topical applications of phorbol ester as a promotor.

## V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for One-day, Ten-day, Longer-term (approximately 7 years) and Lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(NOAEL \text{ or } LOAEL) \times (BW)}{(UF) \times (\_\_\_ L/day)} = \_\_\_ mg/L \ (\_\_\_ ug/L)$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect-Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100 or 1,000), in accordance with NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

The study by Chieco and coworkers (1981) has been selected to derive the One-day HA. The authors reported that when 200 mg/kg of 1,1-DCE was given in water containing 0.5% Tween 80, the chemical caused only a slight increase in the plasma levels of alanine, but not aspartate, transaminase. In addition, the pathological changes observed in the liver were limited to a few scattered microfoci of necrosis. Accordingly, the 200 mg/kg is taken to be the LOAEL.

The One-day HA for the 10 kg child is calculated as follows:

$$\text{One-day HA} = \frac{(200 \text{ mg/kg/day})\ (10 \text{ kg})}{(1{,}000)\ (1 \text{ L/day})} = 2.0 \text{ mg/L } (2{,}000 \text{ ug/L})$$

where:

200 mg/kg/day = LOAEL based on hepatic effects.

10 kg = assumed body weight of a child.

1,000 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a LOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

Ten-day Health Advisory

Appropriate studies for the calculation of the Ten-day HA are not available. However, evaluation of all toxicological data for 1,1-DCE suggests that the Longer-term Health Advisory for the 10-kg child of 1,000 ug/L would provide sufficient protection over a ten-day period.

Longer-term Health Advisory

A Longer-term HA can be calculated from a 90-day subchronic study in which rats of both sexes were given 1,1-DCE at nominal concentrations of 0, 50, 100 or 200 ppm (0 to 20 mg/kg bw/day) in their drinking water (Rampy, et al., 1977). Except for a decreased kidney:body weight ratio in males at the low dose, there were no statistically significant differences in organ weights or in organ:body weight ratios at the termination of the study. The only abnormal histopathology noted was an increased cytoplasmic vacuolization of hepatocytes

in the livers of both sexes exposed to the highest dose. A NOAEL of 100 ppm (10 to 12.6 mg/kg) was identified.

A Longer-term HA for the 10-kg child is calculated as follows:

$$\text{Longer-term HA} = \frac{(10\ \text{mg/kg/day})\ (10\ \text{kg})}{(100)\ (1\ \text{L/day})} = 1.0\ \text{mg/L}\ (1{,}000\ \text{ug/L})$$

where:

10 mg/kg/day = NOAEL based on the absence of liver effects.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines foruse with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

A Longer-term HA for the 70-kg adult is calculated as follows:

$$\text{Longer-term HA} = \frac{(10\ \text{mg/kg/day})\ (70\ \text{kg})}{(100)\ (2\ \text{L/day})} = 3.5\ \text{mg/L}\ (3{,}500\ \text{ug/L})$$

where:

10 mg/kg/day = NOAEL based on the absence of liver effects.

70 kg = assumed body weight of an adult.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines foruse with a NOAEL from an animal study.

2 L/day = assumed daily water consumption of an adult.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an

adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed for synthetic organic chemicals and a value of 10% is assumed for inorganic chemicals. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

The Lifetime HA can be calculated from the 2-year chronic study in rats (Quast et al., 1983). 1,1-Dichloroethylene, at nominal concentrations of 0, 50, 100 or 200 ppm (0 to 20 mg/kg/day) in drinking water, was administered to animals of both sexes. No consistent treatment-related biochemical changes were observed in any parameter measured. The only abnormal histopathology observed was mid-zonal fatty accumulation in the livers of both sexes receiving the highest dose. No liver degeneration was noted. A LOAEL of 100 ppm (10 mg/kg) was identified, based upon a trend towards increased fatty deposition in the liver.

A Drinking Water Equivalent Level (DWEL) and Lifetime HA for the 70-kg adult are calculated as follows:

Step 1: Determination of the Reference Dose (RfD)

$$RfD = \frac{(10\ mg/kg/day)}{(1,000)} = 0.01\ mg/kg/day$$

where:

10 mg/kg/day = LOAEL for hepatic effects.

1,000 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a LOAEL from an animal study.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$DWEL = \frac{(0.01\ mg/kg/day)\ (70\ kg)}{(2\ L/day)} = 0.35\ mg/L\ (350\ ug/L)$$

where:

0.01 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

$$Lifetime\ HA = \frac{(0.35\ mg/L)\ (20\%)}{(10)} = 0.007\ mg/L\ (7\ ug/L)$$

where:

0.35 mg/L = DWEL.

20% = assumed relative source contribution from water.

10 = additional uncertainty factor for class C carcinogens.

Evaluation of Carcinogenic Potential

- Qualitative and quantitative assessment of the carcinogenic potential of 1,1-DCE is complicated by the fact that there is only one positive bioassay (Maltoni et al., 1985) among the 18 oncogenic studies (U.S. EPA, 1985c).

- IARC (1982) reported that the data were inadequate to assess the carcinogenic potential in humans, but that it would reevaluate the assessment after reviewing the rat drinking water study (Rampy et al., 1977; Quast et al., 1983) and the NTP gavage bioassays (NTP, 1982). At the present time, this has not been done.

- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986), 1,1-dichloroethylene may be classified in Group C: Possible human carcinogen. Group C includes agents with limited evidence of carcinogenicity in animals in the absence of human data.

## VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- In June, 1984, EPA proposed a Recommended Maximum Contaminant Level (RMCL) of zero for 1,1-dichloroethylene in drinking water (U.S. EPA, 1984b). In 1985, a RMCL of 7 was promulgated for 1,1-dichloroethylene. This value also was proposed for the MCL (U.S. EPA, 1985a).

- In 1980, EPA estimated a range of excess cancer risks for lifetime exposure to 1,1-dichloroethylene when developing ambient water quality criteria (U.S. EPA, 1980a). This range was 23 ug/L, 2.3 ug/L and 0.23 ug/L, respectively, for risks of $10^{-4}$, $10^{-5}$ and $10^{-6}$, assuming consumption of 2 liters of water and 6.5 grams of contaminated fish per day by 70-kg adult.

- The National Academy of Sciences calculated a chronic SNARL (Suggested-No-Adverse-Response-Level) of 100 ug/L, based upon non-carcinogenic effects only (NAS, 1983). The Academy identified a NOAEL of 2 mg/kg from the 1982 NTP bioassay in mice. An uncertainty factor of 100 was applied. It was assumed that a 70 kg adult consumes 2 liters of water daily and 20% of the exposure of most individuals would be from drinking water. In addition, a factor of 5/7 to correct from 5- to 7-day/week exposure was used.

- The World Health Organization has established a guideline for 1,1-DCE in drinking water of 0.3 ug/L, set on evidence of carcinogenicity (WHO, 1984).

- The threshold limit value (TLV) for 1,1-DCE in occupational settings is 5 ppm (20 mg/m$^3$) (ACGIH, 1982).

## VII. ANALYTICAL METHODS

- Analysis of 1,1-DCE is by a purge-and-trap gas chromatographic procedure used for the determination of volatile organohalides in drinking water (U.S. EPA, 1985). This method calls for the bubbling of an inert gas through the sample and trapping 1,1-DCE on an adsorbant material. The adsorbant material is heated to drive off the 1,1-DCE onto a gas chromatographic column. This method is applicable to the measurement of 1,1-DCE over a concentration range of 0.03 to 1500 ug/L. Confirmatory analysis for 1,1-DCE is by mass spectrometry (U.S. EPA, 1985b). The detection limit for confirmation by mass spectometry is 0.2 ug/L.

## VIII. TREATMENT TECHNOLOGIES

- Granular activated carbon (GAC) adsorption and aeration treatment technologies are available for the removal of 1,1-DCE from water and have been reported to be effective. Selection of individual or combinations of technologies to achieve chemical reduction must be based on a case-by-case technical evaluation and an assessment of the economics involved.

- Aeration has been shown to be effective in removing 1,1-DCE from water, based upon its carbon adsorption isotherm (Henry's Law Constant = 498 atm) and pilot and full-scale testing. The chemical was removed successfully from contaminated ground water at 12-14°C in an EPA pilot packed tower aerator containing 18 feet of 1-inch plastic saddle packing (ESE, 1984). The average percent removal varied with air-to-water volume ratio, from 90.6% to 99.99% at ratios of 5 to 80, respectively. Similarly, the concentration of 1,1-DCE in contaminated well water decreased from 122 ug/L to 4 ug/L (97%) using diffused aeration (ESE, 1984). Aeration was conducted in a pilot (1.5 inch diameter, 4-foot long) countercurrent glass column, using a 10-minute contact time and an air-to-water ratio of 4.

- Air stripping is an effective, simple and relatively inexpensive process for removing 1,1-DCE from water. However, the use of this process transfers the contaminant directly to the air stream. When considering use of air stripping as a traetment process, it is suggested that careful consideration be given to the overall environmental occurrence, fate, route of exposure and various hazards associated with the chemical.

## IX. REFERENCES

ACGIH. 1982. American Conference of Government Industrial Hygienists. TLVs. Threshold limit values for chemical substances in work air.

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

Andersen, M.E., O.E. Thomas, M.L. Gargas, R.A. Jones and L.J. Jenkins, Jr. 1980. The significance of multiple detoxification pathways for reactive metabolites in the toxicity of 1,1-dichloroethylene. Toxicol. Appl. Pharmacol. 52:422-432.

Anderson, D. 1977. Dominant lethal studies with the halogenated olefins vinyl chloride and vinylidene chloride in male CD-1 mice. Environ. Health Perspect. 21:71-78.

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

CEH. 1983. Chemical Economics Handbook, Stanford Research Institute, Menlo Park, California.

Chieco, P., M.T. Moslen and E.S. Reynolds. 1981. Effect of administrative vehicle on oral 1,1-dichloroethylene toxicity. Toxicol. Appl. Pharmacol. 57:146-155.

Chieco, P., M.T. Moslen and E.S. Reynolds. 1982. Histochemical evidence that plasma and mitochondrial membranes are primary foci of hepatocellular injury caused by 1,1-dichloroethylene. Lab. Invest. 46:413-421.

Dobbs, R.A., and J.M. Cohen. 1980. Carbon adsorption isotherms for toxic organics. EPA 600/80-023. MERL, Cincinnati, OH.

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

ESE. 1984. Environmental Science and Engineering. Draft technologies and costs for the removal of volatile organic chemicals from potable water supplies. ESE No. 84-912-0300. Prepared for the U.S. EPA, Science and Technology Branch, CSD, ODW, Washington, DC.

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

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

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

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

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

NAS. 1983. National Academy of Sciences. Drinking Water and Health. Volume 5. National Academy Press, Washington, DC.

NIOSH. 1978. National Institute for Occupational Safety and Health. 1,1-Dichloroethylene. Registry of toxic effects of chemical substances. p. 563.

NIOSH. 1979. [ C.D. for Occupational Standard]

Nitschke, K.D., F.A. Smith, J.F. Quast, J.M. Norris and B.A. Schwetz. 1983. A three-generation rat reproductive toxicity study of vinylidene chloride in the drinking water. Fund. Appl. Toxicol. 3:75-79.

NTP. 1982. National Toxicology Program. Carcinogenesis bioassay of vinylidene chloride (CAS No. 75-35-4) in F344 rats and B6C3F1 mice (gavage study). U.S. HHS. PHS. NIH NTP-80-2 NIH Publication No. 82-1784.

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

Prendergast, J.A., R.A. Jones, L.J. Jenkins, Jr. and J. Siegel. 1967. Effects on experimental animals of long-term inhalation of trichloroethylene, carbon tetrachloride, 1,1,1-trichloroethane, dichlorodifluoromethane, and 1,1-dichloroethylene. Toxicol. Appl. Pharmacol. 10:270-289.

Quast, J.F., C.G. Humiston, C.E. Wade, J. Ballard, J.E. Beyer, R.W. Schwetz and J.M. Norris. 1983. A chronic toxicity and oncogenicity study in rats and subchronic toxicity study in dogs on ingested vinylidene chloride. Fund. Appl. Toxicol. 3:55-62.

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

Reitz, R.H., P.G. Watanabe, M.J. McKenna, J.F. Quast and P.J. Gehring. 1980. Effects of vinylidene chloride on DNA synthesis and DNA repair in the rat and mouse: A comparative study with dimethylnitrosamine. Toxicol. Appl. Pharmacol. 52:357-370.

Reynolds, E.S., M.T. Moslen, S. Szabo, R.J. Jaeger and S.D. Murphy. 1975. Hepatotoxicity of vinyl chloride and 1,1-dichloroethylene. Amer. J. Pathol. 81:219.

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

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

U.S. EPA. 1979. U.S. Environmental Protection Agency. Water Related Environmental Fate of 129 Priority Pollutants. Office of Water Planning and Standards, EPA-440/4-79-029, December.

U.S. EPA. 1980. U.S. Environmental Protection Agency. Ambient water quality criteria for dichloroethylenes. Office of Water Regulations and Standards. Criteria and Standards Division. Washington, D.C. EPA 440/5-80-041.

U.S. EPA. 1983. U.S. Environmental Protection Agency. Vinylidine chloride occurrence in drinking water, food, and air. Office of Drinking Water.

U.S. EPA. 1984a. U.S. Environmental Protection Agency. Draft criteria document for the dichloroethylenes. Criteria and Standards Division, Office of Drinking Water, Washington, DC.

U.S. EPA. 1984b. U.S. Environmental Protection Agency. National primary drinking water regulations; Volatile synthetic organic chemicals; Proposed rulemaking. Federal Register 49(114):24330-24355. June 12.

U.S. EPA. 1984c. U.S. Environmental Protection Agency. Method 501.1. Volatile halogenated organic compounds in water by purge and trap gas chromatography. Environmental Monitoring and Support Laboratory, Cincinnati, Ohio 45268. June.

U.S. EPA. 1985a. U.S. Environmental Protection Agency. Final RMCL, proposed MCLs for VOCs. November 13, 1985.

U.S. EPA. 1985b. U.S. Environmental Protection Agency. Method 524.1. Volatile organic compounds in water by purge and trap gas chromatography/ mass spectrometry. Environmental Monitoring and Support Laboratory, Cincinnati, Ohio. June.

U.S. EPA. 1985c. U.S. Environmental Protection Agency. Health assessment document for vinylidene chloride. August.

U.S. EPA. 1986. U.S. Environmental Protection Agency. Guidelines for carcinogen risk assessment. Federal Register. 51(185):33992-34003. September 24.

U.S. ITC. 1982. United States International Trade Commission. Synthetic organic chemicals United States production. 1983 USITC Publication 1422, Washington, D.C. 20436.

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

WHO. 1984. World Health Organization. Guidelines for drinking water quality. Volume 1. Recommendations. Geneva, Switzerland.

Windholz, M., ed. 1976. The Merck Index. 10th edition. Merck and Co., Inc. Rahway, NJ.

# CIS-1,2-DICHLOROETHYLENE

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

## I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

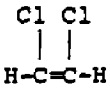
Health Advisories are developed for One-day, Ten-day, Longer-term (approximately 7 years, or 10% of an individual's lifetime) and Lifetime exposures based on data describing noncarcinogenic end points of toxicity. Health Advisories do not quantitatively incorporate any potential carcinogenic risk from such exposure. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

This Health Advisory is based on information presented in the Office of Drinking Water's Health Effects Criteria Document (CD) for the Dichloroethylenes (U.S. EPA, 1984a). The HA and CD formats are similar for easy reference. Individuals desiring further information on the toxicological data base or rationale for risk characterization should consult the CD. The CD is available for review at each EPA Regional Office of Drinking Water counterpart (e.g., Water Supply Branch or Drinking Water Branch), or for a fee from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Rd., Springfield, VA 22161, PB #86-117785/AS. The toll-free number is (800) 336-4700; in the Washington, D.C. area: (703) 487-4650.

## II. GENERAL INFORMATION and PROPERTIES

CAS No. 156-59-2

Chemical Structure



Synonyms

1,2-DCE; cis-1,2-DCE; 1,2-dichloroethene

Uses

In a mixture with the trans-1,2- isomer, as a captive intermediate in the manufacture of other chlorinated solvents

Properties (Irish, 1963; Windholz et al., 1976)

| | |
|---|---|
| Chemical Formula | $C_2H_2Cl_2$ |
| Molecular Weight | 96.95 |
| Physical State | clear, colorless liquid |
| Freezing Point | -80.5°C |
| Boiling Point | 60°C |
| Melting Point | -- |
| Density | -- |
| Vapor Pressure | 208 mm Hg (25°C) |
| Specific Gravity | 1.27 (25°C) |
| Water Solubility | 3500 ug/L (20°C) |
| Log Octanol/Water Partition Coefficient | -- |
| Taste Threshold | Not available |
| Odor Threshold | Not available |
| Conversion Factor | -- |

Occurrence

- The 1,2-dichloroethylenes are synthetic chemicals with no known natural sources (U.S. EPA, 1983).

- There is little information on the current production and use of the 1,2-dichloroethylenes. The production volume for 1,2-dichloroethylene (mixed isomers) was 1,000 lbs or less in 1978 (U.S. EPA, 1978).

- The major releases of the 1,2-dichloroethylenes are from the manufacturing plants in the Gulf Coast region of the U.S., where they are used as a captive intermediate. Releases are expected to be small. The 1,2-dichloroethylenes, particularly the cis- isomer, have been identified as the degradation products of trichloroethylene and tetrachloroethylene in ground water (Parsons et al., 1984; Vogel and McCarty, 1985).

- There is little direct information on the fate of the 1,2-dichloroethylenes in the environment. However, the behavior of the compounds has been estimated based upon the information on similar chlorinated compounds (U.S. EPA 1979). 1,2-Dichloroethylenes released to the atmosphere are expected to chemically degrade in a matter of hours; when released to surface waters, they are expected to volatilize rapidly to air. 1,2-Dichloroethylenes are chemically stable in water and mobile in soils. Once released to land the 1,2-dichloroethylenes are expected to migrate with ground water. 1,2-Dichloroethylenes have been shown to biologically degrade to vinyl chloride in some groundwaters. These compounds are not expected to bioaccumulate in plants or animals. Based upon their similar physical properties, the two isomers of 1,2-dichloroethylene are not expected to behave differently in the environment.

- Monitoring studies have found that the 1,2-dichloroethylenes occur as widespread but relatively rare contaminants of ground water. The cis- isomer has been reported to occur at higher levels than the trans- isomer. The majority of the 1,2-dichloroethylenes has been found to co-occur with trichloroethylene. Levels of the 1,2-dichloroethylenes in approximately 1 % of all ground waters are greater than 0.5 ug/L. Levels as high as 300 ug/L have been reported for the trans- isomer, while levels of 800 ug/L have been reported for the cis- isomer. The 1,2-dichloroethylenes occur in surface water at lower amounts. Levels of 1,2-dichloroethylenes in air are in the ppt range except near production sites where they may reach levels in the low ppb range. Based upon these compounds' volatility and limited use, levels of 1,2-dichloroethylenes in food are expected to be negligible (U.S. EPA, 1983).

- The major source of exposure to the 1,2-dichloroethylenes is from contaminated water except in the areas near production sites where air exposures may dominate.

## III. PHARMACOKINETICS

### Absorption

- cis-1,2-Dichloroethylene is a neutral, low molecular weight, lipid soluble material which would be expected to be readily absorbed following exposure by any route (oral, inhalation, dermal) at the levels expected to be encountered in contamination incidents (U.S. EPA, 1984a).

Distribution

- Kinetic data to define the tissue distribution of cis-1,2-dichloroethylene after oral exposure are not available. If this isomer, however, follows the same absorption and distribution pattern as observed for 1,1-dichloroethylene, the highest concentrations would be expected to be found in the liver and kidney (McKenna et al., 1978).

Metabolism

- The metabolic end products of chlorinated ethylenes are predominantly alcohols and carboxylic acids. Perfusion of cis-1,2-dichloroethylene through isolated rat liver yielded dichloroethanol and dichloroacetic acid, possibly indicating the initial formation of dichloroacetaldehyde (Bonse et al., 1975).

- The position of the chlorine moeity on the chlorinated ethylenes appears to play an important role in their metabolism. Cis-1,2-dichloroethylene was metabolized at a faster rate than trans-1,2-dichloroethylene (which possesses a relatively greater degree of asymmetry) in an in vitro hepatic microsomal system (Costa, 1983).

- Using isolated rat liver microsomes, Freundt and Macholz (1978) reported that cis-1,2-dichloroethylene showed competitive and reversible interaction with the mixed function oxygenase system, resulting in decreased drug metabolism.

Excretion

- No data concerning the excretion of cis-1,2-dichloroethylene are available. If it is similar to 1,1-dichloroethylene, then the rate of elimination would be expected to be relatively rapid, with most of a single dose being excreted in the urine within 24 to 72 hours after cessation of exposure (Jaeger et al., 1977).

## IV. HEALTH EFFECTS

Humans

- At high concentrations, the dichloroethylenes, like other chlorinated ethylenes, possess anesthetic properties. cis-1,2-Dichloroethylene was used as an anesthetic with some success prior to introduction of newer anesthetic gases, and appeared to be safe (Irish, 1963).

Animals

Short-term Exposure

- No cis- isomer-specific $LD_{50}$s have been reported. An oral $LD_{50}$ of 770 mg/kg of the isomer mixture was reported for rats (NIOSH, 1978).

° At high exposure levels, general anesthetic and narcotic effects are observed (Irish, 1963).

° Administration of a single dose of cis-1,2-dichloroethylene at 400 mg/kg to rats caused a significant elevation of liver alkaline phosphatase (Jenkins et al., 1972).

Long-term Exposure

° No information was found in the available literature on the effects of long-term exposures to cis-1,2-dichloroethylene.

Reproductive Effects

° No information was found in the available literature on the potential of cis-1,2-dichloroethylene to produce reproductive effects.

Developmental Effects

° No information was found in the available literature on the potential of cis-1,2-dichloroethylene to produce developmental effects.

Mutagenicity

° cis-1,2-Dichloroethylene was not mutagenic, with or without metabolic activation, when assayed in E. coli K12 at a medium concentration of 2.9 mM (Greim et al., 1975)

° Galli et al. (1982a) reported that cis-1,2-dichloroethylene did not induce point mutation, mitotic gene conversion or mitotic recombination in yeast. In addition, they (1982b) reported that cis-1,2-dichloroethylene was not mutagenic in an in vivo (intravenous host-mediated assay) test. (Both manuscripts are in Italian.)

Carcinogenicity

° No information was found in the available literature on the carcinogenic potential of cis-1,2-dichloroethylene.

## V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for One-day, Ten-day, Longer-term (approximately 7 years) and Lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(NOAEL \text{ or } LOAEL) \times (BW)}{(UF) \times (\_\_\_ L/day)} = \_\_\_ mg/L \ (\_\_\_ ug/L)$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect-Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100 or 1,000), in accordance with NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

There are few animal studies which provide dose-response data on the effects of cis-1,2-dichloroethylene (Irish, 1963; Jenkins et al., 1972; Freundt and Macholz, 1978). Only the study by Jenkins et al. provides sufficient information from which a One-day Health Advisory can be calculated. These authors monitored levels of liver glucose-6-phosphatase, liver alkaline phosphatase, liver tyrosine transaminase, plasma alkaline phosphatase and plasma alkaline transaminase and observed that a single, oral dose of 400 mg/kg to the rat produced a significant change only in liver alkaline phosphatase. The LOAEL of 400 mg/kg reported by Jenkins et al. (1972) will be used for the one-day calculations.

The One-day Health Advisory for the 10 kg child is calculated as follows:

$$\text{One-day HA} = \frac{(400 \text{ mg/kg/day})\ (10 \text{ kg})}{(1{,}000)\ (1 \text{ L/day})} = 4 \text{ mg/L } (4{,}000 \text{ ug/L})$$

where:

400 mg/kg/day = LOAEL based on increase in liver alkaline phosphatase.

10 kg = assumed body weight of a child.

1,000 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a LOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

Ten-day Health Advisory

Appropriate studies for the calculation of a Ten-day Health Advisory are not available. Evaluation of the available toxicological data on cis-1,2-dichloroethylene and 1,1-dichloroethylene suggests that the Longer-term Health Advisory of 1 mg/L should provide adequate protection over a 10-day exposure period as well.

Longer-term Health Advisory

A Longer-term HA for cis-1,2-dichloroethylene cannot be derived directly from compound-specific data since appropriate data do not exist at this time. The available information from shorter-term exposure to 1,1-dichloroethylene and cis- and trans 1,2-dichloroethylene suggests that the non-carcinogenic effects induced by the 1,2- isomers is likely to be no more, and conceivably less, severe than those induced by 1,1-dichloroethylene. Since the non-carcinogenic end-points of toxicity for all three isomers appear to be essentially identical, adopting the Longer-term HA derived for 1,1-dichloroethylene for use as the Longer-term HA for cis-1,2-dichloroethylene may even result in an added margin of safety.

The Longer-term HA will be derived from a 90-day subchronic study in which rats of both sexes were administered 1,1-dichloroethylene at nominal concentrations of 0, 50, 100 or 200 ppm (0-25.6 mg/kg/day) in their drinking water (Rampy et al., 1977). Except for a decreased kidney:body weight ratio in males at the low dose, there were no statistically significant differences in organ weights or organ:body weight ratios at the end of the study. The only histopathology noted was an increased cytoplasmic vacuolization of hepatocytes in the livers of both sexes exposed to the highest dose. A NOAEL of 100 ppm (10 to 12.6 mg/kg) was identified.

The Longer-term HA for the 10-kg child is calculated as follows:

$$\text{Longer-term HA} = \frac{(10\ \text{mg/kg/day})\ (10\ \text{kg})}{(100)\ (1\ \text{L/day})} = 1\ \text{mg/L}\ (1000\ \text{ug/L})$$

where:

10 mg/kg/day = NOAEL based on the absence of liver effects.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

The Longer-term HA for the 70-kg adult is calculated as follows:

$$\text{Longer-term HA} = \frac{(10\ \text{mg/kg/day})\ (70\ \text{kg})}{(100)\ (2\ \text{L/day})} = 3.5\ \text{mg/L}\ (3500\ \text{ug/L})$$

where:

10 mg/kg/day = NOAEL based on the absence of liver effects.

70 kg = assumed body weight of an adult.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

2 L/day = assumed daily water consumption of an adult.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed for synthetic organic chemicals and a value of 10% is assumed for inorganic chemicals. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

Lifetime toxicity data for cis-1,2-dichloroethylene do not exist. Data from the chronic drinking water study in rats as used for the Lifetime Health Advisory for 1,1-dichloroethylene will be used instead. The same caveats and assumptions as were described above for the Longer-term HA also apply here.

The Lifetime HA can be calculated from the 2-year chronic study in rats (Quast et al., 1983). 1,1-Dichloroethylene, at nominal concentrations of 0, 50, 100 or 200 ppm (0 to 20 mg/kg/day) in drinking water, was administered to animals of both sexes. No consistent treatment-related changes were observed in any parameter measured. The only histopathology observed was in the livers of both sexes receiving the highest dose, changes characterized by a minimal amount of mid-zonal fatty accumulation. No liver degeneration was noted. A LOAEL of 100 ppm (10 mg/kg) was identified, based upon a trend towards increased fatty deposition in the liver.

A Drinking Water Equivalent Level (DWEL) and Lifetime HA for the 70-kg adult are calculated as follows:

Step 1: Determination of the Reference Dose (RfD)

$$RfD = \frac{(10\ mg/kg/day)}{(1{,}000)} = 0.01\ mg/kg/day$$

where:

10 mg/kg/day = LOAEL based on adverse liver effects.

1,000 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a LOAEL from an animal study.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$DWEL = \frac{(0.01 \text{ mg/kg/day})\ (70 \text{ kg})}{(2 \text{ L/day})} = 0.35 \text{ mg/L } (350 \text{ ug/L})$$

where:

0.01 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of Lifetime Health Advisory

Lifetime HA = (0.35 mg/L) (20%) = 0.07 mg/L (70 ug/L)

where:

0.35 mg/L = DWEL.

20% = assumed relative source contribution from water.

Evaluation of Carcinogenic Potential

- There are no data available on the carcinogenic potential of cis-1,2-dichloroethylene.
- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986), cis-1,2-dichloroethylene is classified in Group D: Not classified. This category is for agents with inadequate animal evidence of carcinogenicity.

## VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- The Threshold Limit Value (TLV) in the occupational setting for the 1,2-dichloroethylene isomer mixture is 200 ppm (790 mg/m$^3$) (ACGIH, 1982).

## VII. ANALYTICAL METHODS

- Analysis of cis-1,2-dichloroethylene is by a purge-and-trap gas chromatographic procedure used for the determination of volatile organohalides in drinking water (U.S. EPA, 1984b). This method calls for the bubbling of an inert gas through the sample and trapping 1,2-dichloroethylene on an adsorbant material. The adsorbant material is heated to drive off the 1,2-dichloroethylene onto a gas chromatographic column. This method will differentiate between the two isomers of 1,2-dichloroethylene. This method is applicable to the

measurement of 1,2-dichloroethylene over a concentration range of 0.03 to 1500 ug/L. Confirmatory analysis for 1,2-dichloroethylene is by mass spectrometry (U.S. EPA, 1985a). The detection limit for confirmation by mass spectometry 0.2 ug/L.

## VIII. TREATMENT TECHNOLOGIES

- Treatment technologies which will remove cis-1,2-dichloroethylene from water include granular activated carbon (GAC) adsorption, aeration and boiling.

- Dobbs and Cohen (1980) developed adsorption isotherms for cis-1,2-dichloroethylene It was reported that Filtrasorb® 300 carbon exhibited adsorptive capacities of 1.3 mg and 0.26 mg cis-1,2-dichloroethylene/gm carbon at equilibrium concentrations of 100 and 10 ug/L, respectively.

- USEPA-DWRD installed pilot-scale adsorption columns at three locations in New England (U.S. EPA, 1985b,c). Cis-1,2-dichloroethylene was present in the contaminated groundwater at concentrations ranging from 2 to 18 ug/L. The raw water was passed through a Filtrasorb ® 400 GAC column until breakthrough concentration of 0.1 ug/L was achieved which after approximately 10 weeks of continuous operation.

- cis-1,2-Dichloroethylene is amenable to removal by aeration on the basis of its Henry's Law Constant of 225 atm (U.S. EPA, 1985b,c). In a pilot-scale diffused air aeration column, removal efficiency of 85% was achieved from original concentrations of 18 to 118 ug/L at an air-to-water ratio of 30:1. At an air-to-water ratio of 5:1 and the same operating conditions, 58% of cis-1,2-dichloroethylene was removed from the same source water (Love, 1983). In another pilot-scale study, a countercurrent diffused air aeration column removed 80% of cis-1,2-dichloroethylene from well water with 0.5 ug/L, at an air-to-water ratio of 4:1 (Love and Eilers, 1982). Numerous packed column air stripping plant studies have been performed by EPA. All of the studies (using identical column size) indicated that packed column aeration is effective in removing cis-1,2-dichloroethylene from drinking water supplies at different concentrations. The best removal, i.e., 99%+, was achieved at an optimum air-to-water ratio of 80-85:1 (U.S. EPA, 1985b,c; ESE, 1985).

- Boiling also is effective in eliminating cis-1,2-dichloroethylene from water on a short-term, emergency basis. Studies have shown that five minutes of vigorous boiling will remove 96% of cis-1,2-dichloroethylene present in the water (Love and Eilers, 1982).

- Air stripping is an effective, simple and relatively inexpensive process for removing cis-1,2-dichloroethylene and other volatile organics from water. However, this process transfers the contaminant directly into the air stream. When considering this method as a treatment process, it is suggested that careful consideration be given to the overall environmental occurrence, fate, route of exposure and various hazards associated with the chemical.

## IX. REFERENCES

ACGIH. 1982. American Council of Governmental Industrial Hygienists. TLVs. Threshold limit values for chemical substances and physical agents in the workroom environment. Cincinnati, Ohio. p.

Bonse, G., T. Urban, R. Montessano and L. Tomatis. 1975. Chemical reactivity, metabolic oxirane formation and biological reactivity of chlorinated ethylenes in the isolated perfused rat liver preparation. Biochem. Pharmacol. 24:1829-1834.

Costa, A.K. 1983. The chlorinated ethylenes: Their hepatic metabolism and carcinogenicity. Diss. Abst. Int [B]. 44(6):1791-B.

Dobbs, R.A. and J.M. Cohen. 1980. Carbon adsorption isotherms for toxic chemicals. Cincinnati, Ohio. EPA-600/8-80-023.

ESE. 1985. Environmental Science and Engineering. Technologies and costs for the removal of volatile organic chemicals from potable water supplies. ESE No. 84-912-300. Prepared for U.S. EPA Science and Technology Branch, CSD, PDW, Washington, DC.

Freundt, J.J., and J. Macholz. 1978. Inhibition of mixed function oxidases in rat liver by trans-and cis-1,2-dichloroethylene. Toxicology. 10:131-139.

Galli, A., C. Bauer, G. Brenzetti, C. Corsi, R. Del Carratore, R. Nieri and M. Paolini. 1982a. (a) Studio in vitro. Attivita genetica dell' 1,2-dichloroetilene. Boll. Soc. It. Biol. Sper. 58:860-863.

Galli, A., C. Bauer, G. Brenzetti, C. Corsi, R. Del Carratore, R. Nieri and M. Paolini. 1982b. (a) Studio in vivo. Attivita genetica dell' 1,2-dichloroetilene. Boll. Soc. It. Biol. Sper. 58:864-869.

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

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

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

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

Love, D.T., Jr. 1983. Treatment of volatile organic compounds in drinking water. U.S. Dept. of Commerce. NTIS.

Love, D.T., Jr., and R.G. Eilers. 1982. Treatment of drinking water containing trichloroethylene and related industrial solvents. J.A.W.W.A. 74:413-425.

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

NIOSH. 1978. National Institute for Occupational Safety and Health. 1,2-Dichloroethylene. Registry of toxic effects of chemical substances. p. 563.

Parsons, F., P.R. Wood and J. DeMarco. 1984. Transformation of tetrachloroethene and trichloroethene in microcosms and groundwater. J.A.W.W.A. 76:56.

Quast, J.F., C.G. Humiston, C.E. Wade, J. Ballard, J.E. Beyer, R.W. Schwetz and J.M. Norris. 1983. A chronic toxicity and oncogenicity study in rats and subchronic toxicity study in dogs on ingested vinylidine chloride. Fund. Appl. Toxicol. 3:55-62.

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

U.S. EPA. 1978. U.S. Environmental Protection Agency. TSCA Inventory-Non-confidential portion. Office of Toxic Substances.

U.S. EPA. 1979. U.S. Environmental Protection Agency. Water related environmental fate of 129 priority pollutants. Office of Water Planning and Standards. EPA-440/4-79-029. December.

U.S. EPA. 1983. U.S. Environmental Protection Agency. 1,2-Dichloroethylene occurrence in drinking water, food, and air. Office of Drinking Water.

U.S. EPA. 1984a. U.S. Environmental Protection Agency. Draft health effects criteria document for the dichloroethylenes. Criteria and Standards Division, Office of Drinking Water. Washington, DC. December.

U.S. EPA. 1984b. U.S. Environmental Protection Agency. Method 502.1. Volatile halogenated organic compounds in water by purge and trap gas chromatography. Environmental Monitoring and Support Laboratory, Cincinnati, Ohio 45268. June.

U.S. EPA. 1985a. U.S. Environmental Protection Agency. Method 524.1. Volatile halogenated organic compounds in water by purge and trap gas chromatography/mass spectrometry. Environmental Monitoring and Support Laboratory, Cincinnati, Ohio 45268. June.

U.S. EPA. 1985b. U.S. Environmental Protection Agency. Office of Drinking Water Health Advisory Program. Prepared by ICAIR, Life Systems, Inc. for the U.S. EPA Office of Drinking Water, Criteria and Standards Division.

U.S. EPA. 1985c. U.S Environmental Protection Agency. Draft technologies and costs for the removal of synthetic organic chemicals from potable water supplies. Science and Technology Branch, CSD, ODW, Washington, D.C.

U.S. EPA. 1986. U.S. Environmantal Protection Agency. Guidelines for carcinogen risk assessment. Federal Register. 51(185):33992-34003. September 24.

U.S. ITC. 1983. United States International Trade Commission. Synthetic organic chemicals. United States production. 1982. U.S. ITC Publication 1422, Washington, D.C. 20436.

Vogel, T.M., and P.L. McCarty. 1985. Biotransformation of tetrachloroethylene to trichloroethylene, dichloroethylene, vinyl chloride, and carbon dioxide under methanogenic conditions. Appl. Environ. Microbiol. 49:1080-1083.

Windholz, M., ed. 1976. The Merck Index. 10th edition. Merck & Co., Inc. Rahway, NJ.

# TRANS-1,2-DICHLOROETHYLENE

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

## I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

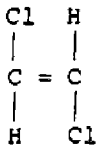
Health Advisories are developed for One-day, Ten-day, Longer-term (approximately 7 years, or 10% of an individual's lifetime) and Lifetime exposures based on data describing noncarcinogenic end points of toxicity. Health Advisories do not quantitatively incorporate any potential carcinogenic risk from such exposure. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

This Health Advisory is based on information presented in the Office of Drinking Water's Health Effects Criteria Document (CD) for the Dichloroethylenes (U.S. EPA, 1984a). The HA and CD formats are similar for easy reference. Individuals desiring further information on the toxicological data base or rationale for risk characterization should consult the CD. The CD is available for review at each EPA Regional Office of Drinking Water counterpart (e.g., Water Supply Branch or Drinking Water Branch), or for a fee from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Rd., Springfield, VA 22161, PB #86-117785/AS. The toll-free number is (800) 336-4700; in the Washington, D.C. area: (703) 487-4650.

## II. GENERAL INFORMATION and PROPERTIES

CAS No. 156-60-5

Structural Formula



Synonyms

- 1,2-DCE; trans-1,2-DCE; 1,2-dichloroethene

Uses

- In a mixture with the cis-1,2- isomer, as captive intermediates in the production of other chlorinated solvents.

Properties (Irish, 1963; Windholz et al., 1976)

| | |
|---|---|
| Chemical Formula | $C_2H_2Cl_2$ |
| Molecular Weight | 96.95 |
| Physical State | clear, colorless liquid |
| Freezing Point | -49.4°C |
| Boiling Point | 47°C |
| Melting Point | -- |
| Density | -- |
| Vapor Pressure | 265 mm Hg (25°C) |
| Specific Gravity | 1.27 (25°C) |
| Water Solubility | 6300 ug/L (25°) |
| Log Octanol/Water Partition Coefficient | -- |
| Taste Threshold (water) | Not available |
| Odor Threshold (water) | Not available |
| Odor Threshold (air) | 1,100 ppm (Lehmann and Schmidt-Kehl, 1936) |
| 1 mg/L | 252 ppm (25°c and 760 Torr.) |
| 1 ppm | 3.97 mg/$m^3$ (25°c and 760 Torr.) |

Occurrence

- The 1,2-dichloroethylenes are synthetic chemicals with no known natural sources (U.S. EPA, 1983).

- There is little information on the current production and use of the 1,2-dichloroethylenes. The production volume for 1,2-dichloroethylene (mixed isomers) was 1,000 lbs or less in 1978 (U.S. EPA, 1978).

- The major releases of the 1,2-dichloroethylenes are from the manufacturing plants in the Gulf Coast region of the U.S., where they used as captive intermediates. Releases are expected to be small. The 1,2-dichloroethylenes, particularly the cis- isomer, have been identified as degradation products of trichloroethylene and tetrachloroethylene in ground water (Parsons et al., 1984; Vogel and McCarty, 1985).

- There is little direct information on the fate of the 1,2-dichloroethylenes in the environment. However, the behavior of these compounds has been estimated based upon the information on similar chlorinated compounds (U.S. EPA, 1979). 1,2-Dichloroethylenes released to the atmosphere are expected to degrade chemically in a matter of hours; when released to surface waters, they are expected to volatilize rapidly to air. 1,2-Dichloroethylenes are chemically stable in water and mobile in soils. Once released to land, 1,2-dichloroethylenes are expected to migrate with ground water. 1,2-Dichloroethylenes have been shown to degrade biologically to vinyl chloride in some groundwaters. These compounds are not expected to bioaccumulate in plants or animals. Based upon their similar physical properties, the two isomers of 1,2-dichloroethylene are not expected to behave differently in the environment.

- Monitoring studies have found that the 1,2-dichloroethylenes occur as widespread, but relatively rare, contaminants of ground water. The cis- isomer has been reported to occur at higher levels than the trans- isomer. The majority of the 1,2-dichloroethylenes has been found to co-occur with trichloroethylene. Levels of the 1,2-dichloroethylenes are greater than 0.5 ug/L in approximately 1 % of all ground waters. Levels as high as 300 ug/L have been reported for the trans- isomer, while levels of 800 ug/L have been reported for the cis- isomer. The 1,2-dichloroethylenes occur in surface water at lower amounts. The 1,2-dichloroethylenes in air are in the ppt range except near production sites where they may reach the low ppb range. Based upon their volatility and limited use, levels of 1,2-dichloroethylenes in food are expected to be negligible (U.S. EPA, 1983).

- The major source of exposure to the 1,2-dichloroethylenes is from contaminated water except in the areas near production sites where air exposures may dominate.

## III. PHARMACOKINETICS

### Absorption

° trans-1,2-Dichloroethylene is a neutral, low molecular weight, lipid soluble material which should be readily absorbed by any route (oral, inhalation, dermal) at the levels expected to be encountered in contamination incidents (U.S. EPA, 1984a).

### Distribution

° Kinetic data to define the tissue distribution of trans-1,2-dichloroethylene after oral exposure are not available. If this isomer follows the same absorption and distribution pattern as 1,1-dichloroethylene, the highest concentrations would be expected to be found in the liver and kidney (McKenna et al., 1978).

### Metabolism

° The metabolic end products of chlorinated ethylenes are predominantly alcohols and carboxylic acids. In rat liver microsomal preparations, supplemented with NADPH, trans-1,2-dichloroethylene was transformed to 2,2-dichloroethanol and 2,2-dichloroacetic acid (Costa and Ivanetich, 1982). Presumably, these products were formed by reduction or oxidation of 2,2-dichloroacetaldehyde.

° The positions of the chlorine moieity on the chlorinated ethylenes appear to play an important role in metabolism. Trans-1,2-dichloroethylene (which possesses a relatively greater degree of asymmetry) was metabolized at a slower rate than cis-1,2-dichloroethylene in an *in vitro* hepatic microsomal system (Costa, 1983).

### Excretion

° No data concerning the excretion of trans-1,2-dichloroethylene are available. If it is similar to 1,1-dichloroethylene, then the rate of elimination will be relatively rapid, with most of a single dose being excreted in the urine within 24 to 72 hours after cessation of exposure (Jaeger et al., 1977).

## IV. HEALTH EFFECTS

### Humans

° At high concentrations, the dichloroethylenes, like other chlorinated ethylenes, possess anesthetic properties (Irish, 1963). It appears that the trans- isomer is about twice as potent as the cis- isomer in depressing the central nervous system (Albrecht, 1927).

Animals

Short-term Exposure

- The oral $LD_{50}$ in the 200 g rat was 1,300 mg/kg (Freundt et al., 1977). When administered intraperitoneally, the $LD_{50}$ was six-fold higher (7,800 mg/kg).

- At high exposure (8,000 to 16,000 ppm) levels, trans-1,2-dichloroethylene can cause narcosis and death in rats in four hours (Torkelson and Rowe, 1981).

- No significant immunological effects were observed in male mice exposed by gavage to 22 or 220 mg/kg for 14 consecutive days (Munson et al., 1982). In addition, no changes in body or organ weights (liver, kidney, thymus and lung) were observed.

Long-term Exposure

- Freundt et al. (1977) exposed Wistar rats to air containing trans-1,2-dichloroethylene at 0, 200, 1,000 or 2,000 ppm (0 to 7,940 mg/$m^3$). Brief (8-hour) or prolonged (8 hours/day, 5 days/week for 1, 2, 8 or 16 weeks) exposure at 200 ppm produced slight degeneration of the liver lobule and lipid accumulation in the Kupffer cells. At 8 and 16 weeks of exposure, severe pneumonic infiltration was observed. Exposure at 1000 ppm for 8 hours resulted in significant reductions in serum albumin, urea nitrogen and alkaline phosphatase. Eight-hour exposures at both 200 and 1,000 ppm produced a significant decrease in the number of leucocytes.

Reproductive Effects

- No information was found in the available literature on the potential of trans-1,2-dichloroethylene to produce reproductive effects.

Developmental Effects

- No information was found in the available literature on the potential of trans-1,2-dichloroethylene to produce developmental effects.

Mutagenicity

- trans-1,2-Dichloroethylene at a medium concentration of 2.3 mM was not mutagenic, with or without microsomal activation, when assayed in *E. coli* K12 (Greim et al., 1975).

- trans-1,2-Dichloroethylene did not cause point mutation, mitotic gene conversion or mitotic recombination in a diploid strain of *Saccharomyces cerevisiae*, with or without microsomal activation (Galli et al. (1982a). They also reported that it had no genetic effects in an *in vivo* (intravenous host-mediated assay) mutagenicity study (Galli et al., 1982b).

Carcinogenicity

- No information was found in the available literature on the carcinogenic potential of trans-1,2-dichloroethylene.

## V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for One-day, Ten-day, Longer-term (approximately 7 years) and Lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(NOAEL \text{ or } LOAEL) \times (BW)}{(UF) \times (\_\_\_ L/day)} = \_\_\_ mg/L (\_\_\_ ug/L)$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect-Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100 or 1,000), in accordance with NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

Freundt et al. (1977) reported the effects of trans-1,2-dichloroethylene after inhalation by mature female Wistar rats (180 to 200g) at 200 ppm (800 $mg/m^3$, the currently established TLV/MAC in many countries) or at 1000 or 3000 ppm (4000 or 12000 $mg/m^3$, respectively). A brief (8 hour) exposure at 200 ppm did not result in significant adverse effects on the liver. There was slight pulmonary capillary hyperemia and distention of the alveolar septum. This effect was, most likely, transitory in nature and would not occur after oral administration.

A number of biochemical and hematological parameters also were tested. No changes in serum cholesterol, albumin, uric acid, urea nitrogen, glucose, alkaline phosphatase, SGOT or SGPT were observed after the single 8-hour exposure at 200 ppm. Exposure at 1,000 ppm for 8 hours resulted in significant reductions in serum albumin, urea nitrogen and alkaline phosphatase. Eight-hour exposures at both 200 and 1,000 ppm caused a significant decrease in the number of leucocytes. Since leucocyte count may be affected by external stimuli [physical exertion, stress and food intake (Lentner, 1984)], the number of leucocytes in this study ($2.5 \times 10^3$) appears to be lower than normal for rats [6 to 17 x $10^3/mm^3$ (Harkness and Agner, 1983)] and there is no dose response noted in the 200 and 1,000 ppm groups, it is difficult to evaluate

the reported decrease in leucocytes. Accordingly, this parameter will not be used in setting the NOAEL. Clinico-chemical parameters were not studied at the 3,000 ppm exposure level.

A NOAEL of 200 ppm over a single 8-hour exposure was identified for trans-1,2-dichloroethylene based upon the normal biochemical parameters and on the slight liver effects in only 1 of 6 rats.

The One-day Health Advisory for the 10-kg child is calculated as follows:

Step 1: Determination of the total absorbed dose (TAD)

$$TAD = \frac{200 \times 3.97\ (mg/m^3) \times 0.006\ (m^3/hr) \times 8}{(0.19\ kg)} = 200\ mg/kg$$

where:

200 x 3.97 ($mg/m^3$) = total absorbed dose converted from ppm to $mg/m^3$.

0.006 = conversion factor to obtain $m^3/hr$ for 190 g rats, i.e., 100 ml/min x 60 min/hr divided by 1,000,000 (ml to $m^3$).

8 = duration of exposure in hours.

0.19 = average weight in kg of exposed rats.

Step 2: Determination of a One-day Health Advisory

$$\text{One-day HA} = \frac{(200\ mg/kg/day)\ (10\ kg)}{(100)\ (1\ L/day)} = 20.0\ mg/L\ (20{,}000\ ug/L)$$

where:

200 mg/kg/day = TAD.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

Ten-day Health Advisory

Appropriate studies for the calculation of the Ten-day HA are not available. The Longer-term HA for a 10 kg child (1.43 mg/L) is recommended as a conservative estimate for a ten-day exposure.

Longer-term Health Advisory

Freundt et al. (1977) also studied the effects of administering trans-1,2-dichloroethylene at 200 ppm (8 hr/day for 5 days/week) for 16 weeks. They found slight to severe fatty infiltration in the parenchymal and Kupffer cells of the liver (5 of 6 rats) and severe pneumonic infiltration (3 of 6 rats).

Based on the liver and lung effects, a LOAEL of 200 ppm was identified for trans-1,2-dichloroethylene.

The Longer-term HA is calculated as follows:

Step 1: Determination of the total absorbed dose (TAD)

$$TAD = 200 \text{ mg/kg (see One-day HA)}$$

Step 2: Determination of a Longer-term HA for a 10-kg child

$$\text{Longer-term HA} = \frac{(200 \text{ mg/kg/day}) (5) (10 \text{ kg})}{(1{,}000) (7) (1 \text{ L/day})} = 1.43 \text{ mg/L } (1{,}430 \text{ ug/L})$$

where:

200 mg/kg/day = LOAEL for hepatic and pulmonary effects.

5/7 = correction factor for 5 day/week dosing regimen.

10 kg = assumed body weight of a child.

1,000 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a LOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

A Longer-term HA for a 70-kg adult is calculated as follows:

$$\text{Longer-term HA} = \frac{(200 \text{ mg/kg/day}) (5) (70 \text{ kg})}{(1{,}000) (7) (2 \text{ L/day})} = 5 \text{ mg/L } (5{,}000 \text{ ug/L})$$

where:

200 mg/kg/day = LOAEL for hepatic and pulmonary effects.

5/7 = correction factor for 5 day/week dosing regimen.

70 kg = assumed body weight of an adult.

1,000 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a LOAEL from an animal study.

2 L/day = assumed daily water consumption of an adult.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed for synthetic organic chemicals and a value of 10% is assumed for inorganic chemicals. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

Lifetime toxicity data for trans-1,2-dichloroethylene do not exist at this time. Data from the chronic drinking water study in rats as used for the Lifetime Health Advisory for 1,1-dichloroethylene will be used instead. The same caveats and assumptions as were described above for the Longer-term HA also apply here.

The Lifetime HA is calculated from a 2-year chronic study in rats (Quast et al., 1983). 1,1-Dichloroethylene, at concentrations of 0, 50, 100 or 200 ppm (0 to 20 mg/kg/day) in drinking water, was administered to animals of both sexes. No consistent treatment-related changes were observed in any parameter measured. The only histopathology observed was in the livers of both sexes receiving the highest dose, changes characterized by a minimal amount of mid-zonal fatty change. No liver degeneration was noted. A LOAEL of 100 ppm (10 mg/kg) was identified, based upon a trend towards increased fatty deposition in the liver.

A Drinking Water Equivalent Level (DWEL) and Lifetime HA for the 70-kg adult are calculated as follows:

Step 1: Determination of the Reference Dose (RfD)

$$RfD = \frac{(10 \text{ mg/kg/day})}{(1,000)} = 0.01 \text{ mg/kg/day}$$

where:

10 mg/kg/day = LOAEL.

1,000 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a LOAEL from an animal study.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$DWEL = \frac{(0.01\ mg/kg/day)\ (70\ kg)}{(2\ L/day)} = 0.35\ mg/L\ (350\ ug/L)$$

where:

0.01 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

Lifetime HA = (0.035 mg/L) (20%) = 0.07 mg/L (70 ug/L)

where:

0.35 mg/L = DWEL.

20% = assumed relative source contribution from water.

Evaluation of Carcinogenic Potential

- There are no data available which describe the carcinogenic potential of trans-1,2-dichloroethylene.
- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986), trans-1,2-dichloroethylene is classified in Group D: Not classified. This category is for agents with inadequate animal evidence of carcinogenicity.

## VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- The Threshold Limit Value (TLV) in the occupational setting for the 1,2-dichloroethylene isomer mixture is 200 ppm (790 $mg/m^3$) (ACGIH, 1982).

## VII. ANALYTICAL METHODS

- Analysis of trans-1,2-dichloroethylene is by a purge-and-trap gas chromatographic procedure used for the determination of volatile organohalides in drinking water (U.S. EPA, 1984b). This method calls for the bubbling of an inert gas through the sample and trapping of 1,2-dichloroethylenes on an adsorbant material. The adsorbant material is heated to drive off the 1,2-dichloroethylene onto a gas chromatographic column. This method will differentiate between the two isomers of 1,2-dichloroethylene. This method is applicable to the measurement of 1,2dichloroethylene over a concentration range of 0.03 to 1500 ug/L. Confirmatory analysis for 1,2-dichloroethylene is done by mass spectrometry (U.S. EPA, 1985a). The detection limit for confirmation by mass spectometry is 0.2 ug/L.

## VIII. TREATMENT TECHNOLOGIES

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

- Dobbs and Cohen (1980) developed adsorption isotherms for trans-1,2-dichloroethylene. It was reported that Filtrasorb® 300 carbon exhibited adsorptive capacities of 0.95 mg, 0.29 mg and 0.09 mg trans-1,2-dichloroethylene/gm carbon at equilibrium concentrations of 100, 10 and 0.1 ug/L, respectively. No field data are available on the adsorption of trans-1,2-dichloroethylene from contaminated water.

- Theoretical considerations indicate that trans-1,2-dichloroethylene is amenable to treatment by aeration on the basis of its Henry's Law Constant of 225 atm (U.S. EPA 1985b,c). In a laboratory study, distilled water containing 217 ug/L of trans-1,2-dichloroethylene was passed through a diffused-air aeration column. A 97% reduction of the compound was reported in a countercurrent operation at an air-to-water ratio of 15:1 (U.S. EPA, 1985b,c).

- Air stripping is an effective, simple and relatively inexpensive process for removing trans-1,2-dichloroethylene and other volatile organics from water. However, the use of this process then transfers the contaminant directly into the air stream. When considering use of air stripping as a treatment process, it is suggested that careful consideration be given to the overall environmental occurrence, fate, route of exposure and various hazards associated with the chemical.

## IX. REFERENCES

Albrecht, P. 1927. Arch. Klin. Chir. 146:273.

ACGIH. 1982. American Council of Government Industrial Hygienists. TLVs. Threshold limit values for chemical substances and physical agents in the workroom environment. Cincinnati, OH.

Bonse, G., T. Urban, R. Montessano and L. Tomatis. 1975. Chemical reactivity, metabolic oxirane formation and biological reactivity of chlorinated ethylenes in the isolated perfused rat liver preparation. Biochem. Pharmacol. 24:1829-1834.

Costa, A.K. 1983. The chlorinated ethylenes: Their hepatic metabolism and carcinogenicity. Diss. Abst. Int. [B]. 44(6):1797-B.

Costa, A.K. and K.M. Ivanetich. 1982. The 1,2-dichloroethylenes: Their metabolism by hepatic cytochrome P-450 in vitro. Biochem. Pharmacol. 31:2093-2102.

Dobbs, R.A., and J.M. Cohen. 1980. Carbon absorption isotherms for toxic chemicals. Cincinnati, Ohio. EPA-600/3-80-023.

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

Freundt, J.J., G.P. Liebaldt and E. Lieberwirth. 1977. Toxicity studies on trans-1,2-dichloroethylene. Toxicology. 7:141-153.

Freundt, J.J., and J. Macholz. 1978. Inhibition of mixed function oxidases in rat liver by trans-and cis-1,2-dichloroethylene. Toxicology. 10:131-139.

Galli, A., C. Bauer, G. Brenzetti, C. Corsi, R. Del Carratore, R. Nieri and M. Paolini. 1982a. (a) Studio in vitro. Attivita genetica dell' 1,2-dichloroetilene. Boll. Soc. It. Biol. Sper. 58:860-863.

Galli, A., C. Bauer, G. Brenzetti, C. Corsi, R. Del Carratore, R. Nieri and M. Paolini. 1982b. (a) Studio in vivo. Attivita genetica dell' 1,2-dichloroetilene. Boll. Soc. It. Biol. Sper. 58:864-869.

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

Hardie, D.W.F. 1964. Dichloroethylene. In: Mark, H.F., J.J. McKetta, Jr., D.F. Othmer, eds. Kirk-Othmer encyclopedia of chemical technology, 2nd ed., Wiley-Interscience, New York, Vol. 5. pp. 178-183.

Harkness, J.E., and J.U. Agner. 1983. The biology and medicine of rabbits and rodents. 2nd Ed., Lea and Fibiger, Philadelphia. p. 46.

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

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

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

Lehmann, K.B. and L. Schmidt-Kehl. 1936. Study of the most important chlorohydrocarbons from the standpoint of industrial hygeine. Arch. Hyg. Bakteriol. 116:131-268.

Lentner, C. 1984. Geigy Scientific Tables. Vol. 3, 8th Ed. Ciba-Geigy, Ltd., Basel. p. 209.

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

Munson, A.E., V.M. Saunders, K.A. Douglas, L.E. Sain, B.M. Kauffman and K.L. White, Jr. 1982. In vivo assessment of immunotoxicity. Environ. Health Perspect. 43:41-52.

Parsons, F., P.R. Wood and J. DeMarco. 1984. Transformation of tetrachloroethene and trichloroethene in microcosms and groundwater. J.A.W.W.A. 76:56.

Quast, J.F., C.G. Humiston, C.E. Wade, J. Ballard, J.E. Beyer, R.W. Schwetz and J.M. Norris. 1983. A chronic toxicity and oncogenicity study in rats and subchronic toxicity study in dogs on ingested vinylidine chloride. Fund. Appl. Toxicol. 3:55-62.

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

Torkelson, T.R., and V.K. Rowe. 1981. Halogenated aliphatic hydrocarbons. In: G.D. Clayton and F.E. Clayton (eds.). Patty's Industrial Hygiene and Toxicology. 3rd ed. Vol. 2B. John Wiley and Sons, Inc., New York. pp. 3550-3553.

U.S. EPA. 1978. U.S Environmental Protection Agency. TSCA Inventory -- Non-confidential portion. Office of Toxic Substances.

U.S. EPA. 1979. U.S. Environmental Protection Agency. Water related environmental fate of 129 priority pollutants. Office of Water Planning and Standards. EPA-440/4-79-029. December.

U.S. EPA. 1983. U.S. Environmental Protection Agency. 1,2-Dichloroethylene occurrence in drinking water, food, and air. Office of Drinking Water, STB.

U.S. EPA. 1984a. U.S. Environmental Protection Agency. Draft health effects criteria document for the dichloroethylenes. Criteria and Standards Division, Office of Drinking Water. Washington, DC. December.

U.S. EPA. 1984b. U.S. Environmental Protection Agency. Method 502.1. Volatile halogenated organic compounds in water by purge and trap gas chromatography. Environmental Monitoring and Support Laboratory, Cincinnati, Ohio 45268. June.

U.S. EPA. 1985a. U.S. Environmental Protection Agency. Method 524.1 Volatile halogenated organic compounds in water by purge and trap gas chromatography/mass spectrometry. Environmental Monitoring and Support Laboratory, Cincinnati, Ohio 45268. June.

U.S. EPA. 1985b. U.S. Environmental Protection Agency. Office of Drinking Water Health Advisory Program. Prepared by ICAIR, Life Systems, Inc. for the U.S. EPA Office of Drinking Water, Criteria and Standards Division.

U.S. EPA. 1985c. U.S. Environmental Protection Agency. Draft technologies and costs for the removal of synthetic organic chemicals from potable water supplies. Science and Technoloby Branch, CSD, ODW, Washington, D.C.

U.S. EPA. 1986. U.S. Environmental Protection Agency. Guidelines for carcinogen risk assessment. Federal Register. 51(185)33992-34003. September 24.

U.S. ITC. 1983. United States International Trade Commission. Synthetic organic chemicals. United States production. 1982 U.S.ITC Publication 1422, Washington, D.C. 20436.

Vogel, T.M., and P.L. McCarty. 1985. Biotransformation of tetrachloroethylene to trichloroethylene, dichloroethylene, vinyl chloride, and carbon dioxide under methanogenic conditions. Appl. Environ. Microbiol. 49:1080-1083.

Windholz, M., S. Budvari, L.Y. Stroumtsos and M.N. Fertig. (eds.) 1976. The Merck Index, 9th ed. Merck & Co., Inc., Rahway, N.J.

# DICHLOROMETHANE

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

## I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

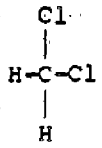
Health Advisories are developed for One-day, Ten-day, Longer-term (approximately 7 years, or 10% of an individual's lifetime) and Lifetime exposures based on data describing noncarcinogenic end points of toxicity. Health Advisories do not quantitatively incorporate any potential carcinogenic risk from such exposure. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

This Health Advisory is based upon information presented in the Office of Health and Environment Assessment Criteria Document (CD) for Dichloromethane (U.S. EPA, 1985a). The HA and CD formats are similar for easy reference. Individuals desiring further information on the toxicological data base or rationale for risk characterization should consult the CD. The CD is available for a fee from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Rd., Springfield, VA 22161, PB85 191559. The toll-free number is (800) 336-4700; in the Washington, D.C. area: (703) 487-4650.

## II. GENERAL INFORMATION AND PROPERTIES

CAS No. 75-09-2

Structural Formula



Synonyms

- Methylene chloride, methylene dichloride, methylene bichloride, DCM

Uses

- Solvent for insecticides, paints, varnish and paint removers and in food processing; degreasing and cleaning fluids.

Properties (Verschueren, 1977; Windholtz, 1983)

| | |
|---|---|
| Chemical Formula | $CH_2Cl_2$ |
| Molecular Weight | 84.94 |
| Physical State | Colorless liquid |
| Boiling Point | 40°C (760 mm Hg) |
| Melting Point | -95 to -97°C |
| Density | 1.3255 (20/4°C) |
| Vapor Pressure | 349 mm Hg (20°C) |
| Water Solubility | 20 g/L (20°C) |
| Log Octanol/Water Partition Coefficient | -- |
| Odor Threshold | -- |
| Taste Threshold | -- |
| Conversion Factor | -- |

Occurrence

- Dichloromethane (DCM) is a synthetic chemical with no known natural sources.

- Production of DCM was approximately 600 million lbs in 1983 (U.S. ITC, 1984).

- The major sources of DCM released to the environment are from its industrial uses where the majority of all DCM produced is released. Most of the releases occur to the atmosphere by evaporation. However, large amounts of DCM are disposed of by burial in landfills or dumping on the ground or into sewers. Because DCM is involved in industrial operations performed nationwide, releases occur in all urban areas. Releases of DCM during its production are relatively minor in comparison to releases during its use.

- Dichloromethane released to the air is degraded in a matter of a few days. Dichloromethane released to surface waters migrates to the atmosphere in a few days or weeks where it also degrades. Volatilization is the major transport process for its removal from aquatic systems (U.S. EPA, 1979). Dichloromethane which is released to the land does not sorb onto soil and migrates readily to ground water where it is expected to remain for months to years. Dichloromethane, unlike some other chlorinated compounds, does not bioaccumulate in individual animals or food chains.

- Because of the large and dispersed releases, DCM occurs widely in the environment. It is ubiquitous in the air with levels in the ppt range and is a common contaminant in ground and surface waters with higher levels found in ground water.

- Very limited information is available on the occurrence of dichloromethane in food. Dichloromethane has been reported to occur in fish. It is used as an extraction solvent for the decaffination of coffee and other food processing operations. Low levels of DCM have been reported to occur in some foods from these operations.

- The major sources of exposure to DCM are from contaminated water. Air and food are only a minor sources (U.S. EPA, 1980c).

## III. PHARMACOKINETICS

### Absorption

- Dichloromethane is expected to be absorbed completely when ingested. A single oral dose of 1 or 50 mg/kg $^{14}$C-DCM administered to male rats (3/dose) was exhaled as unchanged DCM (12.3 or 72.1%, respectively) within 48 hours (McKenna and Zempel, 1981).

### Distribution

- Tissue distribution after administration of 1 or 50 mg/kg of $^{14}$C-DCM in water by gavage to male rats (3/dose) was measured by McKenna and Zempel (1981). The highest concentration of radioactivity was present in liver and the lowest in fat, 48 hours after either dose.

Metabolism

- The major metabolites of DCM are carbon monoxide and carbon dioxide. McKenna and Zempel (1981) studied the metabolism of $^{14}C$-DCM after gavage administration to groups of three male Sprague-Dawley rats dosed at 1 or 50 mg/kg. They metabolized about 88 or 28% of the dose, respectively. The major metabolites exhaled after 48 hours were carbon monoxide (30.9 and 11.9% of the 1 or 50 mg/kg doses, respectively) and carbon dioxide (35.0 and 6.3% of the 1 or 50 mg/kg doses, respectively).

Excretion

- Metabolites of DCM are excreted in urine. McKenna and Zempel (1981) reported that, in rats given 1 or 50 mg/kg $^{14}C$-DCM, 4.52 ±0.05% or 1.96 ±0.05% of the dose, respectively, was excreted in the urine within 48 hours. The fecal elimination of DCM after oral or intraperitoneal administration of DCM is low (<1.0%) (DiVincenzo and Hamilton, 1975; McKenna and Zempel, 1981).

## IV. HEALTH EFFECTS

Humans

- Bonventre et al. (1977) described a fatal intoxication with DCM which was being used as a paint remover. Postmortem examination revealed the presence of DCM in the liver (14.4 mg/100 g tissue), blood (51 mg/dL or 510 mg/L) and brain (24.8 mg/100 g tissue). The carboxyhemoglobin content was 3% saturated.

Animals

Short-term Exposure

- Oral $LD_{50}$s for DCM were reported as 1,987 mg/kg for mice and 2,121 mg/kg for rats (Kimura et al. 1971; Aviado et al. 1977).

- Kimura et al. (1971) administered single oral doses of DCM to young adult Sprague-Dawley rats and determined that an approximate dose of 1.3 g/kg body weight was the lowest dose to induce the first observable signs of toxicity (dyspnea, ataxia, cyanosis and/or coma).

Long-term Exposure

- Bornmann and Loeser (1967) administered DCM in drinking water at 2.25 g/18L (or 125 mg/L) to 30 male and 30 female Wistar rats for 13 weeks. This is equivalent to a dose of about 15 mg/kg/day assuming that 10 mL of water is consumed daily. The animals were examined for changes in behavior, body weight, blood and urine chemistries, reproductive function, organ to body weight ratios and histology. No treatment-related effects were observed, even though some rats may have consumed as much as 250 mg DCM (36.6 mg/kg/day) during this

experiment. The urine albumin test was frequently positive; however, the authors did not attach any biological significance to this observation. From this study, a NOAEL of 125 mg/kg/day was identified.

- Hazelton Labs (1982) reported on the toxicity and carcinogenicity of DCM in a chronic two-year drinking water study in Fischer 344 rats. Two control groups (85 and 50 rats/sex/group) received deionized drinking water. Four groups of animals (85 rats/sex/group) were given DCM in drinking water at target doses of 5, 50, 125 and 250 mg/kg/day. A high-dose recovery group (25 rats/sex) was given DCM in drinking water at a target dose of 250 mg/kg/day for the initial 78 weeks and deionized drinking water subsequently for the remainder of the study. At 26, 52 and 78 weeks of treatment, there were incremental sacrifices of 5, 10 or 20 rats/sex/group, respectively. At 104 weeks of exposure, all survivors were sacrificed. Survival, body weight gains, total food consumption, water consumption, clinical observations, ophthalmoscopic findings, clinical pathology, absolute and relative organ weights and gross and microscopic pathology were examined to evaluate any compound-related effects. The dose of 5 mg/kg was identified as the no-effect level based on the absence of effects on body weight, hematological parameters and histopathological changes in the liver (incidence of foci/areas of cellular alteration and/or fatty changes).

Developmental Effects

- No positive conclusion can be drawn regarding the potential for developmental effects of DCM.

- Maternal exposure of rats and mice to DCM (4337 mg/m$^3$) on days 6 through 15 of gestation was associated with soft tissue abnormalities in the offspring of rats and skeletal changes in the offspring of both rats and mice (Schwetz et al., 1975).

- Other workers have found no increased incidence of gross external, skeletal or soft tissue anomalies in offspring after maternal exposure of rats to DCM at 15,615 mg/m$^3$ (6 hours/day, 7 days/wk) before and during gestation. (Hardin and Manson, 1980).

Mutagenicity

- DCM has been reported to be mutagenic in several bacterial and yeast test systems, as well as in mammalian test systems. DCM was also reported to be positive in a mammalian transformation test (U.S. EPA, 1985a).

Carcinogenicity

- In a pulmonary tumor response assay, DCM administered intraperitoneally did not produce an increased incidence of lung tumors in mice (Theiss et al. 1977).

- An inhalation bioassay conducted in male and female F344/N rats and B6C3F$_1$ mice indicated clear evidence of carcinogenicity in male and female mice as shown by increased incidences of lung (alveolar/bronchiolar adenoma and/or carcinoma) and liver (hepatocellular adenoma and carcinoma combined) tumors (NTP, 1985, as cited in U.S. EPA, 1985c). Some evidence of carcinogenicity in male rats and sufficient or clear evidence of carcinogenicity in female rats was indicated by an increased incidence of benign neoplasms of the mammary gland. These animals were exposed at concentrations of 0, 1,000, 2,000 and 4,000 ppm for rats and 0, 2,000 and 4,000 ppm for mice, 6 hours/day, 5 days/week for 102 weeks.

- Hazelton Laboratories (1982) studied the carcinogenicity of DCM in a chronic two-year drinking water study in Fischer 344 rats, using the protocol as described under longer-term exposure. Hepatic histological alteration detected in the 50 to 250 mg/kg/day dose groups (both sexes) included an increased incidence of foci/areas of cellular alteration. Fatty liver changes were detected in the 125 and 250 mg/kg/day groups after 78 and 104 weeks of treatment. The authors stated that DCM did not induce carcinogenicity under the conditions of the study.

- The U.S. EPA (1985b) performed an independent assessment of the data from the Hazelton Laboratories (1982) study and determined that incidences of hepatic neoplastic nodules and carcinomas (combined in females exposed to 50 mg/kg/day (4.8%), 250 mg/kg/day (7.1%) and 250 mg/kg/day, recovery group (8.0%) were significantly ($P<0.05$) higher than that in matched controls (0%). No significant increase in liver tumors was evident in any of the male dose groups. The U.S. EPA (1985b) considered data on historical control values and concluded that the 250 mg/kg/day dose was borderline for carcinogenicity in Fischer 344 rats.

## V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for One-day, Ten-day, Longer-term (approximately 7 years) and Lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(\text{NOAEL or LOAEL}) \times (BW)}{(UF) \times (\_\_\_\ \text{L/day})} = \_\_\_\ \text{mg/L} \ (\_\_\_\ \text{ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect-Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100 or 1,000), in accordance with NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

The study by Kimura et al. (1971) has been selected to serve as the basis for the One-day HA for the 10 kg child because no other acute oral studies of appropriate duration or design were located in the literature. This study identified a LOAEL in young adult Sprague-Dawley rats on the basis of the first observable gross signs of toxicity (i.e., dyspnea, ataxia, cyanosis and/or coma) following administration of a single oral dose of DCM by gavage. The authors implied that multiple dose levels were administered to define dose-response, although details were not reported. The calculations for a One-day HA for a 10-kg child are given below:

$$\text{One-day HA} = \frac{1{,}326 \text{ mg/kg/day}) (10 \text{ kg})}{(1{,}000) (1 \text{ L/day})} = 13.3 \text{ mg/L } (13{,}300 \text{ ug/L})$$

where:

1,326 mg/kg/day = LOAEL, based on the first observable gross signs of toxicity in rats.

10 kg = assumed body weight of a child.

1,000 = uncertainty factor, chosen in accordance with ODW/NAS guidelines for use with a LOAEL from an animal study.

1 L/day = Assumed daily water consumption of a child.

Ten-day Health Advisory

The study by Bornmann and Loeser (1967) in which DCM was administered in drinking water at 125 mg/L to Wistar rats for 13 weeks. has been selected to serve as the basis for the Ten-day HA for the 10-kg child because it was the most comprehensive short-term oral toxicity study located.

The Ten-day HA for a 10 kg child is calculated as follows:

$$\text{Ten-day HA} = \frac{(15 \text{ mg/kg/day})(10 \text{ kg})}{(100) (1 \text{ L/day})} = 1.5 \text{ mg/L } (1{,}500 \text{ ug/L})$$

where:

15 mg/kg/day = NOAEL, based on absence of effects on body weight gain, blood and urine chemistries, reproductive function, organ/body weight ratios, or histopathological changes in Wistar rats.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with ODW/NAS guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

Longer-term Exposure

There were no suitable data available from which to calculate Longer-Term Health Advisories.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed for synthetic organic chemicals and a value of 10% is assumed for inorganic chemicals. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

Dichloromethane may be classified in Group B2: Probable Human Carcinogen, according to EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986). Because of this, caution must be exercised in making a decision on how to deal with possible lifetime exposure to this substance. The risk manager must balance this assessment of carcinogenic potential against the likelihood of occurrence of health effects related to non-carcinogenic end-points of toxicity. In order to assist the risk manager in this process, drinking water concentrations associated with estimated excess lifetime cancer risks over the range of one in ten thousand to one in a million for the 70-kg adult, drinking 2 liters of water per day, are provided in the following section. In addition, in this section, a Drinking Water Equivalent Level (DWEL) is derived. A DWEL is defined as the medium-specific (in this case, drinking water) exposure which is interpreted to be protective for non-carcinogenic end-points of toxicity over a lifetime of exposure. The DWEL is determined for the 70-kg adult, ingesting 2 liters of water per day. Also provided is an estimate of the excess cancer risk that would result if exposure were to occur at the DWEL over a lifetime.

Neither the risk estimates nor the DWEL take relative source contribution into account. The risk manager should do this on a case-by-case basis, considering the circumstances of the specific contamination incident that has occurred.

The study by Hazelton Laboratories (1982) is most appropriate from which to derive the DWEL because it is an oral chronic (two year) study that administered DCM in drinking water in multiple dose levels to rats. This is the most comprehensive chronic oral study available. There were sufficient numbers of animals in the dose groups and a dose-response was demonstrated. A NOAEL of 5 mg/kg/day was identified in this study.

The DWEL for a 70-kg adult is calculated as follows:

Step 1: Determination of the Reference Dose (RfD)

$$RfD = \frac{(5\ mg/kg/day)}{(100)} = 0.05\ mg/kg/day$$

where:

5 mg/kg/day = NOAEL based on the absence of liver and blood effects in rats.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$DWEL = \frac{(0.05\ mg/kg/day)(70\ kg)}{(2\ L/day)} = 1.75\ mg/L\ (1{,}750\ ug/L)$$

where:

0.05 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption by an adult.

Step 3: Determination of the Lifetime Health Advisory

Dichloromethane is classified in Group B2: Probable Human Carcinogen. A Lifetime HA has not been calculated for DCM.

The estimated excess cancer risk associated with lifetime exposure to drinking water containing DCM at 1,750 ug/L is approximately $3.7 \times 10^{-4}$. This estimate represents the upper 95% confidence limit from extrapolations prepared by EPA's Carcinogen Assessment Group using the linearized, multistage model. The actual risk is unlikely to exceed this value, but there is considerable uncertainty as to the accuracy of risks calculated by this methodology.

Evaluation of Carcinogenic Potential

- IARC (1982) has classified DCM in group 3: Limited evidence of carcinogenicity in animals.

- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986), DCM may be classified in Group B2: Probable human carcinogen. This category is for agents for which there is inadequate evidence from human studies and sufficient evidence from animal studies.

- More recently, EPA's CAG (U.S. EPA, 1985c) estimated that the upper-bound incremental unit carcinogenic risk for drinking water containing 1 ug/L DCM for a lifetime was $2.1 \times 10^{-7}$ $(ug/L)^{-1}$. This risk estimate was the mean of the derived carcinogenic risk estimates based on the finding of liver tumors (not based on lung tumors) in the NTP (1985) draft inhalation study in female mice and the suggestively positive finding of liver tumors in the Hazelton (1982) unpublished ingestion study in male mice. Since the extrapolation model is linear at low doses, additional lifetime cancer risk is directly proportional to the water concentration of DCM. Thus, levels of $10^{-4}$, $10^{-5}$ and $10^{-6}$ are 0.48, 0.048 and 0.005 mg/L, respectively.

- The linear multistage model is only one method of estimating carcinogenic risk. Using the $10^{-6}$ risk level, the following comparisons in micrograms/L may be made: Multistage, 4.8; Probit, 74,000; Logit, 4,000; Weibull, 10. Each model is based on differing assumptions. No current understanding of the biological mechanism of carcinogenesis is able to predict which of these models is more accurate than another. While recognized as statistically alternative approaches, the range of risks described by using any of these modeling approaches has little biological significance unless data can be used to support the selection of one model over another. In the interest of consistency of approach and in providing an upper bound on the potential cancer risk, the Agency has recommended use of the linearized multistage approach.

VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- ACGIH (1984) has recommended a time-weighted average threshold limit value (TWA-TLV) of 100 ppm ( 360 $mg/m^3$) in the absence of occupational exposure to carbon monoxide and is based upon experimental data obtained from nonsmoking males at rest. A short-term exposure level (STEL) of 500 ppm is also recommended.

- The Occupational Health and Safety Administration (OSHA, 1979) has established occupational exposure standards as follows: an eight-hour time-weighted-average (TWA) of 1,737 $mg/m^3$; an acceptable ceiling concentration of 3,474 $mg/m^3$; and an acceptable maximum peak above the ceiling of 6,948 $mg/m^3$ (five minutes in any two hours).

- Due to the metabolic formation of carboxyhemoglobin and the additive toxicity with carbon monoxide, the National Institute of Occupational Safety and Health (NIOSH, 1976) has recommended a ten-hour TWA exposure limit of 261 mg/m$^3$ and a 1737 mg/m$^3$ peak (15 minute sampling), in the presence of carbon monoxide concentrations less than or equal to 9.9 mg/m$^3$ (TWA). Proportionately lower levels of DCM are required in the workplace when carbon monoxide concentrations greater than 9.9 mg/m$^3$ are present.

- Based on noncarcinogenic risks, a water quality criterion of 12.4 mg/L is the acceptable concentration of DCM in drinking water (U.S. EPA, 1980a). This calculation was performed by the U.S. EPA as part of the overall process for developing a U.S. EPA Water Quality Criteria for halomethanes as a group and uses a limit of 200 ppm (694 mg/m$^3$) for protection against excessive carboxy-hemaglobin formation. In that calculation, the EPA assumed that the average person consumes approximately two liters of water and eats 6.5 g of contaminants in fish and seafood per day, and that the estimated coefficient of absorption via inhalation versus ingestion is 0.5.

- The original U.S. EPA Suggested-No-Adverse-Response-Levels (SNARLs, now referred to as Health Advisories) for DCM were set at 13, 1.5 and 0.150 mg/L in drinking water for One-day, Ten-day and Longer-term exposures, respectively (U.S. EPA, 1980b). The U.S. EPA-SNARLs were established for a 10 kg body weight child and did not consider the possible carcinogenic risk that may result from exposure to a chemical.

- The NAS (1980) calculated one-day and seven-day NAS-SNARLs for DCM in drinking water based on the minimal-effect acute oral dose in rats reported by Kimura et al. (1971). The NAS concluded that data on the no-effect dose do not exist. Using the 1 ml/kg (1.3 g/kg) minimal-effect acute oral dose in the rat, assuming two liters/day of drinking water as the only source (consumed by a 70 kg adult) and employing a safety factor of 1,000, the NAS (1980) calculated the one-day SNARL. Since no appropriate data were available for the seven-day SNARL, the one-day SNARL was divided by a factor of seven (days). However, the NAS (1980) erroneously reported a value of 35 mg/L for the one-day and 5 mg/L for the seven-day calculation. Re-examination of calculations indicated that the one-day and seven-day adult NAS-SNARLs should be 45.5 mg/L and 6.5 mg/L, respectively.

## VII. ANALYTICAL METHODS

- Analysis of DCM is by a purge-and-trap gas chromatographic procedure used for the determination of volatile organohalides in drinking water (U.S. EPA, 1985d). This method calls for the bubbling of an inert gas through the sample and trapping DCM on an adsorbant material. The adsorbant material is heated to drive off the DCM onto a gas chromatographic column. This method is applicable to the measurement of DCM over a concentration range of less than 1 to 1500 ug/L; however, measurement of DCM at low concentrations is difficult due to problems with contamination. Dichloromethane vapors readily penetrate tubing

during the purge/trap procedure. Confirmatory analysis for DCM is by mass spectrometry. (U.S. EPA 1985e). The detection limit for confirmation by mass spectrometry is 0.3 ug/L.

## VIII. TREATMENT TECHNOLOGIES

- Limited information is available concerning the removal of dichloromethane from drinking water. However, evaluation of physical and chemical properties and some experimental data suggest that adsorption by granular activated carbon (GAC) and aeration are feasible technologies to remove this contaminant in drinking water supplies.

- Dobbs and Cohen (1980) developed adsorption isotherms for several organic chemicals, including DCM. This study reported that Filtrasorb® 300 exhibited adsorptive capacities of 1.3 mg and 0.09 mg DCM per gm carbon at equilibrium concentrations of 1,000 mg/L and 100 mg/L, respectively.

- Another study reported activated carbon usage of 3.9 lb/1,000 gal of treated water to maintain an effluent DCM concentration below 1 ug/L from a raw water influent concentration above 20 mg/L (ESE, 1982). This particular treatment scheme employed two activated carbon columns operating in series with extremely long empty bed contact time (262 minutes).

- The calculated Henry's Law constant for DCM is $2.5 \times 10^{-3}$ atm-$m^3$/mole (ESE, 1982). In a bench-scale study, distilled water which was spiked with 225 ug/L of DCM was passed through a diffused air aerator. The results showed 82 percent reduction in DCM at an air-to-water ratio of 15:1 (Love, 1983). Dichloromethane will, therefore, be amenable to air stripping treatment. Actual field performance data, however, have not been reported for this compound.

- Air stripping is an effective, simple and relatively inexpensive process for removing DCM and other volatile organics from water. However, use of this process then transfers the contaminant directly to the air stream. When considering use of air stripping as a treatment process, it is suggested that careful consideration be given to the overall environmental occurrence, fate, route of exposure and various hazards associated with the chemical.

- Treatment technologies for the removal of DCM from water have not been extensively evaluated except on an experimental level. Selection of individual or combinations of technologies to attempt DCM reduction must be based on a case-by-case technical evaluation, and an assessment of the economics involved.

## IX. REFERENCES

ACGIH. 1984. American Conference of Governmental Industrial Hygienists. Documentation of the threshold limit values. 4th ed. 1980-1984 supplement. pp. 275-276.

Aviado, D.M., S. Zakhari and T. Watanabe. 1977. Methylene chloride. In: Non-fluorinated propellants and solvents for aerosols, L. Goldberg, ed., CRC Press, Inc., Cleveland, Ohio, pp. 19-45.

Bonventre, J., O. Brennan, D. Jason, A. Henderson and M.L. Bastos. 1977. Two deaths following accidental inhalation of dichloromethane and 1,1,1-trichloroethane. J. Anal. Toxicol. 1:158-160.

Bornmann, G., and A. Loeser. 1967. Zur Frage einer chronisch-toxischen Wirkung von Dichloromethan. Z. Lebensm.-Unters. Forsch. 136:14-18.

DiVincenzo, G.D., and M.L. Hamilton. 1975. Fate and disposition of carbon-14 labelled methylene chloride in the rat. Toxicol. Appl. Pharmacol. 32:385-393.

Dobbs, R.A., and J.M. Cohen. 1980. Carbon adsorption isotherms for toxic organics. EPA 600-8-80-023. Office of Research and Development, MERL, Wastewater Treatment Division, Cincinnati, Ohio.

ESE. 1982. Environmental Science and Engineering. Review of organic contaminants in ODW data base for summary of all available treatment techniques, compound dichloromethane. Prepared for U.S. EPA, Office of Drinking Water, EPA-68-01-6494.

Hardin, B.D., and J.M. Manson. 1980. Absence of dichloromethane teratogenicity with inhalation exposure in rats. Toxicol. Appl. Pharmacol. 52:22-28.

Hazelton Laboratories America, Inc. 1982. National Coffee Association (prepared for the twenty-four month chronic toxicity and oncogenicity study of methylene chloride in rats). Final Report, Vols. I-IV. Vienna, Va.: 2112-101. August 11, 1982.

IARC. 1982. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Supplement 4, Lyon, France.

Kimura, E.T., D.M. Ebert and P.W. Dodge. 1971. Acute toxicity and limits of solvent residue for sixteen organic solvents. Toxicol. Appl. Pharmacol. 19:699-704.

Love, O.T., Jr. 1983. Treatment of volatile organic compounds in drinking water. NTIS, U.S. Department of Commerce.

McKenna, M.J., and J.A. Zempel. 1981. The dose-dependent metabolism of [$^{14}$C]methylene chloride following oral administration to rats. Fd. Cosmet. Toxicol. 19:73-78.

NAS. 1980. National Academy of Sciences. Drinking Water and Health. Vol. 3. National Academy Press, Washington, D.C.

NTP. 1985. National Toxicology Program. NTP technical report on the toxicology and carcinogenesis studies of dichloromethane (methylene chloride) in F344/N rats and B6C3F1 mice (inhalation studies) NTP TR 306. Draft. Research Triangle Park, N.C. 94 pp. As cited in U.S. EPA, 1985c.

NIOSH. 1976. National Institute for Occupational Safety and Health. Criteria for a recommended standard...occupational exposure to methylene chloride. U.S. Department of Health, Education and Welfare (NIOSH). Washington, D.C., pp. 1-3, 76-138, 142.

OSHA. 1979. Occupational Safety and Health Administration. General industry standards. (OSHA) 2206, Revised January, 1978. U.S. Dept. of Labor, Washington, D.C.

Schwetz, B.A., B.J. Leong and P.J. Gehring. 1975. The effect of maternally inhaled trichloroethylene, perchloroethylene, methyl chloroform, and methylene chloride on embryonal and fetal development in mice and rats. Toxicol. Appl. Pharmacol. 32:84-96.

Theiss, J.C., G.D. Stoner, M.B. Shimkin and E.K. Weisberger. 1977. Test for carcinogenicity of organic contaminants of United States drinking waters by pulmonary tumor response in Strain A mice. Cancer Res. 37:2717-2720.

U.S. EPA. 1979. U.S. Environmental Protection Agency. Water Related Environmental Fate of 129 Priority Pollutants. Office of Water Planning and Standards. EPA-440/4-79-029.

U.S. EPA. 1980a. U.S. Environmental Protection Agency. Ambient water quality criteria for halomethanes. Office of Water Regulations and Standards. Criteria and Standards Division. Washington, D.C. EPA 440/5-80-051.

U.S. EPA. 1980b. U.S. Environmental Protection Agency. Advisory opinion for dichloromethane (methylene chloride) (Draft). Office of Drinking Water. Washington, D.C.

U.S. EPA. 1980c. U.S. Environmental Protection Agency. Dichloromethane occurrence in drinking water, food, and air. Office of Drinking Water.

U.S. EPA. 1985a. U.S. Environmental Protection Agency. Health assessment document for dichloromethane (methylene chloride). Office of Health and Environmental Assessment. EPA-600/8-82/004F.

U.S. EPA. 1985b. U.S. Environmental Protection Agency. Health assessment document for dichloromethane (methylene chloride) (Final report). Office of Health and Environmental Assessment. Washington, D.C.

U.S. EPA. 1985c. U.S. Environmental Protection Agency. Addendum to health assessment document for dichloromethane (methylene chloride) (Final report). Office of Health and Environmental Assessment. Washington, D.C. EPA 600/8-82-004FA.

U.S. EPA. 1985d. U.S. Environmental Protection Agency. Method 502.1. Volatile Halogenated Organic Compounds in Water by Purge and Trap Gas Chromatography. Environmental Monitoring and Support Laboratory, Cincinnati, Ohio 45268.

U.S. EPA. 1985e. U.S. Environmental Protection Agency. Method 524.1. Volatile Organic Compounds in Water by Purge and Trap Gas Chromatography/ Mass Spectrometry. Environmental Monitoring and Support Laboratory, Cincinnati, Ohio 45268.

U.S. EPA. 1986. U.S. Environmental Protection Agency. Guidelines for carcinogen risk assessment. Federal Register. 51(185):33992-34003. September 24.

U.S. ITC. 1984. United States International Trade Commission. Synthetic Organic Chemicals United States Production. USITC Publication 1422, Washington, D.C. 20436.

Verschueren, K. 1977. Handbook of Environmental Data on Organic Chemicals. 2nd ed. Van Nostrand Reinhold Company, NY. pp. 451-452.

Windholz, M. 1983. The Merck Index. 10th Edition. Merck and Co., Inc., Rahway, NJ. p. 869.

March 31, 1987

# p-DIOXANE

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

## I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

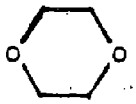
Health Advisories are developed for One-day, Ten-day, Longer-term (approximately 7 years, or 10% of an individual's lifetime) and Lifetime exposures based on data describing noncarcinogenic end points of toxicity. Health Advisories do not quantitatively incorporate any potential carcinogenic risk from such exposure. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

This Health Advisory is based upon information presented in the Office of Drinking Water's Health Advisory Document for p-Dioxane (U.S. EPA, 1981). The 1981 Health Advisory is available for review at each EPA Regional Office of Drinking Water counterpart (e.g., Water Supply Branch or Drinking Water Branch).

## II. GENERAL INFORMATION AND PROPERTIES

CAS No. 123-91-1

Structural Formula



Synonyms

- 1,4-Dioxane; 1,4-Diethylene dioxide

Uses

- Solvent for cellulose acetate, resins, oils and waxes.

Properties (Windholtz, 1983, Verschueren, 1977)

| | |
|---|---|
| Chemical formula | $C_4H_8O_2$ |
| Molecular weight | 88.10 |
| Physical state | Colorless liquid |
| Boiling point | 101.1°C |
| Melting point | 11.8°C |
| Vapor pressure | 30 mm (20°C) |
| Density | 1.033 g/ml (20°C) |
| Solubility | miscible in water at all concentrations |
| Taste/odor threshold | -- |

Occurrence

- 1,4-Dioxane is a synthetic organic compound with no known natural sources. Production of dioxane in 1979 was 6 million lbs.

- Based upon dioxane's physical properties, it is expected to volatilize from soil and surface waters. Dioxane also is expected to be mobile in soil. No information on the biodegradation of dioxane has been identified.

- Dioxane has not been included in Federal and State surveys of drinking water supplies. However, it has been reported to occur in both surface and ground water (U.S. EPA, 1979). No information on the occurrence of dioxane in food or air has been identified.

## III. PHARMACOKINETICS

### Absorption

- Dioxane has been reported to be absorbed readily through the lungs, skin and gastrointestinal tracts of mammals.

- There is evidence that dioxane is absorbed after ingestion. Several investigators administered dioxane in water to rats and observed systemic adverse health effects (Argus et al., 1965; Hoch-Ligeti et al., 1970; Kociba et al., 1974). However, the quantities absorbed following ingestion are not known. Based on the physico-chemical properties of this compound, and for the purpose of HA estimation, 100% absorption will be assumed after ingestion.

### Distribution

- Woo et al. (1977b) studied the binding of $H^3$-dioxane to tissue macromolecules of animals. Male Sprague-Dawley rats, weighing 95 to 130 g, were administered a single intraperitoneal dose of $H^3$-dioxane at 500 uCi/100 g body weight, and sacrificed after 1, 2, 6 or 16 hours. Cystolic, microsomal, mitochondrial and nuclear fractions were examined. The percent covalent binding was highest in the nuclear fraction followed by mitochondrial and microsomal fractions and the whole homogenate. The binding of dioxane to the macromolecules in the cytosol was mainly noncovalent. Pretreatment of rats with inducers of microsomal enzymes had no significant effect on the covalent binding of dioxane to the various subcellular fractions of the liver.

### Metabolism/Excretion

- Dioxane has been reported to be metabolized in animals to 2-hydroxy-ethoxyacetic acid and 1,4-dioxan-2-one. After a single oral dose of 1,000 mg/kg bw of 1,4-($^{14}$C)dioxane to rats, Braun and Young (1977) recovered from the urine 85% of the dose as -hydroxyethoxyacetic acid (HEAA) and most of the remainder as unchanged dioxane. Woo et al. (1977a) isolated and identified p-dioxane-2-one from the urine of rats given intraperitoneal doses of 100 to 400 mg dioxane/kg body weight; the amount of p-dioxane-2-one excreted increased with the dose level administered.

- Humans exposed to 50 ppm dioxane for six hours eliminated it from the body primarily by metabolism to HEAA, which was subsequently eliminated rapidly in the urine (Young et al., 1977).

## IV. HEALTH EFFECTS

### Humans

- The lowest oral lethal dose for humans has been recorded as 500 mg/kg (NIOSH, 1978).

- Johnstone (1959) described a fatal case of dioxane poisoning. The estimated exposure by inhalation in this case was 470 ppm (1,690 mg/m$^3$) for one week; the extent of dermal exposure was not known. Postmortem examination revealed hepatic and renal lesions as well as demyelination and edema of the brain.

Animals

Short-term Exposure

- Oral $LD_{50}$ values for experimental animals are 4200 mg/kg (rat), 5700 mg/kg (mouse), 2000 mg/kg (cat), 2000 mg/kg (rabbit) and 3150 mg/kg (guinea pig) (NIOSH, 1978).

- Fairley et al. (1934) intravenously injected four rabbits with a single dose of either 1, 2, 3 or 5 mL of 80% dioxane diluted with saline to a total volume of 10 mL. Three other rabbits each were given two 5 mL intravenous injections of dioxane mixed with 5 mL of saline with an interval of 48 hours between injections. One rabbit, used as a control, received 10 mL of saline. The immediate effect of dioxane injection in all of the rabbits was violent struggling, which began as soon as the first few drops were injected. With doses of 4 or 5 mL dioxane, the struggling was followed by convulsions and collapse; the rabbits then rapidly returned to normal. The four rabbits given the single doses of 80% dioxane were killed 1 month later. Degeneration of the renal cortices with hemorrhages was observed by microscopic examination. In the rabbit administered the 3 mL dioxane dose, the degenerative changes extended into the medulla and the liver showed extensive cellular degeneration starting at the periphery of the lobules. No abnormality was found in other organs. The livers of the rabbits given the 1- and 5 mL doses showed no microscopic abnormalities; areas of cloudy swelling were seen in the liver of the rabbit given 2 mL of dioxane.

Longer-term Exposure

- Kociba et al. (1974) reported liver and kidney damage in male and female Sherman strain rats. The animals were given drinking water containing 0, 1.0, 0.1 or 0.01% dioxane for up to 716 days. Toxicological analysis included changes in body weights, survival rates, blood chemistry (packed cell volume, total erythrocyte count, hemoglobin, total and differential white blood cell counts) and complete histopathological examination. There was no evidence of toxicity with regard to the tested parameters in animals receiving 0.01% dioxane in drinking water; however, liver and kidney damage was observed at 0.1% dosage level. Decrease in body weight gains, survival rates, water consumption and an increase in the incidence of tumors (hepatocellular and nasal carcinomas) was observed at 1% dosage level.

Reproductive Effects

- No reports were available on the reproductive effects of 1,4-dioxane in humans or other mammalian species.

Developmental Effects

- No reports were available on the developmental effects of 1,4-dioxane in humans or other mammalian species.

Mutagenicity

- No reports were available on the mutagenic potential of 1,4-dioxane.

Carcinogenicity

- Hoch-Ligeti et al. (1970) and Argus et al. (1973) observed a linear relationship between the total dose of 1,4-dioxane in drinking water and the incidence of liver neoplasms in rats. The levels of 1,4-dioxane in the drinking water were 0.75, 1.0, 1.4 and 1.8% for 13 months. A minimum effective tumor dose ($TD_5$), 50% tumor dose ($TD_{50}$), and maximum effective dose ($TD_{95}$) were calculated for 1,4-dioxane. These were 72, 149 and 260 g, respectively.

- In a two-year study in Sherman strain rats (60/sex/level) given 1,4-dioxane in drinking water, Kociba et al. (1974) reported that the group receiving 1% 1,4-dioxane (calculated to be equivalent to approximately 1015 mg/kg/day and 1599 mg/kg/day for male and female rats, respectively) showed a significant increase compared to controls in the incidence of hepatocellular carcinomas and squamous cell carcinomas of the nasal cavity. At 0.01% (9.6 and 19.0 mg/kg/day, respectively for males and females) and 0.1% (94.0 and 148.0 mg/kg/day, respectively), there was no significant difference in the incidence of neoplasms between the control and the experimental groups.

- In a 90-week study in $B6C3F_1$ mice (50/sex/level) on the oncogenic effects of reagent-grade 1,4-dioxane in drinking water, a significant increase in hepatocellular carcinomas over controls was reported in both the 0.5 and 1% groups of both sexes (NCI, 1978). The average daily low dose (0.5% v/v) was 720 (530 to 990) mg/kg/day for males and 380 (180 to 620) mg/kg/day for females; at the 1% level, the doses were 830 (680 to 1150) and 860 (450 to 1560) mg/kg/day, respectively.

- In the NCI (1978) study, Osborne-Mendel rats (35/sex/level) exposed to 1,4-dioxane in drinking water exhibited a dose-related, statistically significant incidence of squamous cell carcinomas of the nasal turbinates in both sexes. Hepatocellular adenomas were observed in female Osborne-Mendel rats at both dose levels. Average doses for 110 weeks for males were 240 (130 to 380) and 530 (290 to 780) mg/kg body weight; for females, the doses were 350 (200 to 580) and 640 (500 to 940) mg/kg body weight.

Effects on Immunologic Status and Competence

- Thurman et al. (1978) reported on the *in vitro* effects of 1,4-dioxane on the mitogenic stimulation of murine lymphocytes. At 2.5 and 5 g/L, 1,4-dioxane greatly enhanced lipopolysaccharide stimulation of

lymphocytes as well as depressing phytohemagglutinin stimulation of lymphocytes. These results were interpreted to indicate stimulation of B-cell proliferation and suppression of T-cell responses. The authors did not discuss the implications of the results in human lymphocytes which appeared to be opposite to the findings with murine lymphocytes. In vitro, at 25 g/L of 1,4-dioxane, a slight enhancement of phytohemagglutinin stimulation of human lymphocytes was seen, indicating a stimulation of T-cell responses and an enhancement of the immune response; little or no effect was seen at lower concentrations. More data confirming this initial finding in murine lymphocytes are necessary before any valid conclusions can be made on the immunosuppressive effects of 1,4-dioxane.

## V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for One-day, Ten-day, Longer-term (approximately 7 years) and Lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(NOAEL \text{ or } LOAEL) \times (BW)}{(UF) \times (\_\_\_ \text{ L/day})} = \_\_\_ \text{ mg/L } (\_\_\_ \text{ ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect-Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100 or 1,000), in accordance with NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

### One-day Health Advisory

A study by Fairley et al. (1934) has been selected for calculating a One-day HA. In this study, a single dose of 1, 2, 3 or 5 mL of 1,4-dioxane was given intravenously to rabbits. Even though one rabbit was used per dose level, the dose-response data generated by this study provide more useful information concerning the toxic effects of dioxane than the other available studies. Rabbits sacrificed one month later had degeneration of the renal cortices with hemorrhages as observed by microscopic examination. With the increasing dose levels, the degenerative change extended into the medulla and the liver also showed extensive and gross cellular degeneration.

A One-day HA for a 10 kg child is calculated as follows:

$$\text{LOAEL (mg/kg/day)} = \frac{(1\ \text{ml/day})\ (1.03\ \text{g/ml})\ (0.80)\ (1000\ \text{mg/g})}{(2\ \text{kg})} = 412\ \text{mg/kg/day}$$

Where:

1 ml/day = Administered dose of p-dioxane (LOAEL)

1.03 g/ml = Density of dioxane

0.80 = Percent composition of dioxane solution

1000 mg/g = Conversion factor for grams to milligrams

2 kg = Assumed body weight of rabbit

$$\text{One-day HA} = \frac{(412\ \text{mg/kg/day})\ (10\ \text{kg})}{(1\ \text{L/day})\ (1{,}000)} = 4.12\ \text{mg/L}\ (4{,}120\ \text{ug/L})$$

Where:

412 mg/kg/day = LOAEL for liver and kidney effects in the rabbit

10 kg = Assumed weight of a child

1 L/day = Assumed volume of water consumed daily by a child

1,000 = uncertainity factor, chosen in accordance with NAS/ODW guidelines for use with a LOAEL from an animal study.

Ten-day Health Advisory

In the absence of an acceptable study for the calculation of a Ten-day HA, the One-day HA value is divided by ten; therefore, the Ten-day HA is estimated as 0.412 mg/L (412 ug/L).

Longer-term Health Advisory

No suitable data are available to determine a Longer-term HA. Kociba et al. (1974) observed a no effect level of 9.6 mg/kg/day based on a two-year drinking water study in rats. This study, although scientifically sound, should not be used for estimating a Longer-term HA because of the carcinogenic potential of p-dioxane. p-Dioxane has been reported to be carcinogenic in both sexes of rats and mice by several independent investigators. This may be compared with trichloroethylene where only one species responded to the carcinogenic effects of the chemical. Another reason for not calculating a Longer-term HA for dioxane is its potential of being chlorinated in water, thus producing a highly toxic chemical. Woo et al. (1980) showed that chlorination of dioxane increased the toxicity by as much as 1,000 fold.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed for synthetic organic chemicals and a value of 10% is assumed for inorganic chemicals. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

Because of its suspected carcinogenicity, a Lifetime Health Advisory for p-dioxane is not recommended.

Evaluation of Carcinogenic Potential

- A number of studies show that p-dioxane is carcinogenic in more than one animal species.
- IARC has classified 1,4-dioxane in Group 2B, indicating sufficient evidence of its carcinogenicity in animals (IARC, 1982).
- EPA has not classified this chemical.
- Drinking water concentrations estimated by EPA to increase the risk by one excess cancer per million ($10^{-6}$) would be 7 micrograms per liter, assuming consumption of 2 liters of water per day by a 70-kg adult over a 70-year lifetime and using the linearized multistage model. The drinking water concentrations associated with a risk of $10^{-4}$ and $10^{-5}$ would be 700 and 70 ug/L, respectively.
- The linearized multistage model is only one method of estimating carcinogenic risk. Using the $10^{-6}$ risk level, the following comparisons in micrograms/L can be made: Multistage, 7; Logit, $10^{-7}$; and Weibull, $10^{-7}$. Each model is based on differing assumptions. No current understanding of the biological mechanisms of carcinogenesis is able to predict which of these models is more accurate than another.

- While recognized as statistically alternative approaches, the range of risks described by using any of these modelling approaches has little biological significance unless data can be used to support the selection of one model over another. In the interest of consistency of approach and in providing an upper bound on the potential cancer risk, the Agency has recommended use of the linearized multistage approach.

## VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- NIOSH has recommended an exposure standard of 1 ppm/30 M in air (NIOSH, 1977).

- TLV = 25 ppm; STEL = 100 ppm (ACGIH, 1980).

## VII. ANALYSIS

- There is no standardized method for the determination of p-dioxane in drinking water. However, p-dioxane can be determined by the purge and trap gas chromatographic-mass spectrometric (GC-MS) procedure used for determination of volatile organic compounds in industrial and municipal discharges (U.S. EPA, 1984). In this method, a 5 mL water sample is spiked with an internal standard of an isotopically stable analog of p-dioxane and purged with an inert gas. The volatile compounds are transferred from the aqueous phase into the gaseous phase where they are passed into a sorbent column and trapped. After purging is completed, the trap is backflushed and heated to desorb the compounds on to a gas chromatograph (GC). The compounds are separated by the GC and detected by a mass spectrometer (MS). The labeled compound serves to correct the variability of the analytical technique. The method detection limit is dependent upon the nature of interferences.

## VIII. TREATMENT

- Treatment technologies which are capable of removing p-dioxane from drinking water include adsorption by granular activated carbon (GAC) or powdered activated carbon (PAC). The only data available demonstrating removal of p-dioxane are for carbon adsorption. Further studies are required to determine the effectiveness of $O_3$ or $O_3$-UV oxidation. The available adsorption data are from laboratory bench-scale studies. Field pilot studies or plant-scale data on p-dioxane are not available.

- McGuire et al. (1978) developed isotherms for a number of organic chemicals, including dioxane. Based on the isotherm data, they reported that the activated carbon Filtrasorb® 400 exhibited adsorptive capacities of 0.6 mg dioxane/g carbon and 3.5 mg dioxane/g carbon at equilibrium concentrations of 1 mg/L and 10 mg/L. They also tested the effectiveness of PAC treatment at 50 mg/L with 5-hour contact time. The results showed poor removal efficiency. However, it was

concluded that greater removal of 1,4-dioxane could be achieved using PAC at higher dosages.

- Suffet et al. (1978) used a pilot-scale test column packed with an experimental polymeric resin and compared its performance to granular activated carbon. The resins showed poor performance with respect to p-dioxane removal.

- A batch laboratory study to demonstrate oxidation of p-dioxane by 100 mg/L chlorine and 100 mg/L permanganate showed no reductions after 12-hour and 3-hour contact times, respectively (McGuire et al., 1978). A batch laboratory study showed diffused aeration to be ineffective, achieving less than 3% removal at an 80:1 air-to-water ratio over a 2.4-hour period (McGuire et al., 1978).

- Treatment technologies for the removal of 1,4-dioxane from drinking water have not been extensively evaluated (except on an experimental level). An evaluation of some of the physical and/or chemical properties of 1,4-dioxane indicates that the following techniques would be candidates for further investigation: adsorbtion by activated carbon and oxidation by ozone or ozone/ultraviolet light. Individual or combinations of technologies selected to attempt 1,4-dioxane reduction must be based on a case-by-case technical evaluation, and an assessment of the economics involved.

## IX. REFERENCES

ACGIH. 1980. American Conference of Governmental Industrial Hygienists. Documentation of the threshold limit values. 4th ed. Cincinnati, OH. pp. 154-155.

Argus, M.F., J.C. Arcos and C. Hoch-Ligeti. 1965. Studies on the carcinogenic activity of protein-denaturing agents: Hepatocarcinogenicity of dioxane. J. Nat. Cancer Inst. 35:949-958.

Argus, M.F., R.S. Sohal, G.M. Bryant, C. Hoch-Ligesti and J.C. Arcos. 1973. Dose-response and ultrastructural alterations in dioxane carcinogenesis. Influence of methylcholanthrene on acute toxicity. Eur. J. Cancer. 9(4):237-243.

Braun, W.H. and J.D. Young. 1977. Identification of -hydroxyethoxyacetic acid as the major urinary metabolite of 1,4-dioxane in the rat. Toxicol. Appl. Pharmacol. 39:33-38.

Fairley, A., E.C. Linton and A.H. Ford-Moore. 1934. The toxicity to animals of 1,4-dioxane. J. Hyg. 34:486-501.

Hoch-Ligeti, C., M.F. Argus and J.C. Arcos. 1970. Induction of carcinomas in the nasal cavity of rats by dioxane. Brit. J. Cancer. 24(1):164-167.

IARC. 1982. International Agency for Research on Cancer. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Supplement 4. IARC, Lyon, France.

Johnstone, R.T. 1959. Death due to dioxane? AMA Arch. Ind. Health. 20:445-447.

Kociba, R.J., S.B. McCollister, C. Park, T.R. Torkelson and P.J. Gehring. 1974. 1,4-Dioxane. I. Results of a 2-year ingestion study in rats. Toxicol. Appl. Pharmacol. 30(2):275-286.

McGuire, M.J., I.H. Suffet and J.V. Radziul. 1978. Assessment of unit processes for the removal of trace organic compounds from drinking water. JAWWA. 10:565-572.

NCI. 1978. National Cancer Institute. Bioassay of 1,4-dioxane for possible carcinogenicity. Washington, D.C.: U.S. Department of Health, Education and Welfare, National Institute of Health. DHEW Pub. No. (NIH) 78-1330.

NIOSH. 1977. National Institute of Occupational Safety and Health. Criteria for a recommended standard -- occupational exposure to dioxane. Washington, D.C.: U.S. Department of Health, Education and Welfare. DHEW (NIOSH) Pub. 77-226.

NIOSH. 1978. National Institute of Occupational Safety and Health. Registry of toxic effects of chemical substances. U.S. Department of Health, Education and Welfare. Washington, D.C.

Suffet, I.H., L. Brenner, J.T. Coyle and P.R. Cairo. 1978. Evaluation of the capability of granular activated carbon and XAD-2 resin to remove trace organics from treated drinking water. Environmental Science and Technology. 1(12):1315-1322.

Thurman, G.B., B.G. Simms, A.L. Goldstein and D.J. Kilian. 1978. The effects of organic compounds used in the manufacture of plastics on the responsivity of murine and human lymphocytes. Toxicol. Appl. Pharmacol. 44:617-641.

U.S. EPA. 1979. U.S. Environmental Protection Agency. Chemical Hazard Information Profile: Dioxane, Office of Toxic Substances.

U.S. EPA. 1981. U.S. Environmental Protection Agency. Health advisory document for p-dioxane. Draft. Office of Drinking Water.

U.S. EPA. 1984. U.S. Environmental Protection Agency. Method 1624 Revision B, Volatile Organic Compounds by Isotope Dilution GC/MS. Federal Register. 49(209):433407-433415.

Verschueren, K. 1977. Handbook of environmental data on organic chemicals. 1st ed. Van Nostrand Reinhold Company, N.Y. p. 377.

Windholz, M., ed. 1983. Merck Index, 10th ed. Merck and Company, Inc. Rahway, NJ. pp. 481-482.

Woo, Y-T, J.C. Arcos and M.F. Argus. 1977a. Metabolism in vivo of dioxane: Identification of p-dioxane-2-one as the major urinary metabolite. Biochem. Pharmacol. 26:1535-1538.

Woo, Y-T, M.F. Argus and J.C. Arcos. 1977b. Tissue and subcellular distribution of $^{3}H$-dioxane in the rat and apparent lack of microsome-catalyzed covalent binding in the target tissue. Life Sci. 21(10):1447-1456.

Woo, Y-T, E.J. Neuburger, J.C. Arcos, M.F. Argus, K. Nishiyama and G.W. Griffin. 1980. Enhancement of toxicity and enzyme-repressing activity of p-dioxane by chlorination: Stereo-selective effects. Toxicol. Letts. 5:69-75.

Young, J.D., W.H. Braun, L.W. Rampy, M.B. Chenoweth and G.E. Blau. 1977. Pharmacokinetics of 1,4-dioxane in humans. J. Toxicol. Environ. Health. 3(3):507-520.

# 2,3,7,8-TETRACHLORODIBENZO-p-DIOXIN

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

## I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

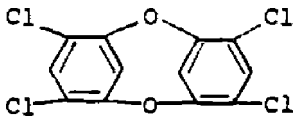
Health Advisories are developed for One-day, Ten-day, Longer-term (approximately 7 years, or 10% of an individual's lifetime) and Lifetime exposures based on data describing noncarcinogenic end points of toxicity. Health Advisories do not quantitatively incorporate any potential carcinogenic risk from such exposure. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

This Health Advisory (HA) is based on information presented in the Office of Drinking Water's Health Effects Criteria Document (CD) for 2,3,7,8-tetrachlorodibenzo-p-dioxin (U.S. EPA, 1985a). The HA and CD formats are similar for easy reference. Individuals desiring further information on the toxicological data base or rationale for risk characterization should consult the CD. The CD is available for review at each EPA Regional Office of Drinking Water counterpart (e.g., Water Supply Branch or Drinking Water Branch), or for a fee from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Rd., Springfield, VA 22161, PB #86-117983/AS. The toll-free number is (800) 336-4700; in the Washington, D.C. area: (703) 487-4650.

## II. GENERAL INFORMATION AND PROPERTIES

CAS No. 1746-01-6

Structural Formula




Synonyms

° Dioxin; TCDBD; TCDD; 2,3,7,8-tetrachlorodibenzodioxin, 2,3,7,8-tetrachlorodibenzo-1,4-dioxin; 2,3,7,8-TCDD.

Uses

° There are no commercial uses for TCDD. (U.S. EPA, 1985a).

Properties (U.S. EPA, 1985a)

| | |
|---|---|
| Molecular Formula | $C_{12}H_4Cl_4O_2$ |
| Molecular Weight | 321.9 |
| Physical State | colorless solid, needle shape |
| Boiling Point | -- |
| Melting Point | 303 - 305°C |
| Vapor Pressure | $3.5 \times 10^{-9}$ mm Hg* at 30.1°C |
| Water Solubility | $7.9 \times 10^{-3}$ ug/L** |
| Log Octanol/Water Partition Coefficient | $1.4 \times 10^{6}$ |
| Odor Threshold | not available |
| Taste Threshold | not available |
| Conversion Factor | -- |

* Cheng et al. (1983-1984). Converted from $4.68 \times 10^{-7}$ pascals.
**Adams and Blaine (1985).

Occurrence

° TCDD is a synthetic chemical which has no natural sources. TCDD is not produced directly but is formed as a by-product in the manufacture of a number of chlorinated phenolic compounds. It can also be present in fly ash and flue gases of incinerators.

- TCDD is extremely resistant to degradation once adsorbed onto soil with a reported half-life of 10-12 years. TCDD has a very low water solubility and binds readily to soil. TCDD has been shown to migrate very slowly in soil. TCDD also has been demonstrated to bioaccumulate in fish and mammals.

- TCDD has not been included in drinking water surveys. Given its limited solubility, it is not expected to occur at detectable levels in either ground or surface water. TCDD has been reported to occur at low levels in some surface waters where it is probably bound to suspended materials. TCDD has been found in a number of freshwater fish at levels ranging from 1-695 ng/kg. TCDD also has been reported to occur at low levels in rice treated with phenolic herbicides and in the fat of animals that grazed on pasture treated with phenolic herbicides. Due to TCDD's physical characteristics, diet is expected to be a greater route of exposure than drinking water; however, the available data are insufficient to evaluate the actual levels of either route (U.S. EPA, 1984a).

## III. PHARMACOKINETICS

### Absorption

- Gavage treatment with single or repeated doses of 2,3,7,8-TCDD in oil has resulted in absorption of approximately 50% of the dose (unspecified) administered to guinea pigs (Nolan et al., 1979) and approximately 70-83% of the dose administered to rats (1 or 50 ug/kg) (Rose et al., 1976; Piper et al., 1973) or to hamsters (650 ug/kg) (Olson et al., 1980a). Absorption of a single oral dose of 1.14 ng $^{3}$H-2,3,7,8-TCDD/kg in corn oil by a male volunteer has been estimated to be 88.5% (Poiger and Schlatter, 1986).

- Dietary administration of 0.5 or 1.4 ug 2,3,7,8-TCDD/kg/day for 42 days resulted in somewhat reduced gastrointestinal absorption by rats (approximately 50-60% of the administered dose was absorbed) (Fries and Marrow, 1975).

- Percutaneous absorption of 2,3,7,8-TCDD (26 ng) has been estimated in rats to be approximately 40% of the absorption of an equivalent dose orally administered (Poiger and Schlatter, 1980).

- Inhalation absorption of 2,3,7,8-TCDD has not been studied (U.S. EPA, 1985a).

- Diamond Shamrock (1985) noted greater oral absorption of 2,3,7,8-TCDD in animals given contaminated soil containing oil than without oil.

### Distribution

- In the Poiger and Schlatter (1986) study, concentrations of 3.0 and 2.8 ppt of $^{3}$H-2,3,7,8-TCDD were detected in adipose tissue 10 and 69 days, respectively, after treatment.

- Tissue distribution following oral or intraperitoneal (i.p.) administration of 2,3,7,8-TCDD to rats appears to be preferentially to the liver and adipose tissue (Fries and Marrow, 1975; Rose et al., 1976; Van Miller et al., 1976; Kociba et al., 1978). Other tissues showed substantially lower concentrations of 2,3,7,8-TCDD. Soon after treatment, the liver may have concentrations about three (Kociba et al., 1978a) to five (Rose et al., 1976) times that in adipose tissue. It was suggested that male rats accumulate 2,3,7,8-TCDD in the liver more efficiently than female rats (Fries and Marrow, 1975). Tissue distribution in mice (Manara et al., 1982) and hamsters (Olson et al., 1980a) seems to be similar to that in rats.

- Monkeys, however, appear to accumulate 2,3,7,8-TCDD preferentially in adipose tissue to a greater extent than in the liver (Van Miller et al., 1976; McNulty et al., 1982). Two years after a single oral dose to a monkey, adipose tissue contained 100 ppt and the liver 15 ppt 2,3,7,8-TCDD (McNulty et al., 1982). Prolonged tissue retention of the compound was thus demonstrated. Tissue distribution in guinea pigs appears to be similar to that in monkeys (Gasiewicz and Neal, 1979; Nolan et al., 1979) since tissue levels in adipose tissue exceed those in the liver.

- Evidence that 2,3,7,8-TCDD accumulates in the adipose tissue of exposed humans was presented by Young et al. (1983) who reported levels of 3 to 99 ppt in the adipose tissue of armed forces veterans claiming health problems related to Agent Orange.

- Fetal distribution of 2,3,7,8-TCDD has been studied in rats (Moore et al., 1976) and mice (Nau and Bass, 1981; Nau et al., 1982). Levels of 2,3,7,8-TCDD were low in rat fetuses on gestation days 14 and 18 of gestation and appeared to be evenly distributed in all fetal tissues. On day 21 of gestation, the fetal liver showed a marked affinity for 2,3,7,8-TCDD (Moore et al., 1976). 2,3,7,8-TCDD was distributed to the fetuses of mice following oral, i.p. or subcutaneous (s.c.) administration (Nau et al., 1982). Maximum fetal concentrations occurred on days 9 and 10 of gestation; lower fetal concentrations were observed on gestation days 11 through 18, coincident with placentation. The fetal liver had less affinity for the compound than did the maternal liver.

- Ryan et al. (1985) reported 2,3,7,8-TCDD levels of 5-10 ppt in adipose tissue samples from humans taken at autopsy across Canada. Higher levels of other dioxins were also found.

Metabolism

- In an early metabolism study, Vinopal and Casida (1973) reported that *in vivo* or *in vitro* studies with mice showed that polar metabolites of 2,3,7,8-TCDD were not produced by this species. In rats, however, hydroxylation and conjugation with glucuronide and sulfate have been demonstrated (Poiger and Schlatter, 1979; Poiger et al., 1982; Olson et al., 1983). Glucuronide conjugates tended to predominate in the bile (Poiger and Schlatter, 1979) and sulfate conjugates were located in the urine (Olson et al., 1983).

- Poiger and Schlatter (1979) stated that metabolism of 2,3,7,8-TCDD proceeds slowly in the liver. Neal et al. (1982) demonstrated that the rate of hepatic metabolism was enhanced by activated cytochrome P-450 mono-oxygenase. It was suggested that metabolism of 2,3,7,8-TCDD proceeds by the formation of reactive epoxide intermediates (Poland and Glover, 1979). Dechlorination also was demonstrated by Olson et al. (1983) and Sawahata et al. (1982), who identified tri- and dichlorodibenzo-p-dioxins as metabolites in in vitro rat hepatocyte systems. From the bile of dogs, six major metabolites have been identified (Poiger et al., 1982); hydroxylated conjugates of tetra-, tri- and dichlorodibenzo-p-dioxin predominated.

- Although metabolite profiles are consistent with an arene oxide intermediate, the covalent interaction of 2,3,7,8-TCDD with cellular macromolecules is minimal.

Excretion

- When the excretion data are plotted semi-logarithmically, a straight line results, suggesting that elimination of 2,3,7,8-TCDD is a first-order phenomenon, especially in rats. Excretion in the guinea pig may be a zero-order process (Gasiewicz and Neal, 1979). The half-life for body elimination varied considerably with estimated ranges of 10 to 15 days in the hamster (Olson et al., 1980a), the species least sensitive to the toxic effects of 2,3,7,8-TCDD, 11 to 24 days in the mouse (Gasiewicz et al., 1983a,b), 17 to 31 days in the rat (Piper, et al., 1973; Allen et al., 1975; Rose et al., 1976) and 22 to 30 days in the guinea pig (Gasiewicz and Neal, 1979; Nolan et al., 1979). One strain of mice, DBA/2J, had a half-life for elimination of approximately 24 days, about twice as long as in other strains tested by Gasiewicz et al. (1983a,b). These authors also noted that this strain of mice had a greater tendency to accumulate 2,3,7,8-TCDD in adipose tissue than did other strains and that this phenomenon probably resulted in slower body elimination. Half-lives for body elimination of 2,3,7,8-TCDD have not been calculated for the monkey, but it was suggested that the tendency of this species to accumulate 2,3,7,8-TCDD in adipose tissue may also result in slow body elimination (Van Miller et al., 1976).

- Recently, Olson and Bittner (1983) examined the elimination of 2,3,7,8-TCDD in rats over a longer period than in the studies previously summarized and determined that biphasic elimination occurred. They estimated a half-life of approximately 7 days for the initial rapid phase and a half-life of approximately 75 days for the slower phase, probably related to release from stores of body fat. McNulty et al. (1982) estimated the half-life for elimination from the fat of monkeys to be approximately 1 year.

- In the Poiger and Schlatter (1986) study, 11.5% of the $^{3}H$-TCDD was excreted in feces during the first three days after treatment, and no $^{3}H$ activity was found in urine. These investigators estimated an elimination half-life of 4.95 years for the $^{3}H$-TCDD.

- The fecal route seems to be the major pathway for the elimination of 2,3,7,8-TCDD-derived radioactivity in rats (Piper et al., 1973; Allen et al., 1975; Rose et al., 1976; Van Miller et al., 1976), guinea pigs (Gasiewicz and Neal, 1979) and mice (Gasiewicz et al., 1983a,b). Urinary excretion played less of a role in these species, accounting for <1 to 28% of total excreted radioactivity while fecal excretion accounted for 72 to >99% of the eliminated radioactivity. Urinary excretion accounted for a more substantial proportion of body elimination in hamsters (41% as compared with 59% by feces) (Olson, et al., 1980a) and that strain of mice (DBA/2J) which preferentially accumulated 2,3,7,8-TCDD in body fat (Gasiewicz et al., 1983a,b).

- The failure to detect metabolites of 2,3,7,8-TCDD in liver and fat (Olson et al., 1963) indicates that elimination of the metabolites occurs rapidly and that the rate of elimination is governed primarily by the rate of hepatic metabolism.

## IV. HEALTH EFFECTS

### Humans

- Either acute or chronic exposure to 2,3,7,8-TCDD (usually in combination with other substances) may result in chloracne, altered liver function, hematological lesions, porphyria cutanea tarda, hyperpigmentation, hirsutism and neural degeneration in the extremities (U.S. EPA, 1985a). Stevens (1981) has estimated that the minimum cumulative toxic dose of 2,3,7,8-TCDD in humans is 0.1 ug/kg.

- Rowe (1968) has described experiments showing a dose-response for chloracne in humans acutely exposed to topical applications of 2,3,7,8-TCDD.

- The toxic effects of chloracne from exposure to 2,3,7,8-TCDD may persist for many years, though other effects noted in various individuals are apparently reversible after a short period. Epidemiological studies have failed to demonstrate a convincing connection between 2,3,7,8-TCDD exposure and spontaneous abortions or malformations in humans. Some evidence of cytogenetic damage has been reported in humans exposed to chemicals contaminated with 2,3,7,8-TCDD, but negative results have also been reported; exposures were not quantitated and the other chemicals cannot be ruled out as causative agents (U.S. EPA, 1985a).

- Swedish case-control studies provide limited evidence for the carcinogenicity of phenoxy acids or chlorophenols or both in humans. However, with respect to the dioxin impurities contained within them, the evidence for the human carcinogenicity for 2,3,7,8-TCDD based on epidemiologic studies is only suggestive because of the difficulty of evaluating the risk of 2,3,7,8-TCDD exposure in the presence of the confounding effects of phenoxy acids and/or chlorophenol (U.S. EPA, 1985a).

Animals

Short-term Exposure

- There are wide variations in species sensitivity to the acute toxicity of 2,3,7,8-TCDD. $LD_{50}$s range from 0.6 ug/kg for the male guinea pig to >5,000 ug/kg bw for the male hamster (Schwetz et al., 1973; Olson, et al., 1980b; Henck et al., 1981). The toxic manifestations seem to be the same whether the compound is given as a single oral dose or as a limited number of multiple treatments, with death occurring from 5 to 45 days post-treatment. Lethal exposures result in weight loss, often described as "wasting away" and thymic atrophy. In some species, particularly rats and mice, extensive liver damage is observed (Gupta et al., 1973). In general, no specific cause of death has been identified, although extensive hemorrhaging has been implicated in mice (Vos et al., 1974).

- In rats, single high doses (200 ug/kg) produce liver necrosis (Jones and Butler, 1974), while lower doses (5 and 25 ug/kg) result in fatty changes in the liver and proliferation of the endoplasmic reticulum (Fowler et al., 1973). Other effects seen in some species include induction of microsomal enzymes, degeneration of plasma membranes with loss of ATPase activity, a decreased ability to excrete some xenobiotics in the bile, porphyria, altered gastrointestinal absorption of some nutrients and decreased blood cellularity (U.S. EPA, 1985a). Turner and Collins (1983) found treatment-related liver lesions in guinea pigs given single gavage doses of 2,3,7,8-TCDD at 0.1 ug/kg and higher.

- 2,3,7,8-TCDD is an immunotoxin in laboratory animals, predominantly affecting cell-mediated immunity. Hypersensitivity, adverse effects on the thymus and increased sensitivity to antigens have demonstrated the immunotoxic potential of 2,3,7,8-TCDD. Weanling rodents show greater susceptibility to immune effects compared to adults (U.S. EPA, 1985a).

Long-term Exposure

- In rats and mice, the liver appears to be the most sensitive organ following chronic or subchronic exposure. Hepatotoxicity develops following a long induction period and the changes persist for long periods following the termination of exposure (King and Roesler, 1974; Goldstein et al., 1982).

- Liver lesions as well as other toxic signs were observed in the following studies in rats and mice. In the subchronic studies, the NOAEL of 0.01 ug/kg/day (Kociba et al., 1976) and 0.5 ug/kg/week (NTP, 1980) have been reported for rats. A NOAEL of 2 ug/kg/week was identified for female mice and a LOAEL of 1 ug/kg/week for male mice in the NTP (1980) subchronic study. A NOAEL of 0.001 ug/kg bw/day, a LOAEL of 0.01 ug/kg/day, and an effect level of 0.1 ug/kg/day have been reported for rats following chronic dietary exposure (Kociba et al., 1978a,b, 1979; NTP, 1980). Toth et al. (1978, 1979) observed

toxic effects in mice at doses as low as 0.007 ug/kg/week given for one year by gavage. Gavage dosing for two years led to toxic hepatitis at a NOAEL of 0.05 ug/kg/week and a LOAEL of 0.5 ug/kg/week in rats, a LOAEL of 0.5 ug/kg/week in male mice, and a LOAEL of 2.0 ug/kg/week in female mice (NTP, 1980).

- DeCaprio et al. (1986) fed 2,3,7,8-TCDD in the diet for 90 days to male and female Hartley guinea pigs, and found NOAELs of 0.12 and 0.61 (male) and 0.68 (female) mg/kg/day; decreased body weight gain, increased relative liver weights, decreased relative thymus weights, and hepatocellular cytoplasmic inclusion bodies at 4.90 (males) and 4.86 (females) mg/kg/day; and, mortality and other mentioned effects at 26 (males) and 31 (females) mg/kg/day.

Reproductive Effects

- Adverse effects of 2,3,7,8-TCDD on reproduction in rats exposed through the diet were observed by Murray et al. (1979) and are detailed under Lifetime Health Advisory.

Developmental Effects

- 2,3,7,8-TCDD has been demonstrated to be teratogenic in mice. The most common malformations observed are cleft palate and kidney anomalies; however, other malformations have been observed occasionally. With an effect level of 1 ug/kg/day, 2,3,7,8-TCDD is the most potent teratogen known. At higher doses, 2,3,7,8-TCDD has a marked fetotoxic effect, as measured by decreased fetal weight and increased fetal toxicity. Hemorrhagic GI tract has been associated with 2,3,7,8-TCDD fetal toxicity (U.S. EPA, 1985a).

- Poland and Glover (1980) produced evidence that responsiveness of mice to cleft palate from 2,3,7,8-TCDD treatment is related to the presence of Ah receptor.

- In rats, it has also been consistently observed that 2,3,7,8-TCDD produces fetotoxic responses. In this species, the most common fetal anomalies observed were edema, hemorrhage and malformation of the kidney with effects observed at doses of $\geq$0.01 ug/kg/day. In addition, there is some evidence that 2,3,7,8-TCDD can induce microsomal enzymes in the fetus exposed in utero, and this induction is accompanied by damage to the fine structure of the liver cell; however, other reports indicate that enzyme induction occurs only after birth following exposure to 2,3,7,8-TCDD through the mother's milk. As in mice, hemorrhagic GI tracts have been observed in rat fetuses exposed in utero to 2,3,7,8-TCDD (U.S. EPA, 1985a).

- Rabbits and monkeys are also susceptible to the fetotoxic effects of 2,3,7,8-TCDD; however, the studies of these species have been too limited to clearly demonstrate a teratogenic response or define a threshold dose for fetotoxicity (U.S. EPA, 1985a).

Mutagenicity

- In vivo and in vitro mutagenicity tests have produced inconclusive evidence as to the mutagenicity of TCDD (U.S. EPA, 1985a).

- Early reports indicated that 2,3,7,8-TCDD was mutagenic in S. typhimurium strain TA1532 (Hussain et al., 1972; Seiler, 1973); however, later attempts to confirm these results have been unsuccessful (Nebert, et al., 1976; McCann, 1978; Gilbert et al., 1980; Geiger and Neal, 1981). 2,3,7,8-TCDD has been reported to be mutagenic to E. coli in vitro (Hussain et al., 1972) and to S. cerevisiae in vitro, and in a host-mediated assay (Bronzetti et al., 1983). Covalent interactions with nucleic acids are minimal if they occur at all (Kondorosi et al., 1973; Poland and Glover, 1979). Only marginal effects have been observed on the incidence of chromosomal aberrations in vivo (Green and Moreland, 1975). A test for unscheduled DNA synthesis in cultured male rat hepatocytes was negative (Althaus et al., 1982). Loprieno et al. (1982) reported 2,3,7,8-TCDD as clastogenic in mice in vivo, negative for cytogenetic effects in vivo, and negative for unscheduled DNA synthesis in a human cell live in vitro. Hay (1983) reported 2,3,7,8-TCDD as mutagenic in the baby hamster kidney cell transformation assay.

Carcinogenicity

- Several bioassays have demonstrated this compound to be a potent carcinogen in rats and mice (Kociba et al., 1978a; Toth et al., 1979; NTP, 1980). Adenomas or carcinomas of the thyroid, hepatocellular carcinomas, carcinomas of the tongue and hard palate, and adenomas of the adrenal gland have been induced in rats and mice.

- Significant ($P < 0.05$) neoplastic effects were evident at dietary levels of 0.01 and 0.1 ug/kg/day but not at 0.001 ug/kg/day in the two-year study with Sprague-Dawley rats by Kociba et al. (1978). In Osborne-Mendel rats given 2,3,7,8-TCDD in corn oil:acetone twice weekly for total weekly doses of 0.01, 0.05 and 0.5 ug/kg/week for two years, significant ($P < 0.05$) tumor increases were thyroid in mid- and high-dose males and liver in high-dose males (NTP, 1980). In the NTP (1980) study in which B6C3F1 mice were dosed like the rats except that females received 0.04, 0.2 and 2.0 ug/kg/week, significant ($P < 0.05$) tumor increases were in liver in high-dose males and females and thyroid in high-dose males.

## V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for One-day, Ten-day, Longer-term (approximately 7 years) and Lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(NOAEL \text{ or } LOAEL) \times (BW)}{(UF) \times (\_\_\_ \text{ L/day})} = \_\_\_ \text{ mg/L } (\_\_\_ \text{ ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect-Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100 or 1,000), in accordance with NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

Turner and Collins (1983) administered single oral doses of 2,3,7,8-TCDD at 0.1, 0.5, 2.5, 12.5 or 20 ug/kg in aqueous methyl cellulose to groups of 4 to 7 female guinea pigs. Survivors were killed 42 days after dosing and examined for histopathologic changes in the liver. Four of the 7 animals in the highest dose group and 1 of 5 in the 12.5 ug/kg group died before the end of the observation period. Mild histopathologic changes including steatosis (fatty change), focal necrosis and cytoplasmic degeneration were noted in animals from all treated groups, but not in controls. The authors indicated that quantitative differences among the dosage groups were not detectable by light microscopy.

A LOAEL of 0.1 ug/kg can be derived from the study of Turner and Collins (1983) for calculating a One-day HA, using an uncertainty factor (UF) of 1,000 for an animal LOAEL. This UF consists of two 10-fold factors to account for both intra- and interspecies variability to the toxicity of this chemical in the absence of chemical-specific data, and an additional 10-fold factor because the HA is based on a LOAEL and not a NOAEL.

For a 10-kg child consuming 1 L of drinking water per day, the One-day HA is calculated as follows:

$$\text{One-day HA} = \frac{(0.1 \text{ ug/kg/day})\ (10 \text{ kg})}{(1{,}000)\ (1 \text{ L/day})} = 0.0010 \text{ ug/L}$$

where:

0.1 ug/kg = LOAEL derived from studies by Turner and Collins (1983).

10 kg = assumed body weight of a child.

1,000 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a LOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

Ten-day Health Advisory

Because of the demonstrated sensitivity of the guinea pig to acute toxicity of 2,3,7,8-TCDD, the Ten-day HA is derived by dividing the One-day HA by ten. The Ten-day HA is, therefore, 0.0001 ug/L.

Longer-term Health Advisory

The three-generation reproduction study in rats by Murray et al. (1979) has been selected because the animals in this study were administered 2,3,7,8-TCDD by diet on a daily basis for an appropriate duration as opposed to the gavage method of treatment used in other studies considered and because the adverse effect was on reproduction. Comparison with the other studies in which different treatment protocols were used suggests that the dose of 0.001 ug/kg/day, concluded by the U.S. EPA as a LOAEL for adverse effects on the pups and dams in the Murray et al. (1979) study would be protective against the toxic effects found in the other studies. Although DeCaprio et al. (1986) found NOAELs of 0.61 and 0.68 ng/kg/day in their 90-day guinea pig study, this dose is slightly below the LOAEL of 0.001 ug/kg/day (1 ng/kg/day) in another species which, in turn, is below the LOAEL of 4.86 ng/kg/day in the DeCaprio et al. (1986) study.

Using an uncertainty factor of 1,000 for an animal LOAEL (i.e., 10-fold for intra- and 10-fold for interspecies variability to the toxicity of a chemical in the absence of specific data, and an additional 10-fold factor because the estimate is based on a LOAEL rather than a NOAEL), a Longer-term HA can be calculated from the LOAEL of 0.001 ug/kg/day concluded for the Murray et al. (1979) study.

For a 10-kg child consuming 1 L of drinking water each day, the Longer-term HA is calculated as follows:

$$\text{Longer-term HA} = \frac{(0.001 \text{ ug/kg/day})\ (10 \text{ kg})}{(1{,}000)\ (1 \text{ L/day})} = 0.00001 \text{ ug/L}$$

where:

0.001 ug/kg/day = LOAEL from study by Murray et al. (1979).

10 kg = assumed weight of child

1,000 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a LOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

By substituting 70-kg body weight and daily consumption of 2L of water for the adult in the above equation, the Longer-term HA for the 70-kg adult becomes 0.000035 ug/L.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed for synthetic organic chemicals and a value of 10% is assumed for inorganic chemicals. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

The EPA has developed for comparison with cancer-based criteria, a presumed safe daily intake level based on noncarcinogenic effects as indicated in U.S. EPA (1984b). For consistency, the rationale used by EPA for the calculation of this value in U.S. EPA (1984b) is used here for the DWEL calculation. The rationale as presented in U.S. EPA (1984b) is as follows:

> 2,3,7,8-TCDD displays an unusually high degree of reproductive toxicity. It is teratogenic, fetotoxic and reduces fertility. In a 3-generation reproductive study, Murray et al. (1979) reported a reduction in fertility after daily dosing at 0.1 or 0.01 ug 2,3,7,8-TCDD/kg in the $F_1$ and $F_2$ generations of Sprague-Dawley rats. Although Murray et al. (1979) considered the lowest dose tested, 0.001 ug/kg, to be a no-observed-effect level (NOEL), a re-evaluation of these data by Nisbet and Paxton (1982), using different statistical methods, indicated that there was a reduction in the gestation index, decreased fetal weight, increased liver to body weight ratio, and increased incidence of dilated renal pelvis at the 0.001 ug/kg dose. The reevaluated data would suggest that equivocal adverse effects were seen at the lowest dose (0.001 ug/kg/day) and that this dose should, therefore, represent a lowest-observed-adverse-effect level (LOAEL). Schantz et al. (1979) found reductions in fertility and various other toxic effects in rhesus monkeys fed a 50 ppt 2,3,7,8-TCDD diet for 20 months. This corresponds to a calculated daily dose of 0.0015 ug 2,3,7,8-TCDD/kg/day. These results suggest that monkeys may be somewhat more sensitive than rats, since the effects in monkeys were more severe and not equivocal. Since the data from the limited study by Schantz et al. (1979) are supportive of the findings by Murray et al. (1979) it seems reasonable to determine an ADI based on the LOAEL.

From these results, a LOAEL of 0.001 ug/kg was identified. Using this LOAEL, the DWEL is derived as follows:

Step 1: Determination of the Reference Dose (RfD)

$$RfD = \frac{(0.001 \text{ ug/kg/day})}{(1{,}000)} = 1 \times 10^{-6} \text{ ug/kg/day}$$

where:

0.001 ug/kg/day = LOAEL,

1,000 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a LOAEL from an animal study.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$DWEL = \frac{(1 \times 10^{-6} \text{ ug/kg/day}) (70 \text{ kg})}{(2 \text{ L/ day})} = 0.000035 \text{ ug/L}$$

where:

$1 \times 10^{-6}$ ug/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/ day = assumed daily water consumption of an adult.

2,3,7,8-TCDD is placed in Group B: Probable human carcinogen. The estimated excess cancer risk associated with lifetime exposure to drinking water containing 2,3,7,8-TCDD at $3.5 \times 10^{-5}$ ug/L is approximately $2 \times 10^{-4}$. This estimate represents the upper 95% confidence limit from extrapolations prepared by EPA's Carcinogen Assessment Group using the linearized, multistage model. The actual risk is unlikely to exceed this value, but there is considerable uncertainty as to the accuracy of risks calculated by this methodology.

Evaluation of Carcinogenic Potential

- Cancer potency estimates were derived using the multistage model and the tumor data on female rats in the chronic feeding study by Kociba et al. (1978a) (U.S. EPA, 1985a,b).

- The 95% upper-limit carcinogenic potency factor for humans, $q_1^*$, is $1.56 \times 10^5$ $(mg/kg/day)^{-1}$. For a 70 kg human drinking 2 L water/day, the water concentration should be $2.2 \times 10^{-6}$ ug/L in order to keep the upper-limit individual lifetime cancer risk at $10^{-5}$. Water concentrations corresponding to excess cancer risk of $10^{-4}$ and $10^{-6}$ are, therefore, $2.2 \times 10^{-5}$ and $2.2 \times 10^{-7}$ ug/L, respectively.

- Maximum likelihood estimates as well as 95% upper limits of cancer risks by the multistage model have been calculated (U.S. EPA, 1985b). For example, at $1 \times 10^{-3}$ ng/kg/day or 0.035 ng/L cancer risk estimates

are 1.1 x $10^{-4}$ (MLE) and 1.5 x $10^{-4}$ (UL) and at 1 x $10^{-2}$ ng/kg/day cancer risk estimates are 1.1 x $10^{-3}$ (MLE) and 1.5 x $10^{-3}$ (UL).

- The EPA's Carcinogen Assessment Group has estimated cancer risks with other models besides the multistage (U.S. EPA, 1985b). As an example, 1 x $10^{-3}$ ng/kg/day lifetime exposure was associated with additional risks (95% upper confidence limit) of 1.5 x $10^{-4}$ by the multistage and one-hit, 2.9 x $10^{-3}$ by the Weibull, and 7.5 x $10^{-8}$ by the log-probit, using the Kociba analysis of the data. While recognized as statistically alternative approaches, the range of risks described by using any of these modeling approaches has little biological significance unless data can be used to support the selection of one model over another. In the interest of consistency of approach and in providing an upper bound on the potential cancer risk, the EPA has recommended use of the linearized multistage approach.

- The IARC (1981) classified TCDD as a 2B chemical (sufficient animal evidence; inadequate human evidence) for carcinogenicity.

- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986), 2,3,7,8-TCDD may be classified in Group B2: Probable human carcinogen. This category is for agents for which there is inadequate evidence from human studies and sufficient evidence from animal studies.

## VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- For 2,3,7,8-TCDD, the U.S. EPA has established criteria of 1.3 x $10^{-7}$, 1.3 x $10^{-8}$ or 1.3 x $10^{-9}$ ug/L in ambient waters, based on an assumed daily consumption of 6.5 g of contaminated fish and shellfish and 2 L of drinking water (U.S. EPA, 1984b). Under these conditions, 94.2% of the total exposure would result from the consumption of aquatic organisms. The recommended levels correspond to estimated human lifetime excess cancer risks of $10^{-5}$, $10^{-6}$ or $10^{-7}$, respectively. These values are considerably lower than the HAs for drinking water, reflecting the high bioaccumulation potential of this compound in aquatic species.

- The FDA advises that fish containing >50 ppt of 2,3,7,8-TCDD should not be consumed and those containing >25 ppt, but <50 ppt, should not be consumed more than twice a month (FDA, 1983). This is reflected in a Canadian limit of 20 ppt in the Lake Ontario commercial fish imported into the United States (NRCC, 1981).

- An ADI of $10^{-4}$ ug/kg bw/day has been proposed previously for 2,3,7,8-TCDD by the National Academy of Sciences Safe Drinking Water Committee (NAS, 1977). This ADI was based on a 13-week rat feeding study by Kociba et al. (1976) and was proposed before convincing evidence for the carcinogenicity of 2,3,7,8-TCDD had accumulated.

## VII. ANALYTICAL METHODS

- Determination of dioxin is by a gas chromatographic/mass spectrometer (GC-MS) method (Method 613. U.S. EPA, 1984c). In this method, a one liter sample is spiked with an internal standard of a labeled dioxin and extracted with methylene chloride using a separatory funnel. The methylene chloride extract is exchanged to hexane during concentration to a volume of approximately 1 mL. The extract is then analyzed by capillary column GC/MS to separate and measure dioxin. The method detection limit is dependent upon the nature of interferences, but it is estimated to be about 0.02 ug/L.

## VIII. TREATMENT TECHNOLOGIES

- Because of its high toxicity and low potential for occurrence in drinking water, very little information is available on the removal of dioxins from drinking water. Granular activated carbon adsorption is likely to be the most reasonable treatment approach and the small amount of empirical evidence available bears this out.

- While looking for a method to concentrate polychlorinated dibenzo-p-dioxins and dibenzofurans, scientists from the U.S. Fish and Wildlife Service's fish-pesticide research laboratory in Columbia, Missouri, found that TCDD is extremely difficult to recover from GAC once it has been adsorbed (Chemical Engineering and News, 1977). Subsequent pilot-scale tests of carbon adsorption of Agent Orange [50-50 mixture of the acid esters of 2,4,5-T and 2,4-dichlorophenoxyacetic acid (2,4-D)] reduced an initial concentration of 10 mg/L dioxin in the herbicide to a final concentration of less than 0.1 mg/L. Details of the adsorption test were not reported by the authors. Based on these data and the reported low water solubility of 0.2 ug/L dioxin in water (Bollen and Norris, 1979), it appears that GAC adsorption of dioxin from water is potentially feasible.

## IX. REFERENCES

Adams, W.J., and K.M. Blaine. A water solubility of 2,3,7,8-TCDD. Monsanto Company, St. Louis, MO. Dioxin 85 -- 5th International Symposium on Chlorinated Dioxins and Related Compounds, Byreuth, F.G.R., Sept. 16-19, 1985.

Allen, J.R., J.P. Van Miller and D.H. Norback. 1975. Tissue distribution, excretion, and biological effects of (14-C) tetrachlorodibenzo-p-dioxin in rats. Food Cosmet. Toxicol. 13(5):501-505.

Althaus, F.R., S.D. Lawrence, G.L. Sattler, D.G. Longfellow and H.C. Pitot. 1982. Chemical quantification of unscheduled DNA synthesis in cultured hepatocytes as an assay for the rapid screening of potential chemical carcinogens. Cancer Res. 42:3010-3015.

Bollen, W.B., and L.A. Norris. 1979. Influence of 2,3,7,8-tetrachlorodibenzo-p-dioxin on respiration in a forest floor and soil. Bull. Environ. Contam. Toxicol. 22:648-652.

Bronzetti, G., E. Zeiger, I. Lee, K. Suzuki and H.V. Malling. 1983. Mutagenicity study of TCDD and ashes from urban incinerator "in vitro" and "in vivo" using yeast D7 strain. Chemosphere. 12:549-553.

Chemical Engineering and News. 1977. Method rids Agent Orange of TCDD contamination. 55(11):25.

Cheng, S.C., F.E. Hileman and J.M. Schroy. Nov., 1983-March, 1984. Monsanto Company. Physical Property Research. Measurement of vapor pressure at lower temperature levels, and development of the heat of sublimation from the correlation of the vapor pressure data using the Clausius-Clapeyron equation. Estimates of the heat of vaporization were made using the measured heat of sublimation and the heat of fusion.

DeCaprio, A.P., D.N. McMartin, P.W. O'Keefe, R. Rej, J.B. Silkworth and L.S. Kaminsky. 1986. Subchronic oral toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin in the guinea pig. Comparisons with a PCB-containing transformer fluid pyrolysate. Fund. Appl. Toxicol. 6:454-463.

Diamond Shamrock. 1985. Letter to U.S. EPA, Office of Drinking Water, with comments on 2,3,7,8-TCDD Health Advisory document.

FDA. 1983. Food and Drug Administration. Statement by S.A. Miller, Director, Bureau of Foods, FDA, before the Subcommittee on Natural Resources, Agriculture Research and Environment, U.S. House of Representatives. June 30.

Fowler, B.A., G.W. Lucier, H.W. Brown and O.S. McDaniel. 1973. Ultrastructural changes in rat liver cells following a single oral dose of TCDD. Environ. Health Perspect. 5:141-148.

Fries, G.F., and G.S. Marrow. 1975. Retention and excretion of 2,3,7,8-tetrachlorodibenzo-p-dioxin by rats. J. Agric. Food Chem. 23(2):265-269.

Gasiewicz, T.A., and R.A. Neal. 1979. 2,3,7,8-Tetrachlorodibenzo-p-dioxin tissue distribution, excretion, and effects on clinical chemical parameters in guinea pigs. Toxicol. Appl. Pharmacol. 51(2):329-340.

Gasiewicz, T.A., J.R. Olson, L.E. Geiger and R.A. Neal. 1983a. Absorption, distribution and metabolism of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in experimental animals. In: Human and Environmental Risks of Chlorinated Dioxins and Related Compounds, R.E. Tucker, A.L. Young, and A.P. Gray, Eds. Plenum Press, NY, pp. 495-525.

Gasiewicz, T.A., L.E. Geiger, G. Rucci and R.A. Neal. 1983b. Distribution, excretion and metabolism of 2,3,7,8-tetrachlorodibenzo-p-dioxin in C57B1/6J, DBA/2J and B6D2F$_1$/J mice. Drug Metab. Dispos. 11(5):397-403.

Geiger, L.E., and R.A. Neal. 1981. Mutagenicity testing of 2,3,7,8-tetrachlorodibenzo-p-dioxin in histidine auxotrophs of Salmonella typhimurium. Toxicol. Appl. Pharmacol. 59(1):125-129.

Gilbert, P., G. Saint-Ruf, F. Poncelet and M. Mercier. 1980. Genetic effects of chlorinated anilines and azobenzenes on Salmonella typhimurium. Arch. Environ. Contam. Toxicol. 9(5):533-541.

Goldstein, J.A., P. Linko and H. Bergman. 1982. Induction of porphyria in the rat by chronic versus acute exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin. Biochem. Pharmacol. 31(8):1607-1613.

Green, S., and F.S. Moreland. 1975. Cytogenetic evaluation of several dioxins in the rat. Toxicol. Appl. Pharmacol. 33:161.

Gupta, B.N., J.G. Vos, J.A. Moore, J.G. Zinkl and B.C. Bullock. 1973. Pathologic effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin in laboratory animals. Environ. Health Perspect. 5:125-140.

Hay, A. 1983. The mutagenic properties of 2,3,7,8-tetrachlorodibenzo-p-dioxin. American Chemical Society National Meeting. Abst. 23(2):14.

Henck, J.W., M.A. New, R.J. Kociba and K.S. Rao. 1981. 2,3,7,8-Tetrachlorodibenzo-p-dioxin: Acute oral toxicity in hamsters. Toxicol. Appl. Pharmacol. 59:405-407.

Huetter, R., and M. Philippi. 1982. Studies on microbial metabolism of TCDD under laboratory conditions. Pergamon Ser. Environ. Sci. 5:87-93.

Hussain, S., L. Ehrenberg, G. Lofroth and T. Gejvall. 1972. Mutagenic effects of TCDD on bacterial systems. Ambio. 1:32-33.

IARC. 1982. International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Chemical Industrial Processes and Industries Associated with Cancer in Humans. Suppl. 4. IARC, Lyon, France. pp. 238-243.

Jones, G., and W.H. Butler. 1974. A morphological study of the liver lesion induced by 2,3,7,8-tetrachlorodibenzo-p-dioxin in rats. J. Pathol. 112:93-97.

King, M.E., and A.R. Roesler. 1974. Subacute intubation study on rats with the compound 2,3,7,8-tetrachloridioxin. U.S. EPA. NTIS PB 257 677, p. 27.

Kociba, R.J., P.A. Keeler, C.N. Park and P.J. Gehring. 1976. 2,3,7,8-Tetrachlorodibenzo-p-dioxin results of a 13-week oral toxicity study in rats. Toxicol. Appl. Pharmacol. 35:553-574.

Kociba, R.J., D.G. Keyes, J.E. Beyer et al. 1978a. Results of a two-year chronic toxicity and oncogenicity study of 2,3,7,8-tetrachlorodibenzo-p-dioxin in rats. Toxicol. Appl. Pharmacol. 46(2):279-303.

Kociba, R.J., D.G. Keyes, J.E. Beyer and R.M. Carreon. 1978b. Toxicologic studies of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in rats. Toxicol. Occup. Med. 4:281-287.

Kociba, R.J., D.G. Keyes, J.E. Beyer, R.M. Carreon and P.J. Gehring. 1979. Long-term toxicologic studies of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in laboratory animals. Ann. NY Acad. Sci. 320:397-404.

Kondorosi, A., I. Fedorcsak, F. Solymosy, L. Ehrenberg and S. Osterman-Golkar. 1973. Inactivation of QBRNA by electrophiles. Mutat. Res. 17:149-161.

Loprieno, N., I. Skrana, D. Rusciano, D. Lascialfari and T. Lari. 1982. In vivo cytogenetic studies on mice and rats exposed to tetrachlorodibenzo-p-dioxin (TCDD). Chlorinated Dioxins and Related Compounds, Impact on the Environment. Book 5. pp. 419-428.

Manara, L., P. Coccia and T. Croci. 1982. Persistent tissue levels of TCDD in the mouse and their reduction as related to prevention of toxicity. Drug Metab. Rev. 13(3):423-446.

McCann, J. 1978. Unpublished study. (Cited in Wassom et al., 1978)

McNulty, W.P., K.A. Nielsen-Smith, J.O. Lay, Jr. et al. 1982. Persistence of TCDD in monkey adipose tissue. Food Cosmet. Toxic. 20:985-987.

Moore, J.A., M.W. Harris and P.W. Albro. 1976. Tissue distribution of ($^{14}$C) tetrachlorodibenzo-p-dioxin in pregnant and neonatal rats. Toxicol. Appl. Pharmacol. 37(1):146-147.

Murray, F.J., F.A. Smith, K.D. Nitschke, C.G. Humiston, R.J. Kociba and B.A. Schwetz. 1979. Three-generation reproduction study of rats given 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in the diet. Toxicol. Appl. Pharmacol. 50:241-251.

NAS. 1977. National Academy of Sciences. Drinking Water and Health: Part II. NAS, Washington, D.C. pp. 500-513.

Nau, H., and R. Bass. 1981. Transfer of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) to the mouse embryo and fetus. Toxicology. 20(4):299-308.

Nau, H., R. Bass and D. Neubert. 1982. Transfer of 2,3,7,8-tetrachlordibenzo-p-dioxin (TCDD) to the mouse embryo, fetus and neonate. In: Chlorinated Dioxins and Related Compounds. Impact on the Environment. O. Huntzinger, R.W. Frei, E. Merian, and F. Pocchiari, Eds. Pergamon Press, NY. pp. 325-337.

Neal, R.A., J.R. Olsen, T.A. Gasiewicz and L.E. Geiger. 1982. The toxicokinetics of 2,3,7,8-tetrachlorodibenzo-p-dioxin in mammalian systems. Drug Metab. Rev. 13:355-385.

Nebert, D., S. Thorgiersson and J. Felton. 1976. Genetic differences in mutagenesis, carcinogenesis, and drug toxicity. In: In vitro Metabolic Activation in Mutagenesis Testing, F. de Serros, J. Folets, J. Bend, and R. Philpot, Eds. Elsevier/North Holland Biomedical Press, Amsterdam. pp. 105-124.

Nisbet, I.C.T., and M.B. Paxton. 1982. Statistical aspects of three-generation studies of the reproductive toxicity of TCDD and 2,4,5-T. Am. Stat. Vol. 36(3):290-298.

Nolan, R.J., F.A. Smith and J.G. Hefner. 1979. Elimination and tissue distribution of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in female guinea pigs following a single oral dose. Toxicol. Appl. Pharmacol. 48(1):A162.

NRCC. 1981. National Research Council of Canada. Polychlorinated Dibenzo-p-Dixons: Criteria for Their Effects on Man and His Environment. NRCC/CNRC Associate Committee on Scientific Criteria for Environmental Quality, Ottawa, Canada. Publ. No. NRCC 18574, ISSN 0316-0114. 251 pp.

NTP. 1980. National Toxicology Program. Bioassay of 2,3,7,8-tetrachlorodibenzo-p-dioxin for possible carcinogenicity (gavage study). Carcinogenesis Testing Program, NCI, NIH, Bethesda, MD; NTP, Research Triangle Park, NC. DHHS Publ. No. (NIH) 82-1765.

Olson, J.R., and W.E. Bittner. 1983. Comparative metabolism and elimination of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD). Toxicologist. 3:103.

Olson, J.R., T.A. Gasiewicz and R.A. Neal. 1980a. Tissue distribution, excretion, and metabolism of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in the Golden Syrian Hamster. Toxicol. Appl. Pharmacol. 56:78-85.

Olson, J.R., M.A. Holscher and R.A. Neal. 1980b. Toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin in the Golden Syrian hamster. Toxicol. Appl. Pharmacol. 55:67-78.

Olson, J.R., T.A. Gasiewicz, L.E. Geiger and R.A. Neal. 1983. The metabolism of 2,3,7,8-tetrachlorodibenzo-p-dioxin in mammalian systems. In: Accidental Exposure to Dioxins: Human Health Aspects, R. Coulston, and F. Pocchiari, Eds. Academic Press, NY. pp. 81-100.

Piper, W.N., R.Q. Rose and P.J. Gehring. 1973. Excretion and tissue distribution of 2,3,7,8-tetrachlordibenzo-p-dioxin in the rat. Environ. Health Perspect. 5:241-244.

Poiger, H., and C. Schlatter. 1979. Biological degradation of TCDD in rats. Nature. 281(5733):706-707.

Poiger, H., and C. Schlatter. 1980. Influence of solvents and adsorbents on dermal and intestinal absorption of TCDD. Food Cosmet. Toxicol. 18(5):477-481.

Poiger, H., and C. Schlatter. 1986. Pharmacokinetics of 2,3,7,8-TCDD in man. Chemosphere. In press. Presented at the Fifth International Symposium on Chlorinated Dioxins and Related Compounds. Final Programme. September 16-21, 1985. Bayreuth, F.R.G.

Poiger, H., H. Weber and Ch. Schlatter. 1982. Special aspects of metabolism and kinetics of TCDD in dogs and rats. Assessment of toxicity of TCDD-metabolite(s) in guinea pigs. In: Chlorinated Dioxins and Related Compounds. Impact on the Environment. O. Hutzinger, R.W. Frei, E. Merian and F. Pocchiari, Eds. Pergamon Press, NY. pp. 317-325.

Poland, A., and E. Glover. 1979. An estimate of the maximum in vivo covalent binding of 2,3,7,8-tetrachlorodibenzo-p-dioxin to rat liver protein, ribosomal RNA and DNA. Cancer Res. 39(9):3341-3344.

Poland, A., and E. Glover. 1980. 2,3,7,8-Tetrachlorodibenzo-p-dioxin: Segregation of toxicity with the Ah locus. Molec. Pharmacol. 17:86-94.

Rose, J.Q., J.C. Ramsey, T.H. Wentzler, R.A. Hummel and P.J. Gehring. 1976. The fate of 2,3,7,8-tetrachlorodibenzo-p-dioxin following single and repeated oral doses to the rat. Toxicol. Appl. Pharmacol. 36(2):209-226.

Rowe, V.K. 1968. Klogman/Rowe correspondence, Exhibits 865 and 866 before the Environmental Protection Agency of the United States of America. RICA.

Ryan, J.J., R. Lizotte and B.P-Y. Lau. 1985. Chlorinated dibenzo-p-dioxins and chlorinated dibenzofurans in Canadian human adipose tissue. Chemosphere. 14:697-706.

Sawahata, T., J.R. Olson and R.A. Neal. 1982. Identification of metabolites 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) formed on incubation with isolated rat hepatocytes. Biochem. Biophys. Res. Commun. 105(1):341-346.

Schantz, S.L., D.A. Barsotti and J.R. Allen. 1979. Toxicological effects produced in nonhuman primates chronically exposed to 50 parts per trillion 2,3,7,8-tetrachlordibenzo-p-dioxin (TCDD). Toxicol. Appl. Pharmacol. 48:A180.

Schwetz, B.A., J.M. Norris, G.L. Sparschu et al. 1973. Toxicology of chlorinated dibenzo-p-dioxins. Environ. Health Perspect. 5:87-99.

Seiler, J.P. 1973. A survey on the mutagenicity of various pesticides. Experientia. 29:622-623.

Stevens, K.M. 1981. Agent Orange toxicity: A quantitative perspective. Human Toxicol. 1:31-39.

Toth, K., J. Sugar, S. Somfai-Relle and J. Bence. 1978. Carcinogenic bioassay of the herbicide, 2,4,5-trichlorophenoxyethanol (TCPE) with different 2,3,7,8-tetrachlorodibenzo-p-dioxin (dioxin) content in Swiss mice. Prog. Biochem. Pharmacol. 14:82-93.

Toth, K., S. Somfai-Relle, J. Sugar and J. Bence. 1979. Carcinogenicity testing of herbicide 2,4,5-trichlorophenoxyethanol containing dioxin and of pure dioxin in Swiss mice. Nature. 278(5704):548-549.

Turner, J.N., and D.N. Collins. 1983. Liver morphology in guinea pigs administered either pyrolysis products of a polychlorinated biphenyl transformer fluid or 2,3,7,8-tetrachlorodibenzo-p-dioxins. Toxicol. Appl. Pharmacol. 67:417-429.

U.S. EPA. 1984a. U.S. Environmental Protection Agency. Miscellaneous synthetic organic chemicals, occurrence in drinking water, food, and air. EPA 600/8-84-014A.

U.S. EPA. 1984b. U.S. Environmental Protection Agency. Ambient water quality criteria for 2,3,7,8-tetrachlorodibenzo-p-dioxin. Office of Water Regulations and Standards, EPA 440/5-84-007.

U.S. EPA. 1984c. U.S. Environmental Protection Agency. Method 613. 2,3,7,8-Tetrachlorodibenzo-p-Dioxin, Federal Register. 49(209):433368-78. October 26, 1984.

U.S. EPA. 1985a. U.S. Environmental Protection Agency. Drinking Water Criteria Document for 2,3,7,8-Tetrachlorodibenzo-p-Dioxin. U.S. EPA. Office of Drinking Water. EPA 600/X-84-194-1.

U.S. EPA. 1985b. U.S. Environmental Protection Agency. Health assessment document for polychlorinated dibenzo-p-dioxins. Environmental Criteria and Assessment Office, Cincinnati, OH. EPA/600/8-84/014F.

U.S. EPA. 1986. U.S. Environmental Protection Agency. Guidelines for carcinogenic risk assessment. Fed. Reg. 51(185):33992-34003. September 24.

Van Miller, J.P., R.J. Marlar and J.R. Allen. 1976. Tissue distribution and excretion of tritiated tetrachlorodibenzo-p-dioxin in non-human primates and rats. Food Cosmet. Toxicol. 14(1):31-34.

Vinopal, J.H., and J.E. Casida. 1973. Metabolic stability of 2,3,7,8-tetrachlorodibenzo-p-dioxin in mammalian liver microsomal systems and in living mice. Arch. Environ. Contam. Toxicol. 1(2):122-132.

Vos, J.G., J.A. Moore and J.G. Zinkl. 1974. Toxicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in C57B1/6 mice. Toxicol. Appl. Pharmacol. 29:229-241.

Young, A.L., H.K. Kang and B.M. Shepard. 1983. Chlorinated dioxins as herbicide contaminants. Environ. Sci. Technol. 17:530A-540A.

# EPICHLOROHYDRIN

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

## I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

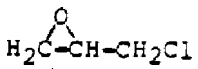
Health Advisories are developed for One-day, Ten-day, Longer-term (approximately 7 years, or 10% of an individual's lifetime) and Lifetime exposures based on data describing noncarcinogenic end points of toxicity. Health Advisories do not quantitatively incorporate any potential carcinogenic risk from such exposure. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

This Health Advisory (HA) is based on information presented in the Office of Drinking Water's Health Effects Criteria Document (CD) for Epichlorohydrin (U.S. EPA, 1985a). The HA and CD formats are similar for easy reference. Individuals desiring further information on the toxicological data base or rationale for risk characterization should consult the CD. The CD is available for review at each EPA Regional Office of Drinking Water counterpart (e.g., Water Supply Branch or Drinking Water Branch), or for a fee from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Rd., Springfield, VA 22161, PB #86-118023/AS. The toll-free number is (800) 336-4700; in the Washington, D.C. area: (703) 487-4650.

## II. GENERAL INFORMATION AND PROPERTIES

CAS No. 106-89-8

Structural Formula



Synonyms

° 1-Chloro-2,3-epoxypropane, 3-chloro1-1,2-epoxypropane, (chloromethyl) oxirane, 2-(chloromethyl) oxirane and chloropropylene oxide.

Uses

° Used in the manufacture of: epoxide resins, surface active agents, pharmaceuticals, and agricultural chemicals (Verschueren, 1983).

Properties (U.S. EPA, 1985a)

| | |
|---|---|
| Molecular Formula | $C_3H_5ClO$ |
| Molecular Weight | 92.53 |
| Physical State | Colorless liquid |
| Boiling Point | 116.1°C |
| Melting Point | -57.2°C |
| Density | -- |
| Vapor Pressure | 12 mm at 20°C |
| Specific Gravity | 1.18 at 20°C |
| Water Solubility | 66 g/L at 20°C |
| Log Octanol/Water Partition Coefficient | 0.26 |
| Taste Threshold | -- |
| Odor Threshold | 0.5 - 1.0 mg/L; 3 mg/L (Amoore and Hautala, 1983) |
| Conversion Factor | 1 $mg/m^3$ = 0.265 ppm<br>1 ppm = 3.78 $mg/m^3$ |
| Irritation Threshold | 0.1 mg/L |

Occurrence

- Total epichlorohydrin production in 1982 was approximately 350 million pounds. Though epichlorohydrin reportedly hydrolyzes readily in aqueous solution (hydrolysis half-life of 8.2 days at 20°C and pH 7) to water soluble alcohols, its use in water treatment resins and coatings make exposure possible (Mabey and Mill, 1978).

- No information has been located in either State or Federal surveys to indicate the presence or absence of epichlorohydrin in drinking water.

## III. PHARMACOKINETICS

Absorption

- Epichlorohydrin is absorbed readily following either oral, inhalation or dermal exposures (U.S. EPA, 1985a).

- Gingell et al. (1985) assessed the pharmacokinetics and metabolism of epichlorohydrin in male Fischer 344 rats treated (6 mg/kg once by gavage) with [2-$^{14}$C] epichlorohydrin (98% pure) in water and sacrificed after 3 days. Ready absorption was shown by an initial elimination half-life of 2 hours and total excreta recovery of 91.61% of the radiolabel.

- Smith et al. (1979) have reported the extensive absorption of epichlorohydrin in water by male Fischer 344 rats (190 to 220 g) following a single gavage exposure. Based on excretion data, the extent of absorption, approximately 100% within 72 hours after administration, appeared to be similar following doses of either 1 or 100 mg/kg bw.

- Smith et al. (1979) indicated that epichlorohydrin was absorbed readily by male Fischer 344 rats (190 to 220 g) following a 6-hour exposure to atmospheres containing 1 or 100 ppm epichlorohydrin (approximately 3.78 or 378 mg/m$^3$). Uptake rates of 15.48 and 1394 ug/hr were calculated for exposures to 1 and 100 ppm, respectively. The investigators stated that these exposures correspond to doses of 0.37 and 33 mg/kg bw.

- The toxicity study of Kremneva and Tolgskaya (1961) indicates that epichlorohydrin also is absorbed following dermal exposure. When the tails of mice were immersed in epichlorohydrin either for a single exposure of 1 hour or for repeated exposures of 20 to 30 minutes/day on 2 to 3 successive days, toxic signs and death were observed within 3 days.

Distribution

- In the study by Gingell et al. (1985), 8-9% of $^{14}$C was in tissues, with the highest levels (specific activity, dpm x 10$^{-3}$/g tissue wet weight) in liver (177.5; 2.82% of dose), kidney (127.1; 0.41% of dose), and forestomach (81.6; 0.03% of dose).

- Smith et al. (1979) compared the distribution of [1,3-$^{14}$C]-epichlorohydrin in male Fischer 344 rats following oral (100 mg/kg bw) or inhalation (100 ppm for 6 hours) exposure. At 3 hours post-exposure in the oral study and at the termination of inhalation exposure, the plasma levels of radioactivity were 36.1 and 18.3 mg/g, respectively. Concentrations in tissues were expressed as ug equivalents of epichlorohydrin per g of tissue. After oral treatment, the greatest concentrations were in stomach, followed by intestine, kidney, liver, pancreas and lung. Following inhalation exposure, the highest levels were in nasal turbinates, followed by intestine, liver and kidney.

Metabolism

- Gingell et al. (1985) concluded that the initial elimination half-life of 2 hours indicated rapid metabolism in their study. Main urinary metabolites were N-acetyl-S-(3-chloro-2-hydroxypropyl)-L-cysteine and $\alpha$-chlorohydrin, representing 36 and 4% of the delivered dose, respectively. One major metabolite and 4 minor metabolites were identified in urine. These investigators stated that the presence of the two dominant urinary metabolites is consistent with initial metabolic reactions being conjugation of the epoxide with glutathione and hydration of the epoxide.

- Smith et al. (1979) administered [1,3-$^{14}$C]-epichlorohydrin to male Fischer 344 rats as single oral doses of 1 or 100 mg/kg bw or as 6-hour inhalation exposures to 1 or 100 ppm (approximately 3.78 or 378 mg/m$^3$). Urinary metabolites were separated by ion-exclusion chromatography. Seven radioactive peaks were found in the urine following oral dosing and six radioactive peaks following inhalation exposure, but none corresponded to epichlorohydrin. The authors noted that the patterns of urinary metabolite excretion were similar following oral or inhalational dosing; metabolites were not identified.

- Epichlorohydrin has two electrophilic centers and may bind to cellular nucleophiles. It is also a substrate for epoxide hydratase resulting in the formation of $\alpha$-chlorohydrin which may be oxidized to oxalic acid, converted to glycidol or phosphorylated to 3-chloroglycerophosphate (U.S. EPA, 1985a). However, Gingell et al. (1985) did not find oxalic acid as a metabolite in their study.

- Rossi et al. (1983) found that epichlorohydrin rapidly disappeared from the blood of CD1 mice, with a half-life of approximately five minutes, with $\alpha$-chlorohydrin appearing as epichlorohydrin levels dropped. $\alpha$-Chlorohydrin, however, had a much longer half-life for disappearance (50-60 minutes).

Excretion

- In the study by Gingell et al. (1985), the half-life of initial elimination of $^{14}$C in both urine and exhaled air was about 2 hours. Approximately 38% of the radioactive dose was exhaled as $CO_2$, 50% was excreted as urinary metabolites, and 39% was eliminated in feces.

° Smith et al. (1979) administered [1,3-$^{14}$C]-epichlorohydrin by single gavage doses of 1 or 100 mg/kg to groups of four male Fischer 344 rats. In parallel experiments, four rats were exposed (head only) to atmospheres containing 100 ppm (378 mg/m$^3$) epichlorohydrin for six hours. An additional three rats were exposed to atmospheres containing 1 ppm (3.78 mg/m$^3$) for six hours. The rates or routes of excretion essentially were unaffected by either the route of exposure or the dose administered. Urine was the major route of excretion, accounting for 46% to 54% of the dose. An additional 25% to 42% was recovered as $^{14}CO_2$ in the expired air. Only 3% to 6% of the dose was recovered in the feces. Excretion was biphasic, with an initial rapid phase that dominated the first 24 hours post-exposure and a slower second phase that was dominant after 24 hours. The calculated half-lives for elimination from the plasma were 1 to 2 hours and 26 to 27 hours for the fast and slow phases, respectively.

## IV. HEALTH EFFECTS

### Humans

° In humans, acute effects have been reported following both dermal and inhalation exposures (U.S. EPA, 1985a). Dermal exposure produces predominantly local irritation effects, but inhalation produces significant systemic effects, including hepatic and renal toxicity. In one case report of a worker exposed to epichlorohydrin vapor, systemic effects were evident for at least 2 years after the exposure. (U.S. EPA, 1985a) Chronic exposure to epichlorohydrin has been associated with chromosome and chromatid breaks, decreased hemoglobin concentration, decreased erythrocyte counts and decreased leukocyte counts. Increases (not statistically significant) in the mortality due to lung cancer have been reported in workers sequentially exposed to isopropyl alcohol and epichlorohydrin (U.S. EPA, 1985a). No effects on reproductive function have been detected.

### Animals

#### Short-term Exposure

° Epichlorohydrin is acutely toxic following oral, percutaneous, subcutaneous or respiratory exposure, producing similar symptoms in each case. At the site of application, epichlorohydrin is a strong irritant. The major acute systemic effects occur in the central nervous system, with death being due to depression of the respiratory center. The major internal organs affected are the lungs, liver and kidneys (U.S. EPA, 1985a).

° Oral doses as low as 10 mg/kg for 5 days/week for 2 weeks resulted in decreased ($p < 0.05$) erythrocyte counts in male rats and decreased ($p < 0.01$) kidney/body weight ratios in females (Van Esch, 1981). Similar exposures to 40 or 6[illegible] mg/kg resulted in degenerative changes in the kidneys of both male and female rats.

Long-term Exposure

- Epichlorohydrin given in drinking water at levels of 375, 750 and 1,500 ppm (18, 39 and 89 mg/kg/day) to male Wistar rats for 81 weeks induced forestomach hyperplasia and decreased body weights at all doses (Konishi et al., 1980).

- With gavage administration of epichlorohydrin in water at doses of 2 and 10 mg/kg, 5 days/week for 104 weeks, stomach hyperplasia and a dose-related decrease in white blood cells were observed in male and female Wistar rats (Van Esch, 1982).

- Inhalation exposure of Fischer 344 rats, Sprague-Dawley rats, B6C3F1 mice and New Zealand rabbits to epichlorohydrin at 19 mg/m$^3$ for 90 days was without observable effect. Higher exposure levels induced nasal irritation, eye irritation, kidney lesions and respiratory tract lesions (Quast et al., 1979; John et al., 1983).

- Lifetime inhalation exposure of male Sprague-Dawley rats to 38 and 114 mg/m$^3$ epichlorohydrin elicited kidney lesions (Laskin et al., 1980).

Reproductive Effects

- Male and female Wistar rats were given epichlorohydrin in water starting 10 days before mating and continuing for three months (Van Esch, 1981). A dose of 2 mg/kg was ineffective. A 10 mg/kg dose reduced fertility and crossmating with untreated rats attributed the antifertility effect to males. Sterility of male rats given epichlorohydrin orally also was observed by Hahn (1970) and Cooper et al. (1974) with gavage doses of 15 mg/kg and higher for 15 and 5 days, respectively; however, these investigators showed the effect to be reversible.

- Exposure of male rats to epichlorohydrin by inhalation at levels above 19 mg/m$^3$ for 10 weeks resulted in reversible sterility, and the fertility of male rabbits was unaffected by inhalation exposure levels of epichlorohydrin as high as 189 mg/m$^3$ (John et al., 1983).

Developmental Effects

- Epichlorohydrin was not teratogenic when given by gavage in cottonseed oil to pregnant CD rats and CD-1 mice on days 6 through 15 of gestation (Marks et al., 1982). Doses above 40 mg/kg were maternally toxic (reduced body weight, increased liver weight, death) in rats. Doses above 80 mg/kg were maternally toxic (increased liver weight, death) and fetotoxic (reduced body weight) to mice.

- Inhalation exposures of pregnant Sprague-Dawley rats and New Zealand rabbits to 9.5 and 95 mg/m$^3$ of epichlorohydrin during gestation days 6 through 15 (rats) and 6 through 18 (rabbits) were neither teratogenic nor fetotoxic. Pregnant rats exposed to 95 mg/m$^3$ weighed less than controls (Pilny et al., 1979).

Mutagenicity

- Epichlorohydrin is a mutagen in several systems (U.S. EPA, 1985a). It is a potent inducer of base-pair substitution-type mutations in prokaryotic systems. Incubation with mammalian liver homogenates results in a marked reduction in mutation frequency. Epichlorohydrin also induces gene mutations and very likely chromosomal aberrations in mouse lymphoma cell cultures (Moore-Brown and Clive, 1979) and clastogenesis in human lymphocytes in vitro (Norppa et al., 1981) but not in rat liver cell cultures (Dean and Hodson-Walker, 1979). Epichlorohydrin was found to induce sister chromatid exchange in cultured human lymphocytes (Norppa et al., 1981; Carbone et al., 1981; White, 1980). Examination of occupationally exposed workers indicates that chromosomal aberrations also occur in vivo (Picciano, 1979a,b; Kucerova et al., 1977; Sram et al., 1976).

- In in vivo studies, epichlorohydrin treatment results in an increased incidence of sex-linked recessive lethals in Drosophila when administered by injection, but not when incorporated in the food (Knapp et al., 1982; Wurgler and Graf, 1981). In other in vivo studies, epichlorohydrin has produced negative results in the mouse dominant lethal assay (Epstein et al., 1972; Sram et al., 1976) and the mouse micronucleus assay (Kirkhart, 1981; Tsuchimoto and Matter, 1981). Clastogenic effects of epichlorohydrin in bone marrow cells in vivo were found in mice (Sram et al., 1976) but not in rats (Dabney et al., 1979).

Carcinogenicity

- Epichlorohydrin is carcinogenic at the site of administration.

- Administration of 375, 750 and 1,500 ppm epichlorohydrin in drinking water [equivalent to 18, 39 and 89 mg/kg/day based on data by the authors (total doses of 5.0, 8.9 and 15.1 g/rat during 81 weeks of treatment divided by body weight)] to male Wistar rats for 81 weeks resulted in forestomach hyperplasia at all doses and papillomas and carcinomas of the forestomach at the two highest doses (Konishi et al., 1981).

- Lifetime gavage treatment of male and female Wistar rats with aqueous epichlorohydrin solution at doses of 2 and 10 mg/kg induced papillomas and carcinomas of the forestomach (Wester et al., 1985; Van Esch, 1982).

- Laskin et al. (1980) found nasal carcinomas in male Sprague-Dawley rats exposed to 378 mg/m$^3$ of epichlorohydrin by inhalation 6 hours/day, 5 days/week for six weeks followed by lifetime observation.

- Subcutaneous injection of epichlorohydrin in ICR/Ha Swiss mice induced local sarcomas; epichlorohydrin was effective as an initiator but not as a complete carcinogen on the skin of ICR/Ha Swiss mice (Van Duuren et al., 1972; 1974).

## V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for One-day, Ten-day, Longer-term (approximately 7 years) and Lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(NOAEL \text{ or } LOAEL) \times (BW)}{(UF) \times (\_\_\_ \text{ L/day})} = \_\_\_ \text{ mg/L } (\_\_\_ \text{ ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect-Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100 or 1,000), in accordance with NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

### Organoleptic Properties

A reported threshold for odor perception of epichlorohydrin is 0.5 to 1.0 mg/L, and 0.1 mg/L was cited as the threshold for its irritant action by the NAS (1980). Amoore and Hautala (1983) reported an odor threshold of 3 mg/L.

### One-day Health Advisory

Because appropriate data for calculation of a One-day HA are not available, the Ten-day HA (0.14 mg/L) is recommended for use as the One-day HA.

### Ten-day Health Advisory

The reproductive toxicity study by Van Esch (1981) can be used to derive the Ten-day HA. In this study, male and female rats were given epichlorohydrin by gavage 5 days/week at doses of 0, 2 or 10 mg/kg. Exposure was started 10 days prior to mating and continued until the $F_{1b}$ generation was produced. The fertility index at the first mating was reduced in the high-dose group but not in the low-dose group. The study of Hahn (1970) which reported infertility in male rats exposed by gavage to epichlorohydrin at 15 mg/kg/day for 12 days supports an assumption that at least a portion of the reduced fertility index observed by Van Esch (1981) was the result of infertility in the males associated with the ten-day exposure prior to mating. In this study, 2 mg/kg was a NOAEL for reproductive effects and is appropriate for use in deriving the Ten-day HA.

Using the NOAEL of 2 mg/kg/day, the Ten-day HA for a 10-kg child is calculated as follows:

$$\text{Ten-day HA} = \frac{2 \text{ mg/kg/day}) \ (10 \text{ kg}) \ (5)}{(100) \ (1 \text{ L/day}) \quad (7)} = 0.14 \text{ mg/L } (140 \text{ ug/L})$$

where:

2 mg/kg/day = NOAEL based on absence of reproductive toxicity in rats.

10 kg = assumed body weight of a child.

5/7 = conversion of dose to represent continuous exposure (7 days per week).

1 L/day = assumed daily water consumption of a child.

Although the antifertility effect in male rats in the Van Esch (1981) study relates to men as a specific sensitive subpopulation for this effect, this study is preferred for the calculation of a Ten-day HA for the general population because of its design with oral short-term exposure and its demonstration of no-effect and effect levels. Additionally, the 2 mg/kg NOEL in the Van Esch (1981) study appears consistent with the dose responses in the overall Van Esch (1981) work where both systemic and reproductive effects were found with 10-day oral exposures to 10 mg/kg of epichlorohydrin.

Longer-term Health Advisory

There are insufficient data for calculation of a Longer-term HA. The DWEL (0.07 mg/L), is recommended as a conservative estimate of the Longer-term HA.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed for synthetic organic chemicals and a value of 10% is assumed for inorganic chemicals. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

Of the reviewed studies in which the effects of long-term exposure to epichlorohydrin were investigated (Laskin et al., 1980; Konishi et al., 1980, also reported by Kawabata, 1981; Wester et al., 1985, also reported by Van Esch, 1982), the Laskin et al. (1980) study was selected as the most appropriate from which to derive the DWEL. Forestomach hyperplasia in all three treatment groups and papillomas and carcinomas of the forestomach in the two highest dose groups were found in the study by Konishi et al. (1980). Since the hyperplasia could be considered a pre-neoplastic effect and the progression of forestomach lesions beyond the 81-week duration of this study is uncertain, it would be questionable to use this effect in the low-dose group (18 mg/kg/day) for calculating a DWEL for drinking water exposure. Dose-response for toxicity/carcinogenicity in the Konishi et al. (1980) drinking water study is given preference over that in the bolus gavage dosing study by Wester, et al. (1985), and use of the estimated 2.16 mg/kg/day dose in the Laskin, et al. (1980) study is concluded to be consistent with the dose-response indicated by the Konishi et al. (1980) study. The LOAEL based on renal damage of 2.16 mg/kg/day estimated from the data in the Laskin et al. (1980) study was, therefore, used to derive a DWEL. Additionally, carcinogenic effects were not apparent at the LOAEL in the Laskin et al. (1980) study. Using this LOAEL, the DWEL is derived as follows:

Step 1: Conversion of Inhalation Exposure to Oral Exposure

Applying the 38 mg/m$^3$ inhalation LOAEL in the Laskin et al. (1980) study and the assumptions in U.S. EPA (1985a) for converting inhalation exposure to oral exposure for the rat, the estimated oral dose would be:

$$\frac{(38\ mg/m^3)(0.0093\ m^3/hr)(6\ hr/day)(5)(0.5)}{(0.35\ kg)\qquad\qquad(7)} = 2.16\ mg/kg/day$$

where:

38 mg/m$^3$ = LOAEL based on kidney toxicity in rats.

0.0093 m$^3$ = amount of air breathed by a rat/hour.

6 hr/day = a 6-hour exposure each day.

5/7 = adjust from a 5 days/week exposure to 7 days/week.

0.5 = the assumed inhalation absorption factor.

0.35 kg = the assumed weight of a rat.

Step 2: Determination of the Reference Dose (RfD)

$$RfD = \frac{(2.16\ mg/kg/day)}{(1,000)} = 0.002\ mg/kg/day\ (2\ ug/kg/day)$$

where:

2.16 mg/kg/day = LOAEL based on kidney toxicity in rats.

1,000 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a LOAEL from an animal study.

Step 3: Determination of the Drinking Water Equivalent Level (DWEL)

$$DWEL = \frac{(0.002\ mg/kg/day)\ (70\ kg)}{(2\ L/day)} = 0,07\ mg/L\ (70\ ug/L)$$

0.002 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Epichlorohydrin may be classified in Group B: Probable human carcinogen. The estimated excess cancer risk associated with lifetime exposure to drinking water containing epichlorohydrin at 70 ug/L is approximately $2 \times 10^{-5}$. This estimate represents the upper 95% confidence limit from extrapolations prepared by EPA's Carcinogen Assessment Group using the linearized, multistage model. The actual risk is unlikely to exceed this value, but there is considerable uncertainty as to the accuracy of risks calculated by this methodology.

Evaluation of Carcinogenic Potential

- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986), epichlorohydrin may be classified in Group B2: Probable human carcinogen. This category is for agents for which there is inadequate evidence from human studies and sufficient evidence from animal studies.

- The study of Konishi et al. (1980) provides appropriate data for a quantitative risk assessment based on the relevant route of exposure and the observed dose-response pattern. Using the calculated $q_1^*$ of $9.9 \times 10^{-3}$ $(mg/kg/day)^{-1}$, the 95% upper-limit lifetime dose associated with a $10^{-5}$ risk level may be calculated to equal 70.7 ug/day. Assuming an average water consumption of 2 L/day, this risk level corresponds to a water concentration of 35.4 ug/L. Corresponding levels for $10^{-6}$ and $10^{-4}$ are 3.54 and 354 ug/L, respectively.

- Maximum likelihood estimates as well as 95% upper limits of cancer risks by the multistage model have been calculated (U.S. EPA, 1984). For example, at 10 ug/L cancer risk estimates are $1.4 \times 10^{-17}$ (MLE) and $2.8 \times 10^{-6}$ (UL) and at 100 ug/L cancer risk estimates are $2.6 \times 10^{-14}$ (MLE) and $2.8 \times 10^{-5}$ (UL).

- The EPA's Carcinogen Assessment Group has estimated cancer risks with other models besides the multistage (U.S. EPA, 1984). As an example, 10 ug/L lifetime exposure was associated with additional risks (95% upper confidence limit) of $2.8 \times 10^{-5}$ by the multistage, $3.4 \times 10^{-5}$ by the one-hit, 0 by the Weibull, and 0 by the log-probit. While recognized as statistically alternative approaches, the range of risks described by using any of these modeling approaches has little biological significance unless data can be used to support the selection of one model over another. In the interest of consistency of approach and in providing an upper bound on the potential cancer risk, the EPA has recommended use of the linearized multistage approach.

° Epichlorohydrin is classified as a 2B carcinogen by IARC (1982) with sufficient animal evidence and inadequate human evidence.

## VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

° The NAS (1980) SNARLs (Suggested-No-Adverse-Response-Levels) for 1- or 7-day exposures to epichlorohydrin are 0.84 and 0.53 mg/L, respectively. An ADI (Acceptable Daily Intake) or a cancer risk was not calculated by the NAS (1980).

° The ACGIH has recommended a TLV (Threshold Limit Value) of 2 ppm (10 $mg/m^3$) (ACGIH, 1982). Current OSHA standards allow a TWA occupational exposure of 19 $mg/m^3$ (29 CFR 1910.1000); however, they are currently considering lowering this value to 0.5 ppm (2 $mg/m^3$) with a ceiling value of 15 ppm (60 $mg/m^3$) for 15 minutes. Occupational standards in other countries range from 0.26 ppm in Russia and Czechoslovakia to 3.6 ppm in the Federal Republic of Germany (Sram, et al., 1980).

° Epichlorohydrin has not been regulated under the Safe Drinking Water Act; however, discharge of >1,000 pounds (454 kg) into navigable waters is prohibited under the Clean Water Act (40 CFR 116).

° Epichloronydrin is also classified as a "hazardous waste" by the U.S. EPA and quantities exceeding 100 kg must be disposed of in a special landfill (40 CFR 261; 40 CFR 122).

° The proposed RMCL by the U.S. EPA Office of Drinking Water is zero (U.S. EPA, 1985b).

## VII. ANALYTICAL METHODS

° There is no standardized method for the determination of epichlorohydrin in drinking water samples. However, epichlorohydrin may be determined by a purge-and-trap gas chromatographic/mass spectrometric procedure used for the determination of volatile organic compounds in water (U.S. EPA, 1985c). This method calls for the bubbling of an inert gas through the sample and trapping epichlorohydrin on an adsorbent material. The adsorbant material is heated to drive off epichlorohydrin onto a gas chromatographic column. The gas chromatograph is temperature programmed to separate the method analytes which are then detected by the mass spectrometer.

## VIII. TREATMENT TECHNOLOGIES

° No data are available on the removal of epichlorohydrin from potable water by any treatment technique (ESE, 1984; U.S. EPA, 1985d).

° The amenability of epichlorohydrin to removal by conventional treatment or by adsorption is not known. The Henry's Law Constant for

epichlorohydrin has been estimated to be $2.44 \times 10^{-5}$ atm x $m^3$/mole (ESE, 1984). This value suggests that aeration is unlikely to be a successful removal technique for epichlorohydrin. It also has been concluded that epichlorohydrin would not be removed from water by ozone oxidation (U.S. EPA, 1985d).

## IX. REFERENCES

ACGIH, 1982. American Conference of Governmental Industrial Hygienists. Threshold limit values for chemical substances and physical agents in the workroom environment. Cincinnati, Ohio.

Amoore, J.E., and E. Hautala. 1983. Odor as an aid to chemical safety: Odor threshold compounds with threshold unit values and volatilities for 214 industrial chemicals in air and water dilution. J. Appl. Toxicol. 3:272-290.

Carbone, P., G. Barbata, G. Margiotta, A. Tomasino and G. Granata. 1981. Low epichlorohydrin concentrations induce sister chromatid exchanges in human lymphocytes in vitro. Caryologia. 34(3):261-266.

40 CFR 116. Code of Federal Regulations.

40 CFR 122. Code of Federal Regulations.

40 CFR 261. Code of Federal Regulations.

Cooper, E.R., A.R. Jones and H. Jackson. 1974. Effects of alpha-chlorohydrin and related compounds on the reproductive organs and fertility of the male rat. J. Reprod. Fert. 39(2):379-386.

Dabney, B.J., R.V. Johnston, J.F. Quast and C.N. Park. 1979. Epichlorohydrin -- Subchronic studies. III. Cytogenetic evaluation of bone marrow cells from rats exposed by inhalation to epichlorohydrin for four weeks. ICPEM (International Commission for Protection Against Environmental Mutagens and Carcinogens) Document No. 128. 15 pp.

Dean, B.J., and G. Hodson-Walker. 1979. An in vitro chromosome assay using cultured rat-liver cells. Mutat. Res. 64:329-337.

ESE. 1984. Environmental Science and Engineering. Review of treatability data for removal of twenty-five synthetic organic chemicals from drinking water. U.S. EPA. Office of Drinking Water.

Epstein, S.S., E. Arnold, J. Andrea, W. Bass and Y. Bishop. 1972. Detection of chemical mutagens by the dominant lethal assay in the mouse. Toxicol. Appl. Pharmacol. 23:288-325.

Gingell, R., H.R. Mitschke, I. Dzidic, P.W. Beatty, V.L. Sarvin and A.C. Page. 1985. Disposition and metabolism of [2-$^{14}$C] epichlorohydrin after oral administration to rats. Drug Metab. Dispos. 13:333-341.

Hahn, J.D. 1970. Post-testicular antifertility effects of epichlorohydrin and 2,3-epoxypropanol. Nature (London). 226:87.

IARC 1982. International Agency for Research on Cancer. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Chemical Industrial Processes and Industries Associated with Cancer in Humans. Suppl. 4, pp. 122-123.

John, J.A., J.F. Quast, F.J. Murray, L.S. Calhoun and R.E. Staples. 1983. Inhalation toxicity of epichlorohydrin: Effects on fertility in rats and rabbits. Toxicol. Appl. Pharmacol. 68:415-423.

Kawabata, A. 1981. Studies on the carcinogenic activity of epichlorohydrin by oral administration in male Wistar rats. J. Nara Med. Assoc. 32:270-280.

Kirkhart, B. 1981. Micronucleus test on 21 compounds. In: Evaluation of Short-Term Tests for Carcinogens, F.J. deSerres and J. Ashby, eds. Elsevier/North Holland, Amsterdam. pp. 698-704.

Knapp, A.G.A.C., C.E. Voogd and P.G.N. Kramers. 1982. Comparison of the mutagenic potency of 2-chloroethanol, 2-bromoethanol, 1,2-epoxybutane epichlorohydrin and glycidaldehyde in Klebsiella pneumoniae, Drosophilla melanogaster and L5178Y mouse lymphoma cells. Mutat. Res. 101:199-208.

Konishi, T., A. Kawabata, A. Denda et al. 1980. Forestomach tumors induced by orally administered epichlorohydrin in male Wistar rats. Gann. 71:922-923.

Kremneva, S.N., and M.S. Tolgskaya. 1961. Toxicology of epichlorohydrin. Toksikol. Nov. Prom. Khim. Veschestv. 2:28-41.

Kucerova, M., V.S. Zhurkov, Z. Polwkova and J.E. Ivanova. 1977. Mutagenic effect of epichlorohydrin. II. Analysis of chromosomal aberrations in lymphocytes of persons occupationally exposed to epichlorohydrin. Mutat. Res. 48:355-360.

Laskin, S., A.R. Sellakumar, M. Kuschner et al. 1980. Inhalation carcinogenicity of epichlorohydrin in non-inbred Sprague-Dawley rats. J. Natl. Cancer Inst. 65(4):751-758.

Mabey, W., and T. Mill. 1978. Critical review of hydrolysis of organic compounds in water under environmental conditions. J. Phys. Chem. Ref. Data. 7:383-415.

Marks, T.A., F.S. Gerling and R.E. Staples. 1982. Teratogenic evaluation of epichlorohydrin in the mouse and rat and glycidol in the mouse. J. Toxicol. Environ. Health. 9:87-96.

Moore-Brown, M.M., and D. Clive. 1979. The L5178Y/TK+/- mutagen assay system: In situ results. Banbury Report. 2:71-88.

NAS. 1980. National Academy of Sciences. Drinking Water and Health. Volume 3. National Academy Press. Washington, D.C. pp. 111-124.

Norppa, H., K. Hemminki, M. Sorsa and H. Vainio. 1981. Effect of monosubstituted epoxides on chromosome aberrations and SCE in cultured human lymphocytes. Mutat. Res. 91:423-250.

Picciano, D. 1979a. Cytogenic investigation of occupational exposure to epichlorohydrin. Mutat. Res. 66:169-173.

Picciano, D. 1979b. Faulty experimental design and underutilization of cytogenetic data. Benzene and epichlorohydrin. Ann. NY Acad. Sci. 329:321-327.

Pilny, M.K., T.S. Lederer, J.S. Murray, et al. 1979. Epichlorohydrin subchronic studies. IV. The effects of maternally inhaled epichlorohydrin on rat and rabbit embryonal and fetal development. Unpublished report. Toxicol. Res. Lab., Health Environ. Sci., Dow Chemical U.S.A., Midland, MI.

Quast, J.F., J.W. Henck, B.J. Pastma, D.J. Scheutz and M.J. McKenna. 1979. Epichlorohydrin subchronic studies. I. A 90-day inhalation study in laboratory rodents (Fischer 344 rats, Sprague-Dawley rats, and B6C3F$_1$ mice). Dow Chemical U.S.A., Midland, MI. 166 pp.

Rossi, A.M., D. Migliore, D. Lascialfari, I. Sbrana and N. Loprieno. 1983. Genotoxicity, metabolism, and blood kinetics of epichlorohydrin in mice. Mutat. Res. 118:213-226.

Smith, F.A., P.W. Langvardt and J.D. Young. 1979. Pharmacokinetics of epichlorohydrin (EPI) administered to rats by gavage or inhalation. Dow Chemical U.S.A., Toxicology Research Laboratory, Midland, MI. 52 pp.

Sram, R.J., M. Cerna and M. Kucerova. 1976. The genetic risk of epichlorohydrin as related to the occupational exposure. Biol. Zbl. 95:451-462.

Sram, R.J., Z. Zudova and N.P. Kuleshov. 1980. Cytogenic analysis of peripheral lymphocytes in workers occupationally exposed to epichlorohydrin. Mut. Res. 70:115-120.

Tsuchimoto, T., and B.E. Matter. 1981. Activity of coded compounds in the micronucleus test. In: Evaluation of Short-Term Tests for Carcinogens, F.J. Seeres and J. Ashby, eds. Elsevier/North Holland, Amsterdam. pp. 705-711.

U.S. EPA. 1984. U.S. Environmental Protection Agency. Health assessment document for epichlorohydrin. Final report. Office of Health and Environmental Assessment. Washington, D.C. EPA-600/8-83-032F.

U.S. EPA. 1985a. U.S. Environmental Protection Agency. Drinking water criteria document for epichlorohydrin. Final Draft. Office of Drinking Water. Washington, D.C. ECAD-CFN-413.

U.S. EPA. 1985b. U.S. Environmental Protection Agency. National primary drinking water regulations; Synthetic organic chemicals, inorganic chemicals and microorganisms; Proposed rule. Federal Register. 50(219):4693-47002. November 13.

U.S. EPA. 1985c. U.S. Environmental Protection Agency. Method 524.1. Volatile organic compounds in water by purge and trap gas chromatography/mass spectrometry. Environmental Monitoring and Support Laboratory, Cincinnati, Ohio 45268.

U.S. EPA. 1985d. U.S. Environmental Protection Agency. Technologies and costs for removal of organic chemicals from potable water supplies. Draft. Science and Technology Branch, CSD, ODW, Washington, D.C.

U.S. EPA. 1986. U.S. Environmental Protection Agency. Guidelines for carcinogenic risk assessment. Federal Register 51(185):33992-34003. September 24.

Van Duuren, B.L., C. Katz and B.M. Goldschmidt. 1972. Direct-acting alkylating carcinogens -- Chloro ethers and related compounds. Toxicol. Appl. Pharmacol. 22:279-280.

Van Duuren, B.L., B.M. Goldschmidt, C. Katz, I. Seidman and J.S. Paul. 1974. Carcinogenic activity of alkylating agents. J. Natl. Cancer Inst. 53:695-700.

Van Esch, G.J. 1981. Induction of preneoplastic lesions in the forestomach of rats after oral administration of 1-chloro-2,3-epoxypropane. I. Range finding studies. Prepared by Ryksinstitute Voor De Volksgezondheld Bilthoven Rapport nr. 627805 005.

Van Esch, G.J. 1982. Induction of preneoplastic lesions in the forestomach of rats after oral administration of 1-chloro-2,3-epoxypropane. II. Carcinogenicity study. Prepared by Ryksinstitute Voor De Volksgezondheld Bilthoven Rapport nr. 627805 005.

Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals. 2nd ed. Van Nostrand Reinhold Co., NY. pp. 611-613.

Wester, P.W., C.A. Van Der Heiden, A. Bisschop, and G.J. Van Esch. 1985. Carcinogenicity study with epichlorohydrin (CEP) by gavage in rats. Toxicol. 36:325-329.

White, A.D. 1980. *In vitro* induction of sister chromatid exchange in human lymphocytes by epichlorohydrin with and without metabolic activation. Mutat. Res. 78:171-176.

Wurgler, F.E., and U. Graf. 1981. Mutagenic activity of ten coded compounds in the *Drosophila* sex-linked recessive lethal assay. In: Evaluation of Short-Term Tests for Carcinogens, F.J. de Serres, ed. Elsevier/North Holland, Amsterdam. pp. 666-672.

# ETHYLBENZENE

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

## I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for One-day, Ten-day, Longer-term (approximately 7 years, or 10% of an individual's lifetime) and Lifetime exposures based on data describing noncarcinogenic end points of toxicity. Health Advisories do not quantitatively incorporate any potential carcinogenic risk from such exposure. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

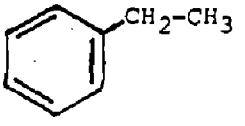
This Health Advisory is based on information presented in the Office of Drinking Water's Health Effects Criteria Document (CD) for Ethylbenzene (U.S. EPA, 1985a). The HA and CD formats are similar for easy reference. Individuals desiring further information on the toxicological data base or rationale for risk characterization should consult the CD. The CD is available for review at each EPA Regional Office of Drinking Water counterpart (e.g., Water Supply Branch or Drinking Water Branch), or for a fee from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Rd., Springfield, VA 22161, PB # 86-117835/AS. The toll-free number is (800) 336-4700; in the Washington, D.C. area: (703) 487-4650.

## II. GENERAL INFORMATION AND PROPERTIES (Verschueren, 1983; Amoore and Hautala, 1983)

Chemical Name Ethylbenzene

Cas No. 100-41-4

Chemical Structure




Synonyms

Phenyl ethane, ethylbenzol, EB

Uses

Styrene manufacture
Acetophenone manufacture
Solvent
Asphalt constituent
Naptha constituent

Properties

| | |
|---|---|
| Chemical Formula | $C_8H_{10}$ |
| Molecular Weight | 106.18 |
| Physical State (25°C) | Colorless liquid |
| Boiling Point | 136.2°C |
| Melting Point | -94.97°C |
| Density | -- |
| Vapor Pressure | 7 mm at 20°C |
| Water Solubility | 152 mg/L (at 20°C) |
| Log Octanol/Water Partition Coefficient | 3.15 |
| Taste Threshold (water) | 0.029 mg/L |
| Odor Threshold (water) | 0.029 mg/L |
| Odor Threshold (air) | 0.062 mg/L |
| Conversion Factor | -- |

Occurrence

- Ethylbenzene, a clear, flammable liquid found in gasoline, is produced commercially by the alkylation of benzene with ethylene. In 1982, the U.S. production of ethylbenzene totaled 3.3 million tons.

- Very little information is available on the occurrence of ethylbenzene in 12,000 drinking water supplies in the U.S. drawing water from surface rivers and streams. However, the testing of 945 ground water supplies has revealed that approximately 0.6 % contain ethylbenzene. The median concentration detected in "non random" segment of the study was 0.87 ug/L (Westrick et al., 1983).

## III. PHARMACOKINETICS

Absorption

- Data regarding the absorption of ethylbenzene from the gastrointestinal tract of humans following oral ingestion could not be located.

- Since approximately 90% of an oral dose of ethylbenzene (1.78 g/rabbit) is excreted as metabolites (El Masry et al., 1956), the chemical is readily absorbed in rabbits.

- For human volunteers exposed by inhalation to ethylbenzene for 8 hours at 100, 187, 200 or 370 $mg/m^3$, the average percent of vapor absorbed (measured spectrophotometrically) through the respiratory tract was 64% (Bardodej and Bardodejova, 1970).

- Absorption of an aqueous solution of ethylbenzene through human hand skin (109.3 to 113.9 mg/L for 1 to 2 hours) was equivalent to 118 $ug/cm^2/hour$ (Dutkiewicz and Tyras, 1967).

Distribution

- Following a 6-hour inhalation exposure at 1 $mg/m^3$, absorbed ethylbenzene is distributed throughout the body in rats. However, the highest levels were detected in the kidney, lung, adipose tissue, digestive tract and liver (Chin et al., 1980).

Metabolism

- After inhalation exposure, ethylbenzene undergoes rapid metabolism in humans, primarily to form mandelic acid and phenylglyoxylic acid. These two metabolites accounted for 64% and 25%, respectively, of the absorbed dose in humans (Bardodej and Bardodejova, 1970). Formation of minor metabolites including methylphenyl carbinol and 2-ethylphenol accounted for approximately 5% and 1%, respectively, in humans (Bardodej and Bardodejova, 1970; Angerer and Lehnert, 1979).

- The major metabolites formed in humans and rats are not the same. Mandelic acid and phenylglyoxylic acid constitute 64 and 25% of the metabolites in humans (Bardodej and Bardodejova, 1970), while in

rats, 1-phenylethanol (25%), benzoic acid (27%) and mandelic acid (25%) are the main metabolites (Engstrom, 1985).

Excretion

- Urinary excretion of metabolites by rabbits was reported to be complete within 24 hours after oral dosing with 1.78 grams/rabbit (El Masry et al., 1956).

- In humans, most of the inhaled dose was eliminated in the urine within 24 hours after exposure was terminated (Engstrom and Bjurstrom, 1978; Hagemann and Angerer, 1979).

## IV. HEALTH EFFECTS

### Humans

- In experiments with human volunteers, an 8-hour inhalation exposure to ethylbenzene at a concentration of 100 ppm (435 mg/$m^3$) did not result in adverse health effects (Bardodej and Bardodejova, 1970). Increasing this level (increase not specified) resulted in sleepiness, fatigue, headache and mild eye and respiratory irritation.

### Animals

#### Short-term Exposure

- Estimated acute $LD_{50}$ values of 3.5 g/kg to 5.46 g/kg were reported in rats (Wolf et al., 1956; Smyth et al., 1962).

- An acute dermal $LD_{50}$ value of 17.8 ml/kg (approximately 15,400 mg/kg) was reported in rabbits (Smyth et al., 1962).

- An inhalation exposure of 4,000 ppm (approximately 17,400 mg/$m^3$) for four hours was lethal to 3 of 6 rats (Smyth et al., 1962).

- During $LD_{50}$ studies systemic toxic effects were observed predominantly in the liver and kidney (Wolf et al., 1956) and central nervous system (Faustov, 1958).

- Other acute effects include irritation of the conjunctiva (Wolf et al., 1956) and slight necrosis of the cornea (Smyth et al., 1962).

#### Long-term Exposure

- Liver and kidney effects were observed in rats (10 females/dose) exposed orally to ethylbenzene in olive oil for six months (Wolf et al., 1956). Doses of 408 and 680 mg/kg/day caused increases in liver and kidney weights, and cloudiness and swelling of hepatocytes and renal tubular epithelium. No effects were observed in rats exposed to 13.6 and 136 mg/kg/day.

- No chronic exposure studies were identified in the available literature.

Reproductive Effects

- No studies on the effects of ethylbenzene on reproduction were located in the available literature.

Developmental Effects

- Ethylbenzene did not elicit embryotoxicity, fetotoxicity or teratogenicity in inhalation studies at concentrations up to 1,000 ppm (4,348 mg/$m^3$) in rats and rabbits for 6 to 7 hours/day on days 1 to 19 and 1 to 24 of gestation, respectively (Hardin et al., 1981).

- Female rats exposed at 1,000 ppm had increased liver, kidney and spleen weights suggestive of maternal toxicity. There was no maternal toxicity observed when the rats were exposed to 100 ppm of ethylbenzene. (Hardin et al., 1981).

Mutagenicity

- No mutagenic activity was detected in S. typhimurium strains TA98, TA100, TA1535, TA1537 following ethylbenzene exposure both with and without metabolic activation in plate assays at concentrations up to 3 mg/plate (Florin et al., 1980; Nestmann et al., 1980).

- Dean et al. (1985) reported that ethylbenzene (0.2 to 2,000 ug/plate) did not induce mutations in bacteria, gene conversion in yeast or chromosome damage in rat liver ($RL_4$) epithelial cells.

- In the Drosophila recessive lethal test, ethylbenzene did not increase the frequency of recessive lethals (Donner et al., 1979).

Carcinogenicity

- Pertinent data on the carcinogenic potential of ethylbenzene were not identified in the available literature. An NCI bioassay is in the planning stage.

## V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for One-day, Ten-day, Longer-term (approximately 7 years) and Lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(NOAEL \text{ or } LOAEL) \times (BW)}{(UF) \times (\_\_\_ \text{ L/day})} = \_\_\_ \text{ mg/L } (\_\_\_ \text{ ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect-Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100 or 1,000), in accordance with NAS/ODW guidelines.

L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

No adequate dose-response data exist using the oral route of exposure from which to calculate a One-day Health Advisory. Therefore, the derivation of the one-day level is based upon a 100 ppm (435 mg/m$^3$) NOAEL identified in 18 human male volunteers following a single 8-hour inhalation exposure as conducted by Bardodej and Bardodejova (1970). An inhalation absorption efficiency of 64% is used, based on data from that study (Bardodej and Bardodejova, 1970).

The total absorbed dose and the One-day HA for a 10 kg child are calculated as follows:

Step 1: Determination of Total Absorbed Dose (TAD)

$$TAD = \frac{(435\ mg/m^3)\ (8\ m^3/day)\ (0.64)}{(70\ kg)} = 31.8\ mg/kg/day$$

Step 2: Determination of One-day HA

$$\text{One-day HA} = \frac{(31.8\ mg/kg/day)\ (10\ kg)}{(10)\ (1\ L/day)} = 32\ mg/L\ \ (32000\ ug/L)$$

where:

435 mg/m$^3$ = NOAEL based on absence of effects in humans following inhalation exposure.

8 m$^3$/day = assumed volume of air inhaled per daily 8-hour exposure.

0.64 = absorption efficiency reported by Bardodej and Bardodejova (1970).

70 kg = assumed body weight of an adult.

10 kg = assumed body weight of a child.

2 L/day = assumed daily water consumption of an adult.

1 L/day = assumed daily water consumption of a child.

10 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from a human study.

Ten-day Health Advisory

Because of the lack of appropriate exposure duration data, the ten-day HA will be calculated from the One-day HA. The One-day HA will be divided by 10 to give estimated Ten-day HA values. The resulting Ten-day HA for a child is as follows:

$$\text{Ten-day HA} = \frac{32 \text{ mg/L}}{10} = 3.2 \text{ mg/L } (3{,}200 \text{ ug/L})$$

Longer-term Health Advisory

There are insufficient data to calculate a Longer-term HA. It is recommended that the DWEL, adjusted for 10 kg, be used as a conservative estimate for a longer-term exposure.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed for synthetic organic chemicals and a value of 10% is assumed for inorganic chemicals. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

The study by Wolf et al. (1956) has been determined to be the most appropriate for derivation of the Lifetime Health Advisory. Rats were administered oral gavage doses of 13.6, 136, 408 or 680 mg/kg/day ethylbenzene in olive oil for 130 days of the 182-day test period. A vehicle control of olive oil (2.5 ml) was run concurrently. No effects were noted in groups of rats exposed at 13.6 and 136 mg/kg/day. Increases in liver and kidney weights were reported following oral administration of 408 or 680 mg/kg/day. There were also slight histopathological changes at these dose levels. These included cloudiness and swelling of hepatocytes and renal tubular epithelium. From these results, a NOAEL of 136 mg/kg/day was identified.

A Drinking Water Equivalent Level (DWEL) and Lifetime Health Advisory are calculated as follows:

Step 1: Determination of the Reference Dose (RfD)

$$RfD = \frac{(136\ mg/kg/day)(5)}{(1,000)\quad(7)} = 0.097\ mg/kg/day$$

where:

136 mg/kg/day = NOAEL for absence of renal and hepatic effects in rats exposed for 130 days.

5/7 = conversion of 5 days/week dosing regimen to continuous 7 days/week exposure pattern.

1,000 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study of less-than-lifetime duration.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$DWEL = \frac{(0.097\ mg/kg/day)(70\ kg)}{(2\ L/day)} = 3.4\ mg/L\ (3,400\ ug/L)$$

where:

0.097 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

Lifetime HA = (3.4 mg/L) (20%) = 0.68 mg/L

where:

3.4 mg/L = DWEL.

20% = assumed relative source contribution from water.

Evaluation of Carcinogenic Potential

- Because of the lack of data, an assessment of the carcinogenic risk of ethylbenzene is not possible at this time.
- The International Agency for Research on Cancer has not classified ethylbenzene in any of its categories of carcinogenic potential.
- Applying the criteria described in EPA's guidelines for assessment of carcinogen risk (U.S. EPA, 1986), ethylbenzene is classified in Group D: not classified. This category is for agents with inadequate animal evidence of carcinogenicity.

## VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- The American Conference of Government Industrial Hygienists has recommended an occupational standard (TWA) in air and TLV of 100 ppm (435 mg/m$^3$; ACGIH, 1980).

- EPA/ODW has proposed a RMCL of 0.68 mg/L (U.S. EPA, 1985e).

## VII. ANALYTICAL METHODS

- Analysis of ethylbenzene is by a purge-and-trap gas chromatographic procedure used for the determination of volatile aromatic organic compounds in water (U.S. EPA, 1985b). This method calls for the bubbling of an inert gas through the sample and trapping ethylbenzene on an adsorbant material. The adsorbant material is heated to drive off ethylbenzene onto a gas chromatographic column. The gas chromatograph is temperature programmed to separate the method analytes which are then detected by the photoionization detector. This method is applicable to the measurement of ethylbenzene over a concentration range of 0.02 to 1500 ug/L. Confirmatory analysis for benzene is by mass spectrometry (U.S. EPA, 1985c). The detection limit for confirmation by mass spectrometry is 0.2 ug/L.

## VIII. TREATMENT TECHNOLOGIES

- Aeration appears to offer the best potential for removing ethylbenzene from contaminated water. Ethylbenzene has a high Henry's Law Constant of 35 atm (U.S. EPA, 1985d).

- In an actual packed aeration column (PAC) pilot testing program, ethylbenzene removal efficiencies ranged from 71.8 to >99.8% (U.S. EPA, 1985d). The column used had a one foot diameter and was packed with Tripack packing material (#2). Influent concentrations of ethylbenzene ranged from <1 to 200 ug/L. Air-to-water ratios varied from 10:1 to 126:1. Liquid loading rates varied from 12.7 to 50.9 gpm/ft$^2$. Ambient water temperature was 70°F. Removal efficiencies were >90% for all test runs but one. In this single exception, an efficiency of 71.8% was obtained. In this test run the ethylbenzene concentration was high (200 ppb) and the air-to-water ratio low - 10:1 (U.S. EPA, 1985d).

- A field test of PAC also was conducted on water contaminated by a gasoline spill (Cummins, 1985). Several benzene derivatives including ethylbenzene were found in this water. The aeration column was 7.3 x 0.6 m and was packed to 5.5 m with 1 inch plastic saddles. Air-to-water ratios of from 8:1 to 88:1 were used. Ethylbenzene was decreased to below detection (<0.5 ug/L) whenever the air-to-water ratios were 20:1 or greater. Ethylbenzene was detected if lower air-to-water ratios were used. A total of 75 samples were tested.

- Decarbonators, which can be considered as modified aerators, were used to remove synthetic organic contaminants including ethylbenzene at Water Factory 21 (U.S. EPA, 1985d). The air-to-water ratio was 22:1. Levels of influent ethylbenzene contamination were 0.067 and 0.23 ug/L. The decarbonators removed 39.8 and 56.51% of the ethylbenzene, respectively.

- Granular activated carbon (GAC) also is at least partially effective in the removal of ethylbenzene from solution by adsorption. Over two separate trial periods, GAC was found to remove some of the ethylbenzene from contaminated drinking water. At an influent concentration of 0.06 ug/L, 45% of the ethylbenzene was removed. When the influent was 0.07 ug/L, 17% was removed (McCarty et al., 1979).

- Application of PAC for ethylbenzene removal was tested at the Sunny Isles Water Treatment Plant (Florida) (U.S. EPA, 1985d). For a 14-month period, 7.1 mg/L PAC was added to the water at the wellfield. For 3 of 5 samples analyzed, >99% of the ethylbenzene was removed; for 2 samples, the removal rate was only 33%.

- In one study, conventional treatment was found to reduce the ethylbenzene in water containing 0.7 ug/L by 43% (U.S. EPA, 1985d).

## IX. REFERENCES

ACGIH. 1980. American Conference of Industrial Government Hygienists. Ethylbenzene. Documentation of the Threshold Limit Values. 4th ed., p. 176.

Amoore, J.E., and E. Hautala. 1983. Odor as an aid to chemical safety; odor threshold compared with Threshold Limit Values and volatilities for 214 industrial chemicals in air and water dilution. J. Appl. Toxicol. 3:272-290.

Angerer, J., and G. Lehnert. 1979. Occupational chronic exposure to solvents. VIII. Phenolic compounds: Metabolites of alkylbenzenes in man: Simultaneous exposure to ethylbenzene and xylenes. Int. Arch. Occup. Environ. Health. 43:145-150.

Bardodej, Z., and E. Bardodejova. 1970. Biotransformation of ethylbenzene, styrene and alpha-methylstyrene in man. Am. Ind. Hyg. Assoc. J. 31:206-209.

Chin, B.H., J.A. McKelvey, T.R. Tyler, L.J. Calisti, S.J. Kozbelt and L.J. Sullivan. 1980. Absorption, distribution and excretion of ethylbenzene, ethylcyclohexane and methylethylbenzene isomers in rats. Bull. Environ. Contam. Toxicol. 24:477-483.

Cummins, M.D. 1985. Field evaluation of packed column stripping, Pastrap, LA. U.S. Environmental Protection Agency, Office of Drinking Water.

Dean, B.J., T.M. Brooks, G. Hodson-Walker and D.H. Hutson. 1985. Genetic toxicology testing of 41 industrial chemicals. Mutat. Res. 153:57-77.

Donner, M., J. Maki-Paakkanen, N. Norppa, M. Sorsa and H. Vaino. 1979. Genetic toxicology of xylenes. Mutat. Res. 74:171-172.

Dutkiewicz, T., and H. Tyras. 1967. Study of the skin absorption of ethylbenzene in man. Br. J. Ind. Med. 24:330-332.

El Masry, A.M., J.N. Smith and R.T. Williams. 1956. The metabolism of alkylbenzenes: n-Propylbenzene and n-butylbenzene with further observations on ethylbenzene. Biochem. J. 64:50-56.

Engstrom, J., and R. Bjurstrom. 1978. Exposure to xylene and ethylbenzene. II. Concentration in subcutaneous adipose tissue. Scand. J. Work Environ. Health. 4:195-203.

Engstrom, K.L. 1984. Metabolism of inhaled ethylbenzene in rats. Scand. J. Work Environ. Hlth. 10:83-87.

Faustov, A.S. 1958. Toxicity of aromatic hydrocarbons. I. Comparative toxicity of some aromatic hydrocarbons. II. Some problems of the toxic-hygiene properties of aromatic hydrocarbons. Tr. Voronezh. Gos. Med. Inst. 35:247-255; 257-262. (Chem. Abstr. 54:25279d)

Florin, I., L. Rutberg, M. Curvall and C.R. Enzell. 1980. Screening of tobacco smoke constituents for mutagenicity using the Ames test. Toxicology. 18:219-232.

Hagemann, J., and J. Angerer. 1979. Biological monitoring in occupational ethylbenzene loading. Kolloq., Ber. Jahrestag. Dtsch. Ges. Arbeitsmed., 19th. pp. 421-425. (Chem. Abstr. 94:196880)

Hardin, B.D., G.P. Bond, M.R. Sikov, F.D. Andrew, R.P. Beliles and R.W. Niemeier. 1981. Testing of selected workplace chemicals for teratogenic potential. Scand. J. Work Environ. Health. 7(Suppl. 4):66-75.

Kiese, M., and W. Lenk. 1973. w- and (w-1)-Hydroxylation of 4-chloropropionanilide by rabbits and rabbit liver microsomes. Biochem. Pharmacol. 22:2565-2574.

McCarty, P.L., D. Argo and M. Reinhard. 1979. Operational experiences with activated carbon adsorbers at Water Factory 21. JAWWA. 11:683-689.

Mihail, G., A. Zlavog, V. Anghelache and J. Bodnar. 1972. Serum ornithine carbamoyltransferase, test for evaluating hepatic alterations caused by some industrial toxic substances. Igiena. 21:267-276. (Chem. Abstr. 79:1036)

NCI. 1983. National Cancer Institute. National Toxicology Program -- Toxicology Testing Program. Chemicals on Standard Protocol: Management Status. June 15, 1983.

Nestmann, E.R., E.G-H. Lee, T.I. Matula, G.R. Douglas and J.C. Mueller. 1980. Mutagenicity of constituents identified in pulp and paper mill effluents using the Salmonella/mammalian-microsome assay. Mutat. Res. 79:203-212.

Smyth, H.F., C.P. Carpenter, C.S. Weil, U.C. Pozzani and J.A. Stregel. 1962. Range-finding toxicity data. List VI. Am. Ind. Hyg. Assoc. J. 23:95-107.

U.S. EPA. 1985a. U.S. Environmental Protection Agency. Draft. Drinking water criteria document for ethylbenzene. Office of Drinking Water.

U.S. EPA. 1985b. U.S. Environmental Protection Agency. Method 503.1. Volatile aromatic organic compounds in water by purge and trap gas chromatography. Environmental Monitoring and Support Laboratory, Cincinnati, Ohio 45268.

U.S. EPA. 1985c. U.S. Environmental Protection Agency. Method 524.1. Volatile organic compounds in water by purge and trap gas chromatography/mass spectrometry. Environmental Monitoring and Support Laboratory, Cincinnati, Ohio 45268.

U.S. EPA. 1985d. U.S. Environmental Protection Agency. (Draft) Technologies and costs for the removal of synthetic organic chemicals from potable water supplies. Science and Technology Branch, CSD, ODW, Washington, D.C.

U.S. EPA. 1985e. U.S. Environmental Protection Agency. Proposed RMCL for SOCs, IOCs and Microbials. Federal Register. 50(219):46936-47023. November 13.

U.S. EPA. 1986. U.S. Environmental Protection Agency. Guidelines for carcinogen risk assesment. Federal Register. 51(185):33992-34003. September 24.

Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals. 2nd ed. Van Nostrand Reinhold Company, NY. pp. 628-630.

Vinokurova, M.I. 1970. Combined effect of styrene, butadiene and ethylbenzene on the functional indexes of the cardiovascular system. Tr. Azerb. Nauchno.-Issled. Inst. Gig. Tr. Prof. Zabol. 4:21-26. (Chem. Abstr. 81:140347)

Westrick, J.J., J.W. Mello and R.F. Thomas. 1983. The ground water supply survey: Summary of volatile organic contaminant occurrence data. EPA-ODW/TSD, Cincinnati, Ohio.

Wolf, M.A., V.K. Rowe, D.D. McCollister, R.L. Hollingsworth and F. Oyen. 1956. Toxicological studies of certain alkylated benzenes and benzene. Arch. Ind. Health. 14:387-398.

# ETHYLENE GLYCOL

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

## I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

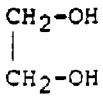
Health Advisories are developed for One-day, Ten-day, Longer-term (approximately 7 years, or 10% of an individual's lifetime) and Lifetime exposures based on data describing noncarcinogenic end points of toxicity. Health Advisories do not quantitatively incorporate any potential carcinogenic risk from such exposure. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

This Health Advisory is based upon information presented in the Office of Drinking Water's Health Advisory Document for Ethylene Glycol (U.S. EPA, 1981). The 1981 Health Advisory is available for review at each EPA Regional Office of Drinking Water counterpart (e.g., Water Supply Branch or Drinking Water Branch).

## II. GENERAL INFORMATION AND PROPERTIES

CAS No. 107-21-1

Structural Formula



Synonyms

1,2-ethanediol

Uses

- Antifreeze in cooling and heating systems, industrial humectant, ingredient of electrolytic condensers, solvent in paint and plastic industries and in the formulation of ink.

Properties (Verschueren, 1977; Windholz, 1983)

| | |
|---|---|
| Chemical Formula | $C_2H_6O_2$ |
| Molecular Weight | 62.1 |
| Physical State | colorless liquid |
| Boiling Point | 197.6°C |
| Melting Point | -12.6°C |
| Density | -- |
| Vapor Pressure | 0.05 mm (20°C) |
| Specific Gravity | 1.113 (20°C) |
| Water Solubility | completely miscible |
| Log Octanol/Water Partition Coefficient | -- |
| Taste Threshold | -- |
| Odor Threshold | -- |
| Conversion Factor | |

Occurrence

- In 1983, 4.5 billion pounds of ethylene glycol were produced (U.S. ITC, 1984). The majority of ethylene glycol is used consumptively (CEH, 1982).

- Releases of ethylene glycol to the environment can occur during production, use and release. The major source of release is from the disposal of used antifreeze. Releases of ethylene glycol occur

largely to water and land during disposal; releases to the atmosphere are limited by ethlyene glycol's low vapor pressure. Releases of ethylene glycol to the environment are dispersed widely.

° Ethylene glycol in the environment rapidly partitions to water due to its solubility and low vapor pressure. Releases to surface water are biodegraded rapidly. Releases of ethylene glycol to land have resulted in the contamination of ground water (U.S. EPA, 1980). Based upon its physical properties, ethylene glycol is not expected to bioaccumulate.

° There is little information on the presence of ethylene glycol in water, food and air. Because of its rapid degradation in the environment, ethylene glycol is not expected to be a common contaminant in air, food or surface water; however, contamination of ground water is possible. A more likely source of ethylene glycol exposure is the inadvertant contamination of drinking water from the misuse of antifreeze.

## III. PHARMACOKINETICS

### Absorption

° Ethylene glycol is absorbed rapidly after ingestion. Reif (1950), on three separate occasions, drank pure ethylene glycol in 100 ml of water. Amounts consumed were 5.5, 11.0 and 13.2 g, which would correspond to 78.5, 157 and 188.6 mg/kg, respectively, assuming a body weight of 70 kg for an adult. Ethylene glycol was recovered in the urine at 24 to 31% of the administered dose within 24 to 48 hours. Oxalic acid concentrations in the urine were higher than normal with a peak on the fourth day.

### Metabolism

° Gessner et al. (1961) studied the fate of ethylene glycol in Chinchilla rabbits, albino rats, guinea pigs and cats. Doses up to 10.0 g/kg of ethylene glycol ($^{14}C_2$) were given orally or subcutaneously, but most of the data were derived from animals receiving 0.1 to 2.0 g/kg (100 to 2000 mg/kg). At low doses (0.124 g/kg), rabbits exhaled about 60% of the dose as $CO_2$ and excreted 20% of it in the urine in a time period of 80 to 100 hours; 50% of the dose was exhaled as $CO_2$ in the first 18 hours after dosing. In one set of experiments with rabbits, urine contained ethylene glycol (10.3%), oxalic acid (0.01%) and urea (0.65%). Nearly one-half of the radioactivity was eliminated in the urine when the dose was increased to 2.5 to 5.0 g/kg. The increase in the radioactivity in the urine was attributed by the authors to unmetabolized ethylene glycol.

° In an *in vitro* experiment utilizing rat liver slices, Gessner et al. (1961) identified the intermediate metabolites of ethylene glycol ($^{14}C$) as glycoaldehyde and glyoxylic acid.

## IV. HEALTH EFFECTS

### Humans

- A controlled study of human exposure to ethylene glycol was reported by Reif (1950). The investigator drank 5.5, 11.0 and 13.2 g of ethylene glycol with 100 ml of water on separate occasions and collected his urine for about 14 days after each trial to quantify ethylene glycol and oxalic acid levels. Assuming a body weight of 70 kg, doses consumed would be 78.5, 157.0 and 188.6 mg/kg. Reif found that 24 to 31% of the ethylene glycol was excreted in the urine in an unchanged form within 24 to 36 hours, while urinary oxalic acid levels were elevated for 8 to 12 days. No oxalate crystals were found in the urine, and he reported no impairment of health from these doses.

- Ethylene glycol ingestion by humans results in a variety of CNS/behavioral effects including numbness, visual disturbances, lightheadedness, headache and lethargy (Berman et al., 1957), with doses estimated at 1,000 mg/kg. After ingesting a dose of approximately 3,000 mg/kg, patients exhibited ataxia, somnolence and slurred speech, followed by disorientation with a mental status alternating between stupor and agitation (Parry and Wallach, 1974). At doses which were eventually fatal, coma developed after a period of restlessness, delerium, convulsive seizures and a loss of reflexes (Pons and Custer, 1946). These same symptoms of ataxia, incoordination, somnolence, coma and eventual death have been reported in dogs (Nunamaker et al., 1971).

### Animals

#### Short-term Exposure

- An extensive series of dose-mortality trials were conducted by Laug et al. (1939) for several species of laboratory animals. Mice, rats and guinea pigs were tested by administering single doses of ethylene glycol by stomach tubes. Calculated $LD_{50}$ values were: mice, 13.1 ml/kg (14,253 mg/kg); rats, 5.5 ml/kg (5,984 mg/kg); guinea pigs, 7.35 ml/kg (7,997 mg/kg). It was noted that the animals showed signs of weakness and lack of motor coordination shortly after receiving doses of ethylene glycol. Prostration and coma were later symptoms, followed by death in 18 hours to 6 days. Congestion of the lungs, bladders filled with protein rich urine, hydropic degeneration of the cells lining the cortical convoluted tubules, and focal necrosis of the liver were nearly always found.

- NIOSH (1983-84) lists the following oral $LD_{50}$ data for ethylene glycol: rat (4,700 mg/kg), mouse (7,500 mg/kg), guinea pig (6,610 mg/kg).

#### Long-term Exposure

- In a study by Blood et al. (1962) ethylene glycol was fed to two male rhesus monkeys and one female Rhesus monkey for three years. Ethylene

glycol was incorporated in the monkey chow and made available to the animals on an ad lib basis. The animals consumed 200 to 250 g of chow/day. From the given body weights of 15.45 and 7.25 kg for the males and 7.4 kg for the female, the amount of ethylene glycol consumed would range from approximately 25 to 69 mg/kg/day for males and 135 to 170 mg/kg/day for females. Prior to the start of the experiment, and at quarterly intervals, the animals were x-rayed to detect the possible appearance of calcification of the urinary tract. At the time of sacrifice all abdominal and endocrine organs, as well as a bone marrow sample, were examined histopathologically. No abnormal calcium deposits were demonstrated by x-ray; microscopic examinations of tissues were unremarkable. The authors concluded that this species was capable of handling the administered ethylene glycol without any discernible toxic effects.

- In a study by Blood (1965), ethylene glycol was fed to groups of 16 male and 16 female Sprague-Dawley rats for 2 years at concentrations of 0.0, 0.1, 0.2, 0.5, 1 or 4% by weight in the diet (corresponds to approximately 0, 50, 100, 250, 500 or 2,000 mg/kg/day (Lehman, 1959)). Increased mortality appeared in males receiving the 1 and 4% diets. Calcification of the kidneys and oxalate-containing calculi were observed in males at doses of 0.5% and greater. Females were similarly affected at the 1% level and greater for calcification and at the 4% level for calculi. Increased water consumption and protein in the urine was evident in males at both 1 and 4% and in females at 4% diet levels. A probable NOAEL of 0.2% was determined (approximately 100 mg/kg/day) and a LOAEL of 0.5% (approximately 250 mg/kg/day).

- A recently completed toxicity study in groups of 130 Fischer 344 rats per sex per level fed ethylene glycol at dosages of approximately 1.0, 0.2, 0.04 or 0.0 g/kg/day for up to 2 years (DePass et al., 1986a) identified a NOAEL of 0.04 g/kg/day (40 mg/kg/day). The mortality rate was increased in the high-dosed males with all dead by 475 days into the study. Oxalate nephrosis was the primary cause of death. Other effects noted in the high-dosed males only included: reduced body weight gain, increased water intake, increased BUN and creatinine, reduced RBCs, hematocrit and hemoglobin, increased neutrophil count, increased urine volume and reduced urinary specific gravity and pH. Additionally, all high-dosed rats had increased kidney weights and urinary calcium oxalate crystals. High-dosed females also showed the presence of uric acid crystals in the urine. Histopathological changes in the high-dosed males included tubular cell hyperplasia, tubular dilation and peritubular nephritis. At the next lower dose, 0.2 g/kg/day, an increase in incidence and amount of calcium oxalate crystals was evident in both sexes. It is apparent in this study that the male rat is more sensitive to the effects of ethylene glycol.

- These same authors treated 80 CD-1 mice per sex per level to the same concentrations of ethylene glycol in the diet and found no clinical or histopathological evidence of toxicity attributable to its intake.

Reproductive Effects

- Timed-pregnant CD rats were dosed by gavage on days 6 through 15 of gestation with ethylene glycol at 0, 1,250, 2,500 or 5,000 mg/kg/day (Price et al., 1985). No maternal deaths or distinctive clinical signs were noted. Significant decreases in maternal weight were dose-related in rats at all levels. Other significant changes included reduced gravid uterus weight, corrected gestational weight gain and reduced fetal body weight per litter at the mid and high doses and increases in post-implantation losses per litter, significant only at the high dose. This study established a LOAEL of 1,250 mg/kg/day for maternal effects and a NOAEL of 1,250 mg/kg/day for fetal effects.

- Timed-pregnant CD-1 mice were dosed by gavage on days 6 through 15 of gestation with ethylene glycol at 0, 750, 1,500 or 3,000 mg/kg/day (Price et al., 1985). No maternal deaths or distinctive clinical signs were noted. Significant decreases in maternal weight, gravid uterus weight and corrected gestational weight gain were evident at the mid and high doses. Fetal body weight per litter was also significantly reduced at all doses. This study established a NOAEL of 750 mg/kg/day for maternal effects and a LOAEL of 750 mg/kg/day for fetal effects.

- In a continuous breeding study, Lamb et al. (1985) dosed CD-1 mice with ethylene glycol by continuous administration in drinking water at 0.0, 0.25, 0.5 or 1%. Slight but statistically significant decreases were found in the numbers of litters per fertile pair ($p < 0.01$), live pups per litter ($p < 0.05$) and mean live pup weight ($p < 0.01$) at the 1% level when compared to $F_0$ controls. No clinical signs of toxicity or significant adverse effects on body weight or water consumption were seen in this study but two deaths at the 0.5% level may have been related to oxalate crystal deposition. This study established a NOAEL for reproductive effects of 0.5% (w/v) in drinking water. (Between days 98 and 105 on the study, this level corresponded to an average daily intake of 0.84 g/kg.)

- In a three-generation reproduction study, DePass et al. (1986b) fed ethylene glycol to Fischer 344 rats at levels of approximately 1.0, 0.2, 0.04 or 0.0 g/kg/day. No evidence of reduced fertility or increased fetal death was observed in any groups receiving the test diet. This study established a NOAEL for maternal and fetal effects at 1,000 mg/kg/day (highest dose tested).

Developmental Effects

- Lamb et al. (1985), in a continuous breeding study using CD-1 mice, administered ethylene glycol on a continuous basis for 126 days at levels of 0.0, 0.25, 0.5 or 1% in drinking water. The final offspring of these continuously bred mice were examined and the authors noted facial anomalies in a number of the offspring of the high-dosed mice. Examination for skeletal effects demonstrated a pattern including reduction in size of the bones in the skull, fused ribs and abnormally

shaped sternabrae and vertebrae. No similar findings were noted at the two lower dose levels. This study established a NOAEL of 0.5% (w/v) in drinking water for developmental effects in mice. (Between days 98 and 105, the average daily intake corresponded to approximately 840 mg/kg for the parental generation.)

- Administration of ethylene glycol by gavage on days 6 through 15 of gestation at levels of 0, 1,250, 2,500 or 5,000 mg/kg/day in rats and 0, 750, 1,500 or 3,000 mg/kg/day in mice resulted in significant increases in the percentage of malformed live fetuses per litter and/or the percent of litters with malformed fetuses at all dose levels with >95% of the litters affected at the high dose for both species. The most common malformations included craniofacial and neural tube closure defects and axial skeletal hyperplasia in both species (Price et al., 1985). This study established a LOAEL of approximately 1,250 mg/kg/day in rats and 750 mg/kg/day in mice (the lowest levels fed).

Mutagenicity

- In a dominant lethal mutagenesis study in rats, DePass et al. (1986b) bred at weekly intervals the $F_2$ males (fed ethylene glycol in the diet at 1.0, 0.2, 0.4 or 0.0 g/kg/day) from a three-generation reproduction study to 3 consecutive lots of untreated females. No evidence of reduced fertility or increased fetal death was observed in any of the groups receiving ethylene glycol. This study established a NOAEL for mutagenic effects at 1,000 mg/kg/day (highest dose tested).

- Ethylene glycol demonstrated no significant mutagenic activity in the Salmonella mutagenicity (Ames) test with or without microsomal activation (Clark et al., 1979).

Carcinogenicity

- No evidence of an oncogenic effect of ethylene glycol in 80 CD-1 mice per sex per level or 130 Fischer 344 rats per sex per level was seen when fed in the diet at approximately 1.0, 0.2, 0.04 or 0.0 g/kg/day for 24 months. Mortality of the high-dosed male rats in this study was 100% after 475 days of feeding. Death was attributed to oxalate nephrosis (DePass et al., 1986a).

- In studies designed to determine the toxic and carcinogenic potential of several biological preservatives, ethylene glycol was administered subcutaneously at 5 dose levels to groups of 20 weanling Fischer 344 rats (Mason et al., 1971). The $LD_{50}$ for a single injection was 5,300 mg/kg. When given subcutaneously, twice weekly for four weeks, the maximum tolerated daily dose was found to be lower than 1,700 mg/kg (total dose of 13,600 mg/kg). In a long-term study, 4 groups of 80, 60, 40 and 20 rats were injected subcutaneously twice weekly for 52 weeks with 1,000, 300, 100 and 30 mg/kg, respectively. Animals were observed for an additional six months following treatment. In these animals, there was no evidence of ethylene glycol toxicity based on survival time, weight gain and drug related organ pathology.

## V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for One-day, Ten-day, Longer-term (approximately 7 years) and Lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(NOAEL \text{ or } LOAEL) \times (BW)}{(UF) \times (\_\_\_ \text{ L/day})} = \_\_\_ \text{ mg/L } (\_\_\_ \text{ ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect-Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100 or 1,000), in accordance with NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

### One-day Health Advisory

Data from the study of Reif (1950) were used to identify an oral NOAEL in humans. This investigator drank a 188.6 mg/kg dose of ethylene glycol with no discernable effects. Thus, a One-day HA for children exposed to ethylene glycol in drinking water may be calculated as follows:

For a child:

$$\text{One-day HA} = \frac{(188.6 \text{ mg/kg/day})(10 \text{ kg})}{(100)\ (1 \text{ L/day})} = 18.86 \text{ mg/L } (19{,}000 \text{ ug/L})$$

where:

188.6 mg/kg/day = NOAEL in humans consuming up to this dose in water.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from a human study. An additional factor of 10 has been added for a study with only one subject.

1 L/day = assumed daily water consumption of a child.

### Ten-day Health Advisory

There are not sufficient data to calculate a Ten-day Health Advisory. The Longer-term HA of 5.5 mg/L for the 10 kg child can serve as a conservative

estimate of an exposure which would be considered adequately protective over a ten-day exposure period.

Longer-term Health Advisory

Exposure of male and female Rhesus monkeys to 55 to 170 mg/kg/day ethylene glycol in the diet for three years caused no adverse response (Blood et al., 1962). A Longer-term HA based on these data is calculated as follows:

For a 10-kg child:

$$\text{Longer-term HA} = \frac{(55 \text{ mg/kg/day})\ (10 \text{ kg})}{(100)\ (1 \text{ L/day})} = 5.5 \text{ mg/L } (5'500 \text{ ug/L})$$

where:

55 mg/kg/day = NOAEL, based on absence of toxic signs in the monkey.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

For a 70-kg adult:

$$\text{Longer-term HA} = \frac{(55 \text{ mg/kg/day})\ (70 \text{ kg})}{(100)\ (2 \text{ L/day})} = 19.25 \text{ mg/L } (19,250 \text{ ug/L})$$

where:

55 mg/kg/day = NOAEL, based on absence of toxic signs in the monkey.

70 kg = assumed body weight of an adult.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

2 L/day = assumed daily water consumption of an adult.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking

water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed for synthetic organic chemicals and a value of 10% is assumed for inorganic chemicals. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

The study of Blood (1965) is considered most appropriate for calculating a Lifetime Health Advisory. In this study rats were fed ethylene glycol in the diet at concentrations of 0.0, 0.1, 0.2, 0.5, 1, or 4% (approximately 0, 50, 100, 250, 500 or 2,000 mg/kg/day according to Lehman, 1959) for up to two years. This study identified a NOAEL of 0.2% (100 mg/kg/day) primarily for kidney effects in rats. Using this NOAEL, the Lifetime HA is calculated as follows:

Step 1: Determination of the Reference Dose (RfD)

$$RfD = \frac{(100\ mg/kg/day)}{(100)} = 1\ mg/kg/day$$

where:

100 mg/kg/day = NOAEL for kidney effects in rats.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$DWEL = \frac{(1\ mg/kg/day)\ (70\ kg)}{(2\ L/day)} = 35\ mg/L\ (35{,}000\ ug/L)$$

where:

1 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

Lifetime HA = (35 mg/L) (20%) = 7 mg/L (7,000 ug/L)

where:

35 mg/L = DWEL.

20% = assumed relative source contribution from water.

Evaluation of Carcinogenic Potential

- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986), ethylene glycol may be classified in Group D: Not classified. This category is for agents with inadequate animal evidence of carcinogenicity. The study by DePass et al. (1986a) was not a definitive indicator for carcinogenicity. The study indicated a difference in time to detection of lymphocarcinomas in the female rat. The incidence of this tumor type was not significantly different.

## VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- ACGIH (1984) has proposed a ceiling limit of 50 ppm ( 125 $mg/m^3$) for vapor and mist to minimize irritation of respiratory passages.

## VII. ANALYTICAL METHODS

- There is no standardized method for the determination of ethylene glycol in drinking water samples. A procedure has been developed (Hartman and Bowman, 1977) to determine the presence of ethylene glycol in drugs and pharmaceutical formulations at concentration levels of 5-200 mg/L. This procedure is based on direct aqueous injection-gas chromatography of samples. It is probable that this procedure also applies to drinking water samples at concentration levels of at least 5 mg/L.

## VIII. TREATMENT TECHNOLOGIES

- Ethylene glycol is completely miscible with water (Windholz, 1983) and has a low vapor pressure of 1 mmHg at 53°C (CRC Handbook of Chemistry and Physics, 1982). These two factors make it impractical to consider aeration as a form of removal. Treatment with activated carbon does not remove much of this compound from solution either. The adsorbability of ethylene glycol is only 0.0136 mg/g carbon with only 6.8% ethylene glycol retention (Veschueren, 1977). No information was found on the removal of this compound from drinking water using other techniques.

- Ethylene glycol may contaminate drinking water due to misapplication of the chemical as an antifreeze in potable water systems or through crossconnections with non-potable fire protection or heating/cooling systems. In these cases vigorous flushing of the contaminated components of the distribution system should be sufficient.

## IX. REFERENCES

ACGIH. 1984. American Conference of Governmental Industrial Hygienists. Documentation of the threshold limit values. 4th ed. 1980-1984 Supplement. pp. 182-183.

Berman, L.B., G.E. Schreiner and J. Feys. 1957. The nephrotoxic lesion of ethylene glycol. Ann. Int. Med. 46:611-619.

Blood, F.R., G.A. Elliott and M.S. Wright. 1962. Chronic toxicity of ethylene glycol in the monkey. Toxicol. Appl. Pharmacol. 4:489-491.

Blood, F.R. 1965. Chronic toxicity of ethylene glycol in the rat. Fd. Cosmet. Toxicol. 3:229-234.

CEH. 1983. Chemical Economics Handbook. Ethylene Glycol. 652.5030. Stanford Research Institute, Menlo Park, California.

Clark, C.R., T.C. Marshall, B.S. Merickel, A. Sanches, D.G. Brownstein and C.H. Hobbs. 1979. Toxicological assessment of heat transfer fluids proposed for use in solar energy applications. Toxicol. Appl. Pharmacol. 51:529-535.

CRC Handbook of Chemistry and Physics. 1982. A Ready-Reference Book of Chemical and Physical Data. 62nd Ed. Boca Raton, Florida, p. D-175.

DePass, L.R., R.H. Garman, M.D. Woodside, W.E. Giddens, R.R. Maronpot and C.S. Weil. 1986a. Chronic toxicity and oncogenicity studies of ethylene glycol in rats and mice. Fund. Appl. Toxicol. 7:547-565.

DePass, L.R., M.D. Woodside, R.R. Maronpot and C.S. Weil. 1986b. Three-generation reproduction and dominant lethal mutagenesis studies of ethylene glycol in the rat. Fund. Appl. Toxicol. 7:566-572.

Gessner, P.K., D.V. Parke and R.T. Williams. 1961. Studies in detoxication 86. The metabolism of $^{14}C$ labelled ethylene glycol. Biochem. J. 79:482-489.

Hartman, P.A., and P.B. Bowman. 1977. Simple GLC determination of ethylene oxide and its reaction products in drugs and formulation. J. Pharm. Sci. 66:789-792.

Lamb, J.C., IV, R.R. Maronpot, D.K. Gulati, V.S. Russell, L. Hommel-Barnes and P.S. Sabharwal. 1985. Reproductive and developmental toxicity of ethylene glycol in the mouse. Toxicol. Appl. Pharmacol. 81:100-112.

Laug, E.P., H.O. Calvery, H.J. Morris and G. Woodward. 1939. The toxicology of some glycols and derivatives. J. Ind. Hyg. Toxicol. 21:173-201.

Lehman, A.J. 1959. Appraisal of the safety of chemicals in foods, drugs and cosmetics. Association of Food and Drug Officials of the United States.

Mason, M.M., C.C. Cate and J. Baker. 1971. Toxicology and carcinogenesis of various chemicals used in the preparation of vaccines. Clin. Toxicol. 4:185-204.

NIOSH. 1983-84. National Institute of Occupational Safety and Health. Registry of toxic effects of chemical substances. U.S. Dept. of Health, Education and Welfare, Supplement. p. 904.

Nunamaker, D.M., W. Medway and P. Berg. 1971. Treatment of ethylene glycol poisoning in the dog. J. Am. Vet. Med. Assoc. 159:310-314.

Parry, M.F., and R. Wallach. 1974. Ethylene glycol poisoning. Am. J. Med. 57:143-150.

Pons, C.A., and R.P. Custer. 1946. Acute ethylene glycol poisoning. A clinico-pathological report of eighteen fatal cases. Am. J. Med. Sci. 211:544-552.

Price, C.J., C.A. Kimmel, R.W. Tyl and M.C. Marr. 1985. The developmental toxicity of ethylene glycol in rats and mice. Toxicol. Appl. Pharmacol. 81:113-127.

Reif, G. 1950. Self-experiments with ethylene glycol. Pharmazie. 5:276-278.

U.S. EPA. 1980. U.S. Environmental Protection Agency. Damages and Threats Caused by Hazardous Material Sites. Oil and Special Materials Control Division. Draft. p. 43.

U.S. EPA. 1987. U.S. Environmental Protection Agency. Health Advisory Document for Ethylene Glycol. Draft. Office of Drinking Water.

U.S. EPA. 1986. U.S. Environmental Protection Agency. Guidelines for carcinogen risk. Federal Register. 51(185):33992-34003. September 24.

U.S. ITC. 1984. U.S. International Trade Commission. Synthetic Organic Chemicals, United States Production and Sales, 1983. Washington, D.C. USITC Publication 1588.

Verschueren, K. 1977. Handbook of environmental data on organic chemicals. New York, NY: Von Nostrand Reinhold Company, p. 322.

Windholz, M., ed. 1983. The Merck Index, 10th ed. Merck and Company, Inc., Rahway, NJ.

# HEXACHLOROBENZENE

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

## I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

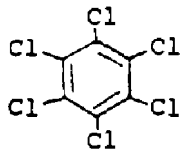
Health Advisories are developed for One-day, Ten-day, Longer-term (approximately 7 years, or 10% of an individual's lifetime) and Lifetime exposures based on data describing noncarcinogenic end points of toxicity. Health Advisories do not quantitatively incorporate any potential carcinogenic risk from such exposure. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

This Health Advisory (HA) is based on information presented in the Office of Drinking Water's Health Effects Criteria Document (CD) for hexachlorobenzene (U.S. EPA, 1985a). The HA and CD formats are similar for easy reference. Individuals desiring further information on the toxicological data base or rationale for risk characterization should consult the CD. The CD is available for review at each EPA Regional Office of Drinking Water counterpart (e.g., Water Supply Branch or Drinking Water Branch), or for a fee from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Rd., Springfield, VA 22161, PB # 86-117777/AS. The toll-free number is (800) 336-4700; in the Washington, D.C. area: (703) 487-4650.

## II. GENERAL INFORMATION AND PROPERTIES

CAS No. 118-74-1

Structural formula




Synonyms

- HCB, HEXA C.B., Perchlorobenzene

Uses

- Hexachlorobenzene is not manufactured as a commercial product in the United States, but an estimated 2-5 million pounds were produced each year during the synthesis of several chlorinated chemicals as of 1979 (Mumma and Lawless, 1975). Hexachlorobenzene also is an ingredient of a fungicide of which 200,000 pounds were imported each year as of 1979 (IARC, 1979).

Properties (U.S. EPA, 1985a)

| | |
|---|---|
| Chemical Formula | $C_6Cl_6$ |
| Molecular Weight | 284.79 |
| Boiling Point | 322.9°C |
| Melting Point | 230°C |
| Density | 1.57 g/mL at 23°C |
| Vapor Pressure (mm Hg) | 1 at 144.4°C |
| | $1.68 \times 10^{-5}$ at 25°C |
| | $1.089 \times 10^{-5}$ at 20°C |
| Water Solubility | 0.005 mg/L at 25°C |
| Henry's Law Constant | 0.12 atm $m^3$ $mol^{-1}$ |
| Odor Threshold | Not available |
| Taste Threshold | Not available |
| Conversion Factor | -- |

Occurrence

- Hexachlorobenzene (HCB) is a synthetic organic compound with no natural sources. HCB is no longer directly produced but occurs as a byproduct during the manufacture of other chlorinated compounds. HCB has been used as a fungicide, but this use has been discontinued. HCB can occur as a contaminant in a number of chemically similar compounds, which are used as pesticides (U.S. EPA, 1984a).

- Because HCB has an extremely low solublity in water, releases to the environment rapidly partition to soil. HCB is resistant to hydrolysis and biodegradation and has a reported half life in soil of approximately 3-6 years. HCB has been demonstrated to bioaccumulate in fresh water fish (Lu and Metcalf, 1975).

- HCB has been included in one Federal Survey of drinking water supplies. HCB was analyzed for in 104 surface water and 12 ground water supplies. No supply contained HCB above the detection limit of 0.1 ug/L. HCB has been detected at levels of 0.005 ug/L in two drinking water supplies in the midwest. HCB has been reported to occur in some surface water samples at less than ug/L levels (U.S. EPA, 1984a).

- HCB has been reported to occur in some foods at the ppb level. Due to HCB's physical properties, diet is probably the major route of exposure (U.S. EPA, 1984a).

## III. PHARMACOKINETICS

Absorption

- Absorption of HCB from the gut has been studied in detail; however, no information has been found in the available literature on HCB absorption through the lungs or skin (U.S. EPA, 1985a).

- Absorption of HCB from the intestinal tract appears to depend on the solvent vehicle used during test material administration. When HCB is administered in olive oil, approximately 80% of the dose is absorbed; when it is administered in an aqueous suspension, in 1% methyl cellulose, or in a solid crystalline form, relatively little (<20%) is absorbed (U.S. EPA, 1985a).

- Intestinal absorption of HCB occurs primarily through lymphatic channels with only a minor portion being absorbed into the portal circulation (U.S. EPA, 1985a).

Distribution

- Following intestinal absorption, HCB, which is lipophilic, distributes to tissues that are rich in lipid content (U.S. EPA, 1985a). The adipose tissue accumulates the greatest concentrations of HCB in all species studied, although bone marrow and skin, which contain large amounts of lipids, also accumulate HCB. The adrenal cortex accumulates

HCB at concentrations approaching those of fat. Other tissues (e.g., liver, kidneys, lungs, heart, spleen and blood) generally contain lower amounts of HCB.

- Intravenous injection of HCB results in a tissue distribution similar to the following oral administration (U.S. EPA, 1985a).

- Hexachlorobenzene is transported via the placenta and is distributed in fetal tissue (U.S. EPA, 1985a).

Metabolism

- The metabolism of HCB has been studied in male and female rats following oral administration, in Rhesus monkeys and beagles following intravenous injection and in rabbits following intraperitoneal injection (Renner, 1981).

- Hexachlorobenzene is metabolized slowly into other lower chlorinated benzenes, chlorinated phenols and other minor metabolites, and forms glucuronide and glutathione conjugates (Renner, 1981).

- Tissues were found to contain mainly unchanged HCB together with small amounts of metabolites (Renner, 1981).

- Only small amounts of HCB metabolites were detected in feces. Most of the HCB metabolites were excreted in the urine together with small amounts of unchanged HCB (U.S. EPA, 1985a).

Excretion

- The excretion of HCB from treated animals is slow and occurs mainly as the parent compound through the feces, with relatively little being excreted in the urine. It is characterized by an initial rapid phase followed by a very slow phase. This slow phase of excretion can be enhanced by the administration of mineral oil, paraffin and n-hexadecane (U.S. EPA, 1985a).

- Both biliary and intestinal excretion contribute to fecal excretion (U.S. EPA, 1985a).

- A three-compartment mammalian model has been reported for the behavior of HCB in beagles and Rhesus monkeys following intravenous injection of a single dose. Radioactivity was not detected in exhaled air following intraperitoneal injection of $^{14}C$-HCB. Hexachlorobenzene has been detected in the milk of nursing mammals (U.S. EPA, 1985a).

## IV. HEALTH EFFECTS

Humans

- The exposure of humans to seed wheat contaminated with HCB in Turkey from 1955-1959 caused an epidemic of HCB-induced PCT, also known as

porphyria turcica, which is manifested by disturbed porphyrin metabolism, cutaneous lesions and hyperpigmentation. Two investigators (Cam and Nigogosyan, 1963) estimated that 0.05 to 0.2 g/day were ingested. In children under 1 year of age, pink sores were observed as well as 95% mortality (U.S. EPA, 1985a).

- Follow-up studies conducted with patients 20 to 25 years after the onset of porphyria showed that a few patients (10%) still had active porphyria, whereas >50% exhibited hyperpigmentation (78%) and scarring (83%) as well as other dermatologic, neurologic and skeletal features of HCB toxicity. Enlarged thyroids were diagnosed in 60% of the female patients. Hexachlorobenzene residues also were found in the blood, fat or breast milk of some patients (U.S. EPA, 1985a).

Animals

Short-term Exposure

- Information on the acute toxicity of HCB is limited to oral $LD_{50}$ values determined with a few mammalian species. The following $LD_{50}$ values were reported in the available literature: rats, 3,500-10,000 mg/kg; rabbits, 2,600 mg/kg; cats, 1,700 mg/kg; and mice, 4,000 mg/kg (NAS, 1977; IARC, 1979; Sax, 1979).

Long-term Exposure

- Subchronic oral toxicity studies with a number of mammalian species indicated statistically significant increases in liver and kidney (rats only) weights in hexachlorobenzene-treated animals. Some studies have shown increases in the weights of other organs as well. Chronic oral toxicity studies revealed similar effects to those seen in the subchronic studies plus HCB-associated mortality and various hepatic and renal lesions. These subchronic and chronic effects were usually dose-related with effect levels as low as 2 mg/kg/day in subchronic studies and 0.29 to 0.4 mg/kg/day in chronic studies. Other effects included multiple alopecia and scabbing, together with neurologic effects in rats, mice and dogs (U.S. EPA, 1985a).

- Dose-related histopathologic changes in the ovaries of monkeys given 8 to 128 mg/kg/day by gavage for 60 days also have been reported (U.S. EPA, 1985a).

- The livers of HCB-exposed animals have shown histologic changes such as irregular shaped and moderately enlarged liver mitochondria and increases in the size of the centrilobular hepatocytes (U.S. EPA, 1985a).

- Increased porphyrin levels in the liver and in urine have been reported for all species studied except the dog. Hexachlorobenzene was found to cause the accumulation of $\delta$-H-steroids which induce porphyrin biosynthesis and to inhibit uroporphyrinogen decarboxylases (U.S. EPA, 1985a).

- The inhibition of uroporphyrinogen decarboxylases appears to be due to pentachlorophenol, a HCB metabolite (U.S. EPA, 1985a).

- Indications are that females are more susceptible to HCB-induced porphyria than are males, which may be related to higher estrogen levels and greater HCB metabolism in females (U.S. EPA, 1985a).

- Hexachlorobenzene was reported to produce a mixed-type induction of cytochromes resembling that produced by a combination of phenobarbital (P-450) and 3,4-benzpyrene (P-448). In addition, the activities of several hepatic microsomal enzymes were found to be induced by HCB (U.S. EPA, 1985a).

Reproductive Effects

- Hexachlorobenzene has been shown to cross the placenta into fetal tissues and to be present in the milk of nursing dams (U.S. EPA, 1985a).

- The NOAEL in a four-generation reproduction study with rats was reported to be 20 ppm of HCB in the diet (Grant et al., 1977). Pups from treated dams receiving diets containing 80 ppm HCB recovered from elevated liver weights when nursed by untested foster dams (Mendoza et al., 1978).

- Hepatomegaly and reduced survival were reported in kittens from cats receiving 263 ppm of HCB in their diets (8.7 mg/day/cat (Hansen et al., 1979).

- Three infant Rhesus monkeys nursed by mothers given HCB by gavage at 64 mg/kg/day for 60 days developed clinical signs of toxicity, and 2 infants which died while nursing had severely congested lungs or bilateral hemorrhagic pneumonia (Bailey et al., 1980).

- Feeding female minks with dietary HCB at doses as low as 1 ppm during gestation and lactation resulted in increased mortality of kits (Rush et al., 1983).

Developmental Effects

- Fetal mice from dams treated with 100 mg HCB/kg/day by gavage during days 7 through 16 of gestation exhibited teratogenic responses, e.g., cleft palate, and decreased fetal weight. Maternal liver:body weights were also increased (Courtney et al., 1976).

- Hexachlorobenzene was not teratogenic in Wistar rats with gavage doses of 10, 20, 40, 60, 80 or 120 mg HCB/kg/day in corn oil or 0.25% aqueous gum tragacanth given during gestation days 6-21. Maternal toxicity (body weight loss, central nervous system effects) and reduced fetal body weight occurred at the two highest doses (Khera, 1974).

Mutagenicity

- Hexachlorobenzene was not found to be mutagenic in 5 strains of S. typhimurium, with or without metabolic activation (Lawlor et al., 1979).

- Hexachlorobenzene was mutagenic in the yeast, S. cerevisiae, at a minimum concentration of 100 ppm (Guerzoni et al., 1976).

- Hexachlorobenzene was negative in dominant lethal mutation studies with rats (Khera, 1974; Simon et al., 1979).

Carcinogenicity

- In a lifetime study with HCB administration to hamsters, hepatoma was induced in both males and females (Cabral et al., 1977). The response at a dose of 4 to 5 mg/kg/day dissolved in corn oil and mixed in the feed was 47% for both sexes; controls had no hepatomas. In addition to hepatomas, hamsters responded to HCB treatment with malignant liver haemangioendotheliomas and thyroid adenomas. The incidence of haemangioendotheliomas was 20% in males (versus 0% in controls) at 8 mg/kg/day and 12% in females (versus 0% in controls) at 16 mg/kg/day. Thyroid adenomas occurred at 14% incidence in males treated with 16 mg/kg HCB (versus 0% in controls).

- Liver cell tumors, described as hepatomas, also were produced in both sexes of Swiss mice (Cabral et al., 1979). At 24 mg/kg/day, the incidence was 34% for females and 16% for males, and the response showed a dose-dependency not only in the number of tumor-bearing animals but also in the latent period, and multiplicity and size of tumors. In ICR mice, HCB administered concurrently with polychlorinated terphenyl induced hepatocellular carcinomas (Shirai et al., 1978).

- In rats, the target organs for HCB-induced tumors in various studies included the liver, kidney, adrenal gland and parathyroid gland. Liver tumors were found in three studies which included three different strains of rat: Agus, Wistar and Sprague-Dawley. These tumors were induced with doses between 1.5 and 8 mg/kg/day. The incidence was as high as 100% in Agus rats but lower for the other strains. Renal cell tumors were found in one study on Sprague-Dawley rats. In two studies with Sprague-Dawley rats, significant increases in adrenal pheochromocytoma in females were found. In one of these studies the incidence of parathyroid tumors in males was increased significantly as well (Smith and Cabral, 1980; Lambrecht, et al., 1983a, 1983b; Arnold, 1983, 1984; Arnold et al., 1985).

- Lambrecht et al. (1983a, 1983b) fed male and female Sprague-Dawley rats HCB in the diet for up to two years at estimated doses of 4-5 mg/kg/day and 8-9.5 mg/kg/day. By 48 weeks, females had gross liver tumors. Significant increases in tumor incidence included hepatoma in both sexes at both doses, hepatocellular carcinomas in females at both doses, renal cell adenomas in females at both doses, and adrenal pheochromocytoma in females at both doses. Hepatocellular carcinoma was slightly higher in males at both doses.

- The data on HCB provide sufficient evidence of the carcinogenicity of HCB since there were increased incidences of malignant tumors of the liver in two species (haemangioendothelioma in hamsters and hepatocellular carcinoma in rats) as well as reports of hepatoma in mice, rats and hamsters.

## V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for One-day, Ten-day, Longer-term (approximately 7 years) and Lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(NOAEL \text{ or } LOAEL) \times (BW)}{(UF) \times (\_\_\_ L/day)} = \_\_\_ mg/L (\_\_\_ ug/L)$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect-Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100 or 1,000), in accordance with NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

The following Health Advisories, which are based on toxicological effects, are above the solubility of hexachlorobenzene in water (0.005 mg/L at 25°C).

### One-day and Ten-day Health Advisories

Available evidence for the acute toxicity of hexachlorobenzene is considered to be insufficient for calculation of One-day and Ten-day Health Advisory (HAs). Therefore, the Longer-term HA (0.05 mg/L) for a 10-kg child is proposed as a conservative estimate for One-day and Ten-day HAs for the 10-kg child.

### Longer-term Health Advisory

In the Kuiper-Goodman et al. (1977) study, groups of 70 male and 70 female Charles River (COBS) rats were fed diets with hexachlorobenzene at 0.5, 2.0, 8.0 or 32.0 mg/kg bw/day dissolved in corn oil for as long as 15 weeks. Female rats were found to be more susceptible to hexachlorobenzene, as indicated by all parameters studied, and an "apparent" NOAEL of 0.5 mg/kg/day was concluded by the authors. Increased liver porphyrin levels in females and increases in the size of centrilobular hepatocytes along with the depletion of hepatocellular marker enzymes were noted with higher doses.

Using the NOAEL of 0.5 mg/kg bw/day reported by Kuiper-Goodman et al. (1977), the Longer-term HA for a 10-kg child is calculated as follows:

$$\text{Longer-term HA} = \frac{(0.5 \text{ mg/kg/day})\ (10 \text{ kg})}{(100)\ (1 \text{ L/day})} = 0.050 \text{ mg/L } (50 \text{ ug/L})$$

where:

0.5 mg/kg/day = NOAEL based on absence of liver effects.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

For a 70 kg-adult:

$$\text{Longer-term HA} = \frac{(0.5 \text{ mg/kg/day})\ (70 \text{ kg})}{(100)\ (2 \text{ L/day})} = 0.175 \text{ mg/L } (175 \text{ ug/L})$$

where:

0.5 mg/kg/day = NOAEL based on absence of liver effects.

70 kg = assumed body weight of an adult.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

2 L/day = assumed daily water consumption of an adult.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed for synthetic organic chemicals and a value of 10%

is assumed for inorganic chemicals. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

The derivation of the DWEL is based on a 130-week study by Arnold et al. (1985). This study involved feeding male and female Sprague-Dawley rats (the $F_0$ generation) diets containing 0, 0.32, 1.6, 8.0 or 40 ppm of hexachlorobenzene (analytical grade) for 90 days before mating and until 32 days after parturition (at weaning).

The number of offspring ($F_1$ generation) from these matings was reduced to 50 males and 50 females per dose group at 28 days of age and fed their respective parents' diets. Thus, the $F_1$ animals were exposed to hexachlorobenzene and metabolites in utero, from maternal nursing and from their diets for the remainder of their lifetime (130 weeks). No hexachlorobenzene-induced effects were reported in the 0.32 ppm hexachlorobenzene $F_1$ group, indicating this level is a NOAEL. Although a significant ($p<0.05$) increase in the incidence of periportal glycogen depletion was found in $F_1$ male rats fed 1.6 ppm hexachlorobenzene, the 1.6 ppm level of hexachlorobenzene also is concluded to be a NOAEL in that this result was not evident in other treated groups of male rats. The 8.0 ppm hexachlorobenzene $F_1$ groups were reported to have an increase ($p<0.05$) in the incidence of hepatic centrilobular basophilic chromogenesis. The 40 ppm hexachlorobenzene $F_1$ groups were reported to have increases ($p<0.05$) in pup mortality, hepatic centrilobular basophilic chromogenesis, peribiliary lymphocytosis and fibrosis, severe chronic nephrosis in males, adrenal pheochromocytomas in females and parathyroid tumors in males. It is difficult to estimate lifetime doses on a mg/kg bw basis in this study because of the initial exposure of the animals to hexachlorobenzene and its metabolites in utero and during lactation. However, in an attempt to estimate the lifetime hexachlorobenzene doses on a mg/kg bw basis, the 1.6 mg/kg hexachlorobenzene dietary level, interpreted from this study as the highest NOAEL level, was converted to a daily intake dose of 0.08 mg/kg bw/day by averaging the dosage data provided by Arnold (1984).

Using this NOAEL, the DWEL is derived as follows:

Step 1: Determination of the Reference Dose (RfD)

$$RfD = \frac{(0.08\ mg/kg/day)\ (1{,}000\ ug/mg)}{(100)} = 0.8\ ug/kg/day$$

where:

0.08 mg/kg/day = NOAEL.

1,000 ug/mg = Conversion of NOAEL in mg to ug.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$DWEL = \frac{(0.8 \text{ ug/kg/day})\ (70 \text{ kg})}{(2 \text{ L/day})} = 28 \text{ ug/L}$$

where:

0.8 ug/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Hexachlorobenzene may be classified as Group B: probable human carcinogen. The estimated excess cancer risk associated with lifetime exposure to drinking water containing hexachlorobenzene at 28 ug/L is approximately $1 \times 10^{-3}$. This estimate represents the upper 95% confidence limit from extrapolations prepared by EPA's Carcinogen Assessment Group using the linearized, multistage model. The actual risk is unlikely to exceed this value, but there is considerable uncertainty as to the accuracy of risks calculated by this methodology.

Evaluation of Carcinogenic Potential

- Data on hepatocellular carcinomas in female rats after oral ingestion from the study by Lambrecht et al. (1983) have been used by the U.S. EPA Carcinogenic Assessment Group to estimate the carcinogenic potency of hexachlorobenzene and the risks associated with one unit of the compound in drinking water (U.S. EPA, 1984b). This particular data set was selected because it is a malignant tumor in the primary target organ and results in the highest potency estimate. The 95% upper bound cancer risks associated with 1 ug/L of hexachlorobenzene in drinking water is estimated to be $4.9 \times 10^{-5}$. Accordingly, upper bound cancer risks of $10^{-6}$, $10^{-5}$ and $10^{-4}$ would be associated with 0.02, 0.2 and 2 ug/L, respectively, of hexachlorobenzene in drinking water.

- Maximum likelihood estimates as well as 95% upper limits of cancer risks by the multistage model have been calculated (U.S. EPA, 1984b, 1985a). For example, at 0.01 mg/kg/day or 0.35 mg/L cancer risk estimates are $1.4 \times 10^{-2}$ (MLE) and $1.7 \times 10^{-2}$ (UL) and at 0.1 mg/kg/day cancer risk estimates are $1.3 \times 10^{-1}$ (MLE) and $1.7 \times 10^{-1}$ (UL).

- The EPA's Carcinogen Assessment Group has estimated cancer risks with other models besides the multistage (U.S. EPA, 1984b, 1985a). As an example, 0.1 mg/kg/day lifetime exposure was associated with additional risks (95% upper confidence limit) of $1.7 \times 10^{-1}$ by the multistage and one-hit, $1.3 \times 10^{-1}$ by the probit, and $2.9 \times 10^{-1}$ by the Weibull. While recognized as statistically alternative approaches, the range of risks described by using any of these modeling approaches has little biological significance unless data can be used to support the selection of one model over another. In the interest of consistency of approach and in providing an upper bound on the potential cancer risk, the EPA has recommended use of the linearized multistage approach.

- In the absence of evidence of human carcinogenicity, hexachlorobenzene would be classed in IARC category 2B, meaning that it has been demonstrated to be carcinogenic in animals and is probably carcinogenic in humans.

- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986), hexachlorobenzene may be classified in Group B2: Probable human carcinogen. This category is for agents for which there is inadequate evidence from human studies and sufficient evidence from animal studies.

## VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- The U.S. EPA (1980) has set ambient water quality criteria for hexachlorobenzene of 7.2, 0.72, and 0.072 ug/L corresponding to cancer risks of $10^{-5}$, $10^{-6}$, and $10^{-7}$, respectively, assuming 70 kg humans daily consume 2 L of water and 6.5 g of fish and shellfish.

- The National Academy of Sciences (1983) estimated a cancer risk of $1.85 \times 10^{-6}$, with lifetime consumption of 1 L of water containing 1 ug of hexachlorobenzene, based on the carcinogenicity study in mice by Cabral et al. (1979). In 1980, the NAS also calculated a 7-day SNARL (suggested-no-adverse-response-level) of 0.03 mg/L.

- The WHO (1984) guideline value for hexachlorobenzene is 0.01 ug/L.

## VII. ANALYTICAL METHODS

- Determination of hexachlorobenzene is by a liquid-liquid extraction gas chromatographic procedure (U.S. EPA, 1978; Standard Methods, 1985). Specifically, the procedure involves the use of 15% methylene chloride in hexane for sample extraction, followed by drying with anhydrous sodium sulfate, concentration of the extract and identification by gas chromatography. Detection and measurement is accomplished by electron capture, microcoulometric or electrolytic conductivity gas chromatography. Identification may be corroborated through the use of two unlike columns or by gas chromatography-mass spectroscopy (GC-MS). The method sensitivity is 0.001 to 0.010 ug/L for single component pesticides and 0.050 to 1.0 ug/L for multiple component pesticides when analyzing a 1-liter sample with the electron capture detector.

## VIII. TREATMENT TECHNOLOGIES

- Treatment technologies for the removal of hexachlorobenzene (HCB) from water have not been evaluated extensively. An evaluation of some of the physical and/or chemical properties of hexachlorobenzene indicates that carbon adsorption is a candidate for further investigation. Individual or combinations of technologies selected to attempt hexachlorobenzene removal must be based on a case-by-case technical evaluation, and an assessment of the economics involved.

- Based on its Freundlich constants (K = 450; 1/n = 0.6) hexachlorobenzene is a viable candidate for removal from water by activated carbon adsorption (U.S. EPA, 1985b). There are, however, limited available data to substantiate this. Home water treatment units of the line bypass faucet and pour-through type were tested by Gulf South Research Institute to determine their effectiveness in removing hexachlorobenzene from water. Six of ten units tested had initial efficiencies of 99%; however, by the end of the test the effectiveness of some units had fallen to as low as 45% (U.S. EPA, 1985b).

- Hexachlorobenzene has a Henry's Law Constant of 2.06 atm at 20°C (U.S. EPA, 1985b). This indicates that air stripping would not be effective in removing HCB from solution.

## IX. REFERENCES

Arnold, D.L. 1983. Personal communication to Murial M. Lippman, ERNACO, Inc. Silver Spring, MD.

Arnold, D.L. 1984. Personal communication to Murial M. Lippman, ERNACO, Inc. Silver Spring, MD.

Arnold, D.L., C.A. Moodie, S.M. Charbonneau, H.R. Grice, P.F. McGuire, F.R. Bryce, B.T. Collins, Z.Z. Zawidzka, D.R. Krewski, E.A. Nera and I.C. Munro. 1985. Long-term toxicity of hexachlorobenzene in the rat and the effect of dietary vitamin A. Food Chem. Toxicol. 23:779-793.

Bailey, J., V. Knauf, W. Mueller and W. Hobson. 1980. Transfer of hexachlorobenzene and polychlorinated biphenyls to nursing infant Rhesus monkeys: Enhanced toxicity. Environ. Res. 21(1):190-196.

Cabral, J.R.P., P. Shubik, T. Mollner and F. Raitano. 1977. Carcinogenic activity of hexachlorobenzene in hamsters. Nature (London). 269:510-511.

Cabral, J.R.P., T. Mollner, F. Raitano and P. Shubik. 1979. Carcinogenesis of hexachlorobenzene in mice. Int. J. Cancer. 23(1):47-52.

Cam, C. and G. Nigogosyan. 1963. Acquired toxic porphyria cutanea tarda due to hexachlorobenzene. J. Am. Med. Assoc. 183(2):88-91.

Courtney, K.D., M.F. Copeland and A. Robbins. 1976. The effects of pentachloronitrobenzene, hexachlorobenzene and related compounds on fetal development. Toxicol. Appl. Pharmacol. 35:239-256.

Guerzoni, M.E., L. Del Cupolo and I. Ponti. 1976. Mutagenic activity of pesticides (Attivita mutagenica degli antiporrositari). Rev. Sci. Technol. Alementi Nutri. Um. 6:161-165.

Grant, D.L., W.E.J. Phillips and G.V. Hatina. 1977. Effect of hexachlorobenzene on reproduction in the rat. Arch. Environ. Contam. Toxicol. 5(2):207-216.

Hansen, L.G., R.H. Teske, S.M. Sundlof and J. Simon. 1979. Hexachlorobenzene and feline reproduction: Effects of ground pork contaminated by dietary exposure or spiked with purified hexachlorobenzene. Vet. Hum. Toxicol. 21(4):248-253.

IARC. 1979. International Agency for Research on Cancer. IARC monographs on the evaluation of the carcinogenic risk of chemical to humans. Hexachlorobenzene. IARC, Lyon, France. 20:155-178.

Khera, K.S. 1974. Teratogenicity and dominant lethal studies on hexachlorobenzene in rats. Food Cosmet. Toxicol. 12:471-477.

Kuiper-Goodman, T., D.L. Grant, C.A. Moodie, G.O. Korsrud and I.C. Munro. 1977. Subacute toxicity of hexachlorobenzene in the rat. Toxicol. Appl. Pharmacol. 40(3):529-549.

Lambrecht, R.W., E. Ertruk, E.E. Grunden, H.A. Peters, C.R. Morris and G.T. Bryan. 1983a. Renal tumors in rats (R) chronically exposed to hexachlorobenzene (HCB). Proc. Am. Assoc. Cancer Res. 24:59. (Abstr.)

Lambrecht, R.W., E. Ertruk, E.E. Grunden, H.A. Peters, C.R. Morris and G.T. Bryan. 1983b. Hepatocarcinogenicity of chronically administered hexachlorobenzene in rats. Fed. Prod. 42(4):786. (Abstr.)

Lawlor, T., S.R. Haworth and P. Voytek. 1979. Evaluation of the genetic activity of nine chlorinated phenols, seven chlorinated benzenes, and three chlorinated hexanes. Environ. Mutagen. 1:143. (Abstr.)

Lu, P.Y., and R.L. Metcalf. 1975. Environmental fate and biodegradability of benzene derivatives as studied in a model aquatic ecosystem. Environ. Health Perspec. 20:269-284.

Mendoza, C.E., B.T. Collins, J.B. Shields and G.W. Laver. 1978. Effects of hexachlorobenzene or hexabromobenzene on body and organ weights of preweaning rats after a reciprocal transfer between the treated and control dams. J. Agric. Food Chem. 26(4):941-945.

Mumma, C.E., and E.W. Lawless. 1975. Survey of industrial processing data. Task I - Hexachlorobenzene and hexachlorobutadiene pollution from chlorocarbon process. Prepared by Midwest Res. Inst. under Contract No. 68-01-2105, EPA 560/3-75-003. NTIS PB 243 641.

NAS. 1980. National Academy of Sciences. Drinking Water and Health. Volume 3. Safe Drinking Water Committee, NAS, Washington, D.C. pp. 210-215.

NAS. 1983. National Academy of Sciences. Drinking Water and Health. Volume 5. Safe Drinking Water Committee, NAS, Washington, D.C. pp. 49-56.

Renner, G. 1981. Biotransformation of the fungicides hexachlorobenzene and pentachloronitrobenzene. Xenobiotica 11(7):435-446.

Rush, G.F., J.H. Smith, K. Maita, et al. 1983. Perinatal hexachlorobenzene toxicity in the mink. Environ. Res. 31:116-124.

Sax, N.I. 1979. Dangerous Properties of Industrial Materials, 5th ed. Van Nostrand Reinhold Col, NY. p. 716.

Shirai, T., Y. Miyata, K. Nakanishi, G. Murasaki and N. Ito. 1978. Hepatocarcinogenicity of polychlorinated terphenyl (PCT) in ICR mice and its enhancement by hexachlorobenzene (HCB). Cancer Lett. 4(5):271-275.

Simon, G.S., R.G. Tardiff and J.F. Borzelleca. 1979. Failure of hexachlorobenzene to induce dominant lethal mutations in the rat. Toxicol. Appl. Pharmacol. 47(2):415-419.

Smith, A.G., and J. Cabral. 1980. Liver-cell tumors in rats fed hexachlorobenzene. Cancer Lett. 11(2):169-172.

Standard Methods. 1985. Method 509A. Organochlorine Pesticides. Standard Methods for the Examination of Water and Wastewater, 16th Edition, APHA, AWWA, WPCF, 1985.

U.S. EPA. 1978. U.S. Environmental Protection Agency. Method for organochlorine pesticides in drinking water. In: Methods for Organochlorine Pesticides and Chlorphenoxy Acid Herbicides in Drinking Water and Raw Source Water, Interim, July 1978.

U.S. EPA. 1980. U.S. Environmental Protection Agency. Ambient water quality criteria for chlorinated benzenes. Environmental Criteria and Assessment Office, Cincinnati, OH. EPA 440/ 5-80-028. NTIS PB 81-117392.

U.S. EPA. 1984a. U.S Environmental Protection Agency. Miscellaneous synthetic organic chemicals, occurrence in drinking water, food and air. Office of Drinking Water.

U.S. EPA. 1984b. U.S. Environmental Protection Agency. Health assessment document for chlorinated benzenes. Office of Health and Environmental Assessment, EPA-600/8-84-015.

U.S. EPA. 1985a. U.S. Environmental Protection Agency. Drinking water criteria document for hexachlorobenzene. Environmental Criteria and Assessment Office, Cincinnati, OH. ECAO-CIN-424. (Final Draft)

U.S. EPA. 1985b. U.S. Environmental Protection Agency. Technologies and costs for the removal of synthetic organic chemicals from potable water supplies. Science and Technology Branch, Criteria and Standards Division, Office of Drinking Water. Washington, DC.

U.S. EPA. 1986. U.S. Environmental Protection Agency. Guidelines for carcinogenic risk assessment. Federal Register 51(185):33992-34003. September 24.

WHO. 1984. World Health Organization. Guidelines for drinking water quality. Volume I. Recommendations. WHO, Geneva, p. 83.

March 31, 1987

# n-HEXANE

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

## I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

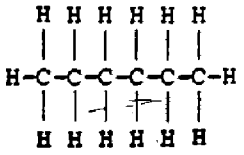
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for One-day, Ten-day, Longer-term (approximately 7 years, or 10% of an individual's lifetime) and Lifetime exposures based on data describing noncarcinogenic end points of toxicity. Health Advisories do not quantitatively incorporate any potential carcinogenic risk from such exposure. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

## II. GENERAL INFORMATION AND PROPERTIES

CAS No. 110-54-3

Structural Formula



Synonyms

- Esani, Heksan, Hexahen (NIOSH, 1978)

Uses

- Hexane is used commercially as a solvent in glues, varnishes, cements and inks (NIOSH, 1977).
- Hexane also is used in the seed oil industry to extract the natural oils from various seeds, including soybeans and cotton seeds.

Properties (Windholz, 1983)

| | |
|---|---|
| Chemical Formula | $CH_3(CH_2)_4CH_3$ |
| Molecular Weight | 86.18 |
| Physical State | Liquid |
| Boiling Point | 68.7°C |
| Melting Point | -- |
| Density | -- |
| Specific Gravity | 0.655 at 25°C |
| Vapor Pressure | 150 mm at 25°C |
| Water Solubility | 23 mg/liter |
| Log Octanol/Water Partition Coefficient | -- |
| Taste Threshold | -- |
| Odor Threshold | -- |
| Conversion Factor | 1 ppm = 2.78 mg/$m^3$ |

Occurrence

- Hexane has not been included in Federal and State surveys of drinking water and no other information on the occurrence of hexane has been located.

## III. PHARMACOKINETICS

Absorption

- Bus et al. (1983) studied the absorption of n-hexane in rats following a single 6-hour inhalational exposure to 1,000 (2,780 mg/$m^3$), 3,000 (8,340 mg/$m^3$) or 10,000 (27,800 mg/$m^3$) ppm $c^{14}$-n-hexane. Total

radioactivity collected in the various excreta fractions was approximately 98% of the total administered dose levels.

Distribution

- No information was found in the available literature on distribution of n-Hexane.

Metabolism

- DiVincenzo et al. (1976) studied the metabolism of n-hexane in guinea pigs. The chemical was dissolved in corn oil and injected intraperitoneally in a single dose of 450 mg/kg body weight in male guinea pigs. Blood samples were collected 1, 2, 4, 6, 8, 12 and 16 hours after the dose was administered. The two major metabolites of n-hexane in the serum were identified as 2,5-hexanedione and 5-hydroxy-2-hexanone; however, they were not quantified.

- Studies in shoe factory workers show that n-hexane is metabolized to 2-hexanol, 2,5-hexanedione, 2,5-dimethylfuran and O-valerolactone (Perbillini et al., 1980).

- Baker and Rickert (1981) studied metabolism of n-hexane in the Fischer-344 rat following inhalation of n-hexane. Male F-344 rats were exposed to 500 (1,390 mg/$m^3$), 1,000 (2,780 mg/$m^3$), 3,000 (8,340 mg/$m^3$) or 10,000 (27,800 mg/$m^3$) ppm n-hexane in the air. n-Hexane and its metabolites, methyl-n-butyl ketone (MBK), 2,5-dimethylfuran (DMFU), 2,5-hexanedione (2,5-HD), 2-hexanol and 1-hexanol, were quantified by GC/MS in several tissues at time intervals during and following a single 6-hr exposure to n-hexane. Urinary metabolites were quantified following a single n-hexane exposure. n-Hexane concentrations achieved an apparent steady state within two hours in all tissues. Peak blood concentrations of n-hexane were 1, 2, 8 and 12 ug/ml and peak sciatic nerve concentrations were 12, 48, 130 and 430 ug/g at 500 (1,390 mg/$m^3$), 1,000 (2,780 mg/$m^3$), 3,000 (8,340 mg/$m^3$) and 10,000 (27,800 mg/$m^3$) ppm, respectively. The halflives of n-hexane and MBK were on the order of 1 to 2 hours in all tissues except the kidneys ($K^{1/2}$ = 5 to 6 hrs). The data showed a complex relationship between n-hexane exposure and peak concentrations of the remaining metabolites. Tissue concentrations of 2,5-HD were not proportional to dose. Highest 2,5-HD concentrations were found following exposure to 1,000 ppm n-hexane in the blood, kidneys and sciatic nerve (6.1, 55 and 25 ug/g, respectively). The data indicated that the metabolism and elimination of n-hexane were dependent upon exposure concentration. Consequently, n-hexane exposure concentration cannot be directly correlated with tissue 2,5-HD concentrations.

Excretion

- The metabolites of n-hexane in urine and their concentrations following n-hexane (commercial) exposure of shoe factory workers were: 2-hexanol (0.5 mg/liter), 2,5-hexanedione (10.1 mg/liter), O-valerolactone (2.4 mg/liter) and 2,5-dimethylfuran (5.2 mg/liter) (Perbillini et al., 1980).

## IV. HEALTH EFFECTS

### Humans

- Hershkowitz et al. (1971) reported the effects of inhalation of n-hexane vapor on three female employees who worked in a furniture factory. n-Hexane concentrations in the room averaged 650 (1,807 $mg/m^3$) ppm with peaks up to 1,300 (3,614 $mg/m^3$) ppm. The first symptoms appeared 2 to 4 months after the beginning of exposure and the three employees were hospitalized 6 to 10 months later when they complained of one or more of the following symptoms: headache, burning sensation of the face, abdominal cramps, numbness and weakness of the distal extremities. Physical examination revealed bilateral foot-drop gait, bilateral wrist drop and absence of Achilles tendon reflexes. Electromyographic examination of these patients indicated fibrillation potentials in the small muscles of the hands and feet. Biopsies of the anterior tibial muscle and sural nerves of two of the patients revealed that the muscles contained small angulated fibers and other fibers with clear central zones (denervation type injury). Small bundles of axons from the muscle sections were studied by electron microscopy and found to contain dense bodies and fibrous formations, increased numbers of neurofilaments and abnormal membranous structures with clumped and degenerated mitochondria. Motor-end plates also were damaged, with swollen terminal axoplasmic expansions, an increased number of degenerated mitochondria and an increased number of glycogen granules, dense bodies, large osmophilic membranes, synaptic folds and vesicles. The investigators reported that the health of these employees improved after leaving their employment.

### Animals

#### Short-term Exposure

- Kimura et al. (1971) studied the oral toxicity of a single dose of n-hexane in different age groups of rats: newborn (1 to 2 days old, 5 to 8 g), 14 days old (16 to 50 g), young adult (80 to 160 g) and older adult (300 to 470 g). The undiluted solvents were administered orally to non-fasted rats. A precise $LD_{50}$ value for n-hexane could not be determined for the newborn rats because of measurement limitations, but doses of less than 1 ml/kg body weight were lethal. The acute oral $LD_{50}$ was 24.0 ml/kg (15.7 g/kg) for 14-day old rats, 49.0 ml/kg (32.1 g/kg) for young adults and 43.5 ml/kg (28.9 g/kg) for older adult rats.

- Hewett et al. (1980) carried out experiments in which groups of male adult Sprague-Dawley rats were given a single oral dose of 1,290 mg/kg of n-hexane solubilized in corn oil (control animals received corn oil alone). This segment of the experiment was to provide evidence of potentiation of chloroform toxicity in rats pretreated with n-hexane, methyl n-butyl ketone or 2,5-hexanedione. n-Hexane-induced hepatotoxicity was estimated 42 hours later by measuring enzyme activity of glutamic-pyruvic transferase (GPT) and ornithine carbamyl transferase (OCT) in the plasma of animals.

The extent of cell damage was assessed by observing histological changes in the liver and nephrotoxicity was evaluated by monitoring the ability of renal cortical slices to accumulate an organic anion (p-aminohippurate) and cation (tetraethylammonium) and by determining the blood urea nitrogen content. The investigators reported that the 1,290 mg/kg dose of n-hexane produced no measurable effects either on organ weight (liver, kidney) or on any parameters described earlier. However, a single oral dose of n-hexane in rats produced minimal changes in renal histology as indicated by the presence of degenerated tubules in sections from these animals.

- Howd et al. (1982) studied the relation between schedules of exposure to n-hexane and plasma levels of 2,5-hexanedione. Male Fischer rats were exposed repeatedly to high concentrations of n-hexane: 4,000 ppm for 8 hours/day for 5 days/week; 48,000 ppm for 10 minutes every half hour for 8 hours/day, 5 days/week; 40,000 ppm for 10 minutes every half hour, on a background of 4,000 ppm continuous, for 8 hours/day, 5 days/week. Concentrations of n-hexane in blood and brain were linearly related to the concentrations of n-hexane in the chamber after a 10-minute exposure, and declined thereafter, with half-lives of about 2-1/2 and 4 minutes in blood and brain, respectively. Despite the rapid elimination of n-hexane, neurotoxic levels of 2,5-hexanedione (2,5-HD) were formed from repeated 10-minute exposures to a high concentration of n-hexane when the inter-exposure interval was 20 minutes. Neurotoxic levels of 2,5-HD also resulted from continuous exposure to much lower concentrations of n-hexane. Both exposure schedules (4,000 ppm for 8 hours/day and 10 minutes every half hour exposure) caused an increase in 2,5-HD concentrations in blood after repeated daily treatments. The authors suggested that the minimal sustained plasma 2,5-HD concentration that will result in neurotoxicity appears to be less than 50 ug/ml in the rat.

- In vitro toxicity of n-hexane and 2,5-hexanedione using isolated perfused rabbit hearts is reported (Raye, 1983). The hearts were perfused using Langendorf's procedure and modified Anderson's coronary perfusion apparatus. The force of cardiac contraction was significantly reduced following one hour perfusion with 9.6 mg/L concentration of n-hexane and with 0.35% v/v concentration of 2,5-hexanedione.

Dermal/Ocular Effects

- Jakobson et al. (1982) reported results of uptake via the blood and elimination of n-hexane (one of 10 organic solvents) following epicutaneous exposure of anesthetized guinea pigs. The concentration of n-hexane in the blood was monitored over a 6-hour period of n-hexane exposure of anesthetized guinea pigs. A glass ring chamber (area: 3.1 $cm^2$) 4 mm in thickness and 10 mm in height was glued to a clipped area of skin on the back of the guinea pigs. This glass ring chamber contained 1.0 ml of n-hexane solvent for the study. With n-hexane, the concentrations in the blood at 0.5 and 6 hrs were 0.58 and 0.23 ug/ml of n-hexane, respectively.

° Nomiyama and Nomiyama (1975) investigated the absorption rates of n-hexane and toluene through the skin of humans. An unspecified number of subjects immersed their hands up to the wrists in a dish containing analytically pure n-hexane (95% n-hexane) for 1 minute. At intervals following skin exposure, breath, blood and urine samples were analyzed for n-hexane by gas chromatographs. The authors were unable to detect hexane in either the breath or the blood of any of the subjects following exposure to n-hexane. The detection limit for n-hexane was 1 ppm in the breath and 3.5 ppm in blood. The authors did not describe any physiological effects.

Long-term Exposure

° Krasavage et al. (1980) studied the relative neurotoxicities of n-hexane by the appearance of hind-limb weakness. Charles River male rats were given oral doses of n-hexane at 570 mg/kg (6.6 mmol/kg) 5 days/week for 90 days or 1,140 or 4,000 mg/kg doses for 120 days. As soon as hind-limb weakness clinical signs occurred, the animals were killed and the tissues were examined for histopathological changes. No clinical or histological signs of neuropathy were observed in the animals at dose levels of 570 or 1,140 mg/kg n-hexane (although body weights were depressed at all three dose levels compared to controls). At a dose level of 4,000 mg/kg n-hexane, the clinical and histological signs of neuropathy occurred at approximately 101 days. The histological changes included multi-focal axonal swellings, adaxonal myelin infolding and paranodal myelin retraction. In addition to neuropathy, histological examination of testicular tissue revealed varying stages of atrophy of the germinal epithelium following the administration of 4,000 mg/kg n-hexane.

° Takeuchi et al. (1980) studied the neurotoxicity of n-hexane in Wistar strain male rats following inhalation exposure to 3,000 ppm (8,340 mg/m$^3$) of n-hexane for 12 hours a day for 16 weeks. The nerve conduction velocity and the distal latency measured before the beginning of the exposure and after the experiment showed that (1) n-hexane disturbed the conduction velocity of the motor nerve and the mixed nerve and prolonged the distal latency in the rat's tail and (2) the neuromuscular junction and the muscle fiber of the rats exposed to n-hexane were impaired severely as seen by light and electron microscopy.

° Cavender et al. (1984) reported the results of a 13-week vapor inhalation study of n-hexane in rats with emphasis on neurotoxic effects. Male and female Fischer-344 rats were exposed to 0, 3,000 (8,340 mg/m$^3$), 6,500 (18,070 mg/m$^3$) or 10,000 (27,800 mg/m$^3$) ppm n-hexane vapors 6 hours per day, 5 days per week, for 13 weeks. The 13-week exposures had no adverse effect on the growth of female rats. However, the mean body weight gain of male rats in the 10,000 (27,800 mg/m$^3$) ppm was significantly lower than for controls at 4 weeks of exposure and thereafter. In addition to the depression in body weight gain, the males exposed to 10,000 (27,800 mg/m$^3$) ppm had slightly but significantly lower brain weights at necropsy. No adverse testicular effects were noted. Axonopathy was observed in the tibial nerve in

four of five male rats from the 10,000 ppm group and one of five male rats in the 6,500 (18,070 mg/m$^3$) ppm group and in the medulla from one male rat in the 10,000 (27,800 mg/m$^3$) ppm group. These axonal changes were detectable only in teased nerve fiber preparations or in Epon embedded specimens. Histopathologic studies on Formalin fixed tissues did not reveal any lesions that were attributed to n-hexane exposure.

Reproductive Effects

- Bus et al. (1979) studied the effects of maternal inhalation exposure to n-hexane on the size and survival of newborn Fischer 344 rats. Pregnant rats were exposed for 6 hours per day to 1,000 (2,780 mg/m$^3$) ppm (3.5 g/m$^3$) n-hexane on days 8 to 12, 12 to 16, or 8 to 16 of gestation. No significant changes in fetal resorption, body weights, visible anomalies or the incidence of soft tissue and skeletal anomalies were noted in any of the treatment groups. The post-natal growth of pups born to dams exposed to n-hexane at 1,000 (2,780 mg/m$^3$) ppm (3.5 g/m$^3$) 6 hours/day on days 8 through 16 of gestation was depressed significantly ($P < 0.05$) compared to controls for up to 3 weeks after birth. However, litter weights of treated pups had returned to control values by 7 weeks after birth. No anatomic defects or neuropathic symptoms were noted in treated pups.

Developmental Effects

- Marks et al. (1980) stated that n-hexane was not teratogenic in mice up to a dose level of 9.90 g/kg/day. In this experiment, pregnant outbred albino mice (CD-1) received n-hexane once daily by gavage at doses up to 2.20 g/kg/day on days 6-15 of gestation. Other pregnant mice received higher hexane doses (up to 9.90 g/kg/day), employing a three times a day injection schedule. At the lower, once-daily doses only one dam died and no teratogenic effects occurred. Higher hexane doses were toxic: 2 of 25 dams treated with 2.83 g/kg/day, 3 of 34 treated with 7.92 g/kg/day and 5 of 33 treated with 9.90 g/kg/day died. At the 7.92 and 9.90 g/kg/day doses, the average fetal weight was significantly ($P < 0.05$) reduced, but the incidence of malformations in treated and vehicle (cottonseed oil) control groups did not differ significantly. Thus, n-hexane was not teratogenic even at doses toxic to the dam.

Mutagenicity

- No information was found in the available literature on the mutagenic effects of n-hexane.

Carcinogenicity

- No information was found in the available literature on the carcinogenic effects of n-hexane.

## V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for One-day, Ten-day, Longer-term (approximately 7 years) and Lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(NOAEL \text{ or } LOAEL) \times (BW)}{(UF) \times (\_\_\_ \text{ L/day})} = \_\_\_ \text{ mg/L } (\_\_\_ \text{ ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect-Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100 or 1,000), in accordance with NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

The results of the Hewlett et al. (1980) study in which a group of Sprague-Dawley male rats were given a single oral dose of 1,290 mg/kg n-hexane can be used for the derivation of a One-day HA, even though these studies (in which other chemicals also were screened) were not designed specifically to examine the toxicity of n-hexane. This dose produced no measurable effects on the following parameters after 42 hours: relative liver weight, relative kidney weight, plasma glutamic-pyruvic transaminase, plasma ornithine carbamyl transferase, hepatic and renal histological changes, uptake of p-aminohippurate and tetraethylammonium ion by kidney slices, and blood urea nitrogen. These negative findings (except for body weight at the single data point are consistent with the results reported by Krasavage et al. (1980) in a 90-day study. However, a single oral dose of n-hexane in rats produced minimal changes in renal histology as indicated by the presence of degenerated tubules in sections from these animals.

The One-day HA for the 10-kg child is calculated as follows:

$$\text{One-day HA} = \frac{(1{,}290 \text{ mg/kg/day}) \ (10 \text{ kg})}{(1 \text{ L/day}) \ (1{,}000)} = 12.9 \text{ mg/L } (13{,}000 \text{ ug/L})$$

where:

1,290 mg/kg/day = LOAEL based on minimal adverse effect in male rats.

10 kg = assumed body weight of a child.

1,000 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a LOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

Ten-day Health Advisory

Appropriate studies for the derivation of a Ten-day HA are not available. Use of the Longer-term HA for the 10-kg child of 4 mg/L is recommended.

Longer-term Health Advisory

The inhalation study by Takeuchi et al. (1980) was not considered because the parameters were not examined in detail. However, a Longer-term HA can be derived from a study (Krasavage et al., 1980) in which Charles River rats were given oral doses of 570 mg/kg n-hexane 5 days/week for 90 days, 1,140 mg/kg or 4,000 mg/kg for 120 days. Clinical and histological signs of neuropathy were absent in the animals at dose levels of 570 and 1,140 mg/kg n-hexane (although body weights were depressed at all three dose levels compared to control). The lowest dose administered (570 mg/kg) can be considered a LOAEL. A safety factor of 1,000 will be used since only one species was considered in the study and the data obtained were part of a broader study dealing with relative neurotoxicity of n-hexane, methyl n-butyl ketone and their metabolites.

The Longer-term HA for a 10-kg child is calculated as follows:

$$\text{Longer-term HA} = \frac{(570 \text{ mg/kg/day})(10 \text{ kg})\ (5)}{(1{,}000)\ (1 \text{ L/day})\quad (7)} = 4.07 \text{ mg/L } (4{,}000 \text{ ug/L})$$

where:

570 mg/kg/day = LOAEL based on depressed body weight in animals.

10 kg = assumed body weight of a child.

5/7 = conversion of 5 day/week dosing schedule to 7 day/week.

1,000 = uncertainty factor, chosen in accordance with NAS/ODW for use with a LOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

The Longer-term HA for a 70 kg adult is:

$$\text{Longer-term HA} = \frac{(570 \text{ mg/kg/day})\ (70 \text{ kg})\ (5)}{(1{,}000)\ (2 \text{ L/day})\quad (7)} = 14.3 \text{ mg/L } (14{,}000 \text{ ug/L})$$

where:

570 mg/kg/day = LOAEL based on depressed body weight in rats.

70 kg = assumed body weight of an adult.

1,000 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a LOAEL from an animal study.

2 L/day = assumed daily water consumption of an adult.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed for synthetic organic chemicals and a value of 10% is assumed for inorganic chemicals. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

Appropriate studies for the derivation of a Lifetime HA are not available at this time. The Krasavage et al. (1980) study was not considered because the data obtained were part of a broader study dealing with other chemicals.

Evaluation of Carcinogenic Potential

- No information was found in the available literature on the carcinogenic effects of n-hexane.
- According to the EPA classification scheme (U.S. EPA, 1986), n-hexane may be classified as Group D.

## VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- An occupational threshold limit value (TLV) of 100 ppm was set by ACGIH (1976).

## VII. ANALYTICAL METHODS

- There is no standardized method for the determination of hexane in drinking water samples. However, hexane may be determined by a

purge-and-trap gas chromatographic/mass spectrometric procedure used for the determination of volatile organic compounds in water (U.S. EPA, 1985). This method calls for the bubbling of an inert gas through the sample and trapping hexane on an adsorbant material. The adsorbant material is heated to drive off n-hexane onto a gas chromatographic column. The gas chromatograph is temperature programmed to separate the method analytes which are then detected by the mass spectrometer.

## VIII. TREATMENT TECHNOLOGIES

- No data are available on the removal of n-hexane by conventional or other treatment technologies. However, the physical properties and structure of the compound, as well as its similarity to other straight chain aliphatic hydrocarbons, suggest that several treatment methods may be effective in removing n-hexane.

- ESE (1982) considered adsorption a potential treatment technique for hexane on the basis of its structure and low solubility. According to McGuire and Suffet (1980), non-polar saturated hydrocarbons such as hexane should be adsorbed on granulated activated carbon (GAC). However, only limited data demonstrating hexane removal by GAC is available. In a full-scale study, average hexane concentrations in water were reduced from 0.2 ppb to 0.1 ppb on passage through each of two 5 ft diameter (1.6 m), 11 ft (3.4 m) GAC contactors containing Westvaco 12 x 40 GAC. The hydraulic loading for each contactor was 7.4 gpm/ft$^2$ and the Empty Bed Contact Time was 15.2 min.

- Packed column aeration also may remove n-hexane from drinking water. McCarty et al. (1979) found that the Henry's Law Constant for a chemical is a good indicator of the relative amenability of that chemical to aeration. Accordingly, the Henry's Law Constant for n-hexane ($1 \times 10^{-1}$ atm-m$^3$/mole) suggests that this substance will be amenable to removal from solution by air stripping. For example, this value is significantly higher than that for chloroform ($3.4 \times 10^{-3}$ atm-m$^3$/mole), a substance known to be amenable to air stripping (Singley and Bilello, 1981). Air stripping is an effective, simple and relatively inexpensive process for removing many organics from water. However, this process transfers the contaminant directly to the air stream. When considering use of air stripping as a treatment process, it is suggested that careful consideration be given to the overall environmental occurrence, fate, route of exposure and potential health hazards associated with the chemical.

- The boiling point of n-hexane (69°C) and of its azeotropic mixture with water [94.4% n-hexane, 61.6°C CCRC, 1979)] suggest that boiling would be an effective means of removing n-hexane from aqueous systems. However, the potential health hazard from hexane inhalation would have to be considered.

- A study reported by Quentin et al. (1977) removed n-hexane in water from 7.3 mg/L to 0.3 mg/L after treatment with alum and a polymeric flocculant. This suggests that a conventional treatment process such as coagulation/sedimentation may be effective in reducing n-hexane.

## IX. REFERENCES

ACGIH. 1976. American Conference of Governmental Industrial Hygienists: TLVs--threshold limit values for chemical substances in workroom air adopted by ACGIH for 1976. Cincinnati, OH. pp. 1-54.

Baker, T.S., and D.E. Rickert. 1981. Dose-dependent uptake, distribution, and elimination of inhaled n-hexane in the Fischer-344 rat. Toxicol. Appl. Pharmacol. 61:414-422.

Bellar, T.A., and J.J. Lichtenberg. 1974. Determining volatile organics at microgram-per-liter levels by gas chromatography. Journal AWWA. 66:739-744.

Bus, J.S., E.L. White, R.W. Tyl and C.S. Barron. 1979. Prenatal toxicity and metabolism of n-hexane in Fischer 344 rats after inhalation exposure during gestation. Toxicol. Appl. Pharmacol. 51:295-302.

Bus, J.S., D. Deyo and M. Cox. 1983. Disposition of radioactivity in rats after acute inhalation exposure to $c^{14}$-n-hexane. The Toxicologist. 3:135.

Cavender, F.L., H.W. Casey, H. Salem, D.G. Graham, J.A. Swenberg and E.G. Gralla. 1984. A 13-week vapor inhalation study of n-hexane in rats with emphasis on neurotoxic effects. Fundam. Appl. Toxicol. 4:191-201.

CRC Handbook of Chemistry and Physics. 1979. R.C. Weast and M.G. Astle, eds. CRC Press. West Palm Beach, Florida.

DiVincenzo, G.D., C.J. Kaplan and J. Dedinas. 1976. Characterization of the metabolites of methyl n-butyl ketone, methyl iso-butyl ketone and methyl ethyl ketone in guinea pig serum and their clearance. Toxicol. Appl. Pharmacol. 36:511-522.

ESE. 1982. Environmental Science and Engineering. Treatment techniques available for removal of n-hexane. In support of Office of Drinking Water Health Advisory prepared for Science and Technology Branch, CSD, ODW, U.S. EPA.

Herskowitz, A., N. Ishii and H. Schaumburg. 1971. N-hexane neuropathy--A syndrome occurring as a result of industrial exposure. N. Engl. J. Med. 285:82-85.

Hewett, W.R., H. Miyajima, M.G. Cote and G.L. Plaa. 1980. Acute alteration of chloroform-induced hepato- and nephrotoxicity by n-hexane, methyl-n-butyl ketone and 2,5-hexanedione. Toxicol. Appl. Pharmacol. 53:230-248.

Howd, R.A., L.R. Bingham, T.M. Steeger, C.S. Rebert and G.T. Pryor. 1982. Relation between schedules of exposure to hexane and plasma levels of 2,5-hexanedione. Neurobehav. Toxicol. Teratol. 4:87-91.

Jakobson, I., J.E. Wahlberg, B. Holmberg and G. Johansson. 1982. Uptake via the blood and elimination of 10 organic solvents following epicutaneous exposure of anesthetized guinea pigs. Toxicol. Appl. Pharmacol. 63:181-187.

Kimura, E.T., D.M. Ebert and P.W. Dodge. 1971. Acute toxicity and limits of solvent residue for sixteen organic solvents. Toxicol. Appl. Pharmacol. 19:699-704.

Kirk-Othmer. 1981. $C_1$ to $C_9$ Alkanes. In Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed. Wiley-Interscience. New York.

Krasavage, W.J., J.L. O'Donoghue, G.D. DiVincenzo and C.J. Terhaar. 1980. The relative neurotoxicity of methyl-n-butyl ketone, n-hexane and their metabolites. Toxicol. Appl. Pharmacol. 52:433-441.

Marks, T.A., P.W. Fisher and E. Staples. 1980. Influence of n-hexane on embryo and fetal development in mice. Drug and Chem. Toxicol. 3:393-406.

McCarty et al. 1979. Treatment for the control of trichloroethylene and related industrial solvents in drinking water. U.S. Environmental Protection Agency, Drinking Water Research Division. Cincinnati, Ohio.

McGuire, M.J. and I.H. Suffet. 1980. Activated carbon adsorption of organics from aqueous phase: Vol. 2. Ann Arbor Science Publishers, Inc. Ann Arbor, Michigan.

Nomiyama, I., and J. Nomiyama. 1975. The effects of the cutaneous absorption of n-hexane on humans. Jpn. J. Hyg. 30:140. (Cited in NIOSH, 1977)

NIOSH. 1977. National Institute for Occupational Safety and Health. Criteria for a recommended standard...occupational exposure to alkanes (C5-C8). Washington, DC. Publication No. 77-151.

NIOSH. 1978. National Institute for Occupational Safety and Health. Registry of Toxic Effects of Chemical Substances (RTECS). 1978.

Perbellini, L., F. Brugnone and I. Pavan. 1980. Identification of the metabolites of n-hexane, cyclohexane and their isomers in men's urine. Toxicol. Appl. Pharmacol. 53:220-229.

Perry, R.H. and C.H. Chilton. 1973. Chemical Engineers' Handbook. 5th Edition. McGraw-Hill Book Company. pp. 3-56.

Quentin, K.E., L. Weil and H. Berger. 1977. U.S. Patent 4,028,233, June 7, 1977, assigned to A.G. Hoechst, Germany Industrial Wastewater Cleanup, Noyes Data Corporation, 1979.

Raye, R. 1983. In vitro toxicity of n-hexane and 2,5-hexanedione using isolated perfused rabbit heart. J. Toxicol. Environ. Health. 11:879-884.

Singley, J.E., and L.J. Diiello. 1981. Advances in the development of design criteria for packed column aeration. Submitted to Journal AWWA, 1981.

Takeuchi, Y., Y. Oho, N. Hisanaga, J. Kitoh and Y. Sugiura. 1980. A comparative study on the neurotoxicity of n-pentane, n-hexane and n-heptane in the rat. Brit. J. Ind. Med. 37:241-247.

U.S. EPA. 1985. U.S. Environmental Protection Agency. Method 524.1. Volatile organic compounds in water by purge and trap gas chromatography/ mass spectrometry. Environmental Monitoring and Support Laboratory, Cincinnati, OH.,45268. June.

U.S. EPA. 1986. U.S. Environmental Protection Agency. Final guidelines for carcinogen risk assessment. Federal Register. 51(185):33992-34003. September 24.

Windholz, M. 1983. The Merck Index. 10th Edition. Merck and Co., Inc., Rahway, N.J. p. 678.

March 31, 198

# METHYL ETHYL KETONE

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

## I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

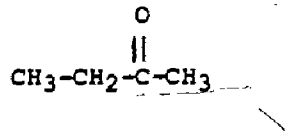
Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for One-day, Ten-day, Longer-term (approximately 7 years, or 10% of an individual's lifetime) and Lifetime exposures based on data describing noncarcinogenic end points of toxicity. Health Advisories do not quantitatively incorporate any potential carcinogenic risk from such exposure. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

## II. GENERAL INFORMATION AND PROPERTIES

CAS No. 78-93-3

Structural Formula



Synonyms

2-Butanone, butan-2-one, ethyl methyl ketone, MEK.

Uses

- As a solvent in processes involving gums, resins, cellulose acetate, and cellulose nitrate
- Used extensively in the synthetic rubber industry
- In production of paraffin wax and high grade lubricating oil
- In household products such as surface coating compounds (lacquer and varnishes), paint remover, and glues.

Properties

| | |
|---|---|
| Chemical Formula | $C_4H_8O$ |
| Molecular Weight | 72.10 |
| Physical State | liquid |
| Boiling Point | 79.6°C |
| Melting Point | -- |
| Density | -- |
| Vapor Pessure | 100 mm Hg at 25°C |
| Water Solubility | 295 mg/L at 25°C |
| Log Octanol/Water Partition Coeffficient | -- |
| Taste Threshold | -- |
| Odor Threshold | -- |
| Conversion Factor | 1 ppm = 2.95 $mg/m_3$ |

Occurrence

- Methyl ethyl ketone (MEK) is a synthetic organic chemical which does not occur naturally. Production of MEK in 1980 was approximately 600 million lbs (U.S. ITC, 1981).
- No information on the environmental fate of MEK has been identified. Based upon its reported vapor pressure and solublity, MEK is expected to slowly volatilize from soil and water. Due to MEK's relatively high solublity in water MEK is expected to be mobile in soil.

- MEK has not been included in Federal and State surveys of drinking water. However, a number of studies have reported that MEK does occur in surface water systems (Scheiman et al., 1974; U.S. EPA, 1976; Coleman et al., 1976).

## III. PHARMACOKINETICS

### Absorption

- Munies and Wurster (1965) studied the dermal absorption of MEK in humans under normal, hydrated and dehydrated skin conditions. MEK was applied at 100 ml to the forearm using an absorption cell; the duration of exposure was 8 hours. MEK was detected in the expired air at 3.6 mg/L 15 minutes after exposure. A steady-state level of 6.5 to 6.6 mg/L in the expired air was attained within 2 to 3 hours after exposure.

- DiVincenzo and coworkers (1974) reported that levels of 11% of administered MEK and metabolites were found in the serum 1 hour following a single intraperitoneal dose of 450 mg/kg in guinea pigs.

### Distribution

- Dietz and Traiger (1979) determined the blood concentrations of 2-butanol, 2,3-butanediol and 3-hydroxy-2-butanone in rats after a single oral dose of 355 mg/kg MEK. The blood concentrations of MEK and metabolites 4 hours after dosing were as follows: MEK (94.1 mg/100 ml), 2-butanol (3.2 mg/100 ml), 3-hydroxy-2-butanone (2.4 mg/100 ml), and 2,3-butanediol (8.6 mg/100 ml).

### Metabolism

- No information was found in the available literature on the metabolism of methyl ethyl ketone.

### Excretion

- Insufficient pharmacokinetic data for MEK are available to assess distribution and elimination of MEK in animals.

## IV. HEALTH EFFECTS

### Humans

- Data regarding the effects of oral exposure to MEK on humans were not located in the available literature. However, Smith and Mayers (1944) reported that two young women exhibited signs of severe intoxication, including convulsions and loss of consciousness, after exposure to MEK and acetone (298 to 560 and 330 to 495 ppm, respectively).

Animals

Short-term Exposure

- The acute $LD_{50}$ and $LD_{50}$ of MEK have been determined for several routes of exposure:

| Species | Route | $LD_{50}$ | Reference |
|---|---|---|---|
| rat | oral | 2.9 g/kg | Kimura et al., 1971 |
| rat | inhalation | 5.9 g/m$^3$ (2,000 ppm/4 hr) | Carpenter et al., 1949 |
| rabbit | dermal | >8 g/kg | Smyth et al., 1962 |

- Kimura and co-workers (1971) also have determined the oral $LD_{50}$ values for weanling and newborn rats to be 2.5 and 0.8 g/kg, respectively.

- Patty and co-workers (1935) studied the toxic effects of MEK inhalation in the guinea pig. The animals were exposed to high concentrations of vapor: 3,300 ppm (9.7 g/m$^3$), 10,000 ppm (29.5 g/m$^3$), 33,000 ppm (97.3 g/m$^3$) or 100,000 ppm (295 g/m$^3$) for various durations up to 14 hours. Pathologic examination was done on animals that died during exposure, on those immediately sacrificed after exposure and on animals sacrificed 4 and 8 days after termination of exposure. At levels of 10,000 ppm (29.5 g/m$^3$), 33,000 ppm (97.3 g/m$^3$) and 100,000 ppm (295 g/m$^3$), MEK exposure produced irritation of the nose and eyes, tearing, respiratory distress, incoordination and narcosis. Exposure to MEK vapor at a concentration of 100,000 ppm (295 g/m$^3$) to guinea pigs for 30 minutes or more resulted in corneal opacity. This condition improved gradually in guinea pigs that lived 4 and 8 days following exposure; at the end of 8 days, the eyes were nearly normal. This condition was not observed in animals exposed to lower concentrations. The pathologic findings in animals that died during exposure or were sacrificed immediately after exposure to MEK (at all levels except 3,300 ppm) were congestion of the liver, kidney, lung and brain congestion and emphysema. Congestion of the visceral organs was not observed in the animals sacrificed 4 and 8 days after termination of MEK exposure.

- Studies have assessed the hepatotoxic effect of MEK after acute exposure (DiVincenzo and Krasavage, 1974). Guinea pigs were administered a single intraperitoneal dose of MEK (750, 1,500 or 2,000 mg/kg). Twenty-four hours after exposure, blood samples of animals were analyzed for ornithine carbamyl transferase (OCT) activity and liver tissues were examined for histopathological changes. Liver effects observed were increased lipid content and elevated serum ornithine carbamyl transferase activity, a sensitive enzymatic assay for liver injury (Davidsohn and Wells, 1965). Elevated serum OCT activity was observed 24 hours after administration of 2,000 mg/kg of MEK. Lipid accumulation in cells of the animal was present at the two higher doses (1,500 and 2,000 mg/kg).

Long-term Exposure

- LaBelle and Brieger (1955) compared the longer-term exposure of composite solvent, containing 235 ppm (0.693 g/m$^3$) MEK and seven other solvents (total of 226 ppm) to MEK alone. In each case, 25 rats were exposed to the composite solvent vapors, MEK vapors or air alone for 7 hours per day, 5 days per week for 12 weeks. There were no deaths or sign of toxicity observed in the animals. There were also no significant gross or microscopic pathological changes observed at autopsy upon examination of control or exposed animals.

- Cavender et al. (1983) exposed rats of both sexes to methyl ethyl ketone at concentrations of 0, 1,250, 2,500 or 5,000 ppm, 6 hours/day, 5 days/week, for 90 days. No animals died during the study. The 90-day exposures had no adverse effect on the clinical health or growth of male or female rats except for a depression of mean body weight in the 5,000 ppm exposure group. However, at necropsy, increases in liver weight were noted in the 1,250 and 2,500 ppm group of female rats. Increases in liver weight, liver weight/body weight ratios and liver weight/brain weight ratios were observed in both male and female rats at the dose level of 5,000 ppm methyl ethyl ketone. In the male rats at the dose level of 5,000 ppm, kidney weight/body weight ratios also were elevated. Spleen and brain weights, and brain weight/body weight ratios were elevated in the 5,000 ppm female rats. Urine volumes in the 5,000 ppm male rats were higher than control values. Mean corpuscular hemoglobin values in male and female rats at the dose level of 5,000 ppm were elevated. Serum glutamic-pyruvic transaminase activity in female rats at the dose level of 2,500 ppm of MEK was elevated while female rats at the dose level of 5,000 ppm MEK exhibited significantly decreased SGPT activity. In addition, alkaline phosphatase, potassium and glucose values for female rats at the dose level of 5,000 ppm were increased relative to controls. While some of these changes were statistically significant, they were considered incidental findings, without toxicological significance.

- Inhalation exposure of rats to methyl ethyl ketone at a level of 200 ppm, 12 hours/day, 7 days/week for 24 weeks resulted in slight neurological effects visible only at 4 months of treatment (Takeuchi et al., 1983), but exposure of rats to 1,125 ppm continuously for 5 months did not result in neuropathy (Saida et al., 1976). In both studies, only a single toxicological endpoint, either motor nerve conduction velocity, mixed nerve conduction velocities, or distal motor latency (Takeuchi et al., 1983) or paralysis (Saida et al., 1976), was examined. It was interesting to note in the study by Saida et al. (1976) that rats exposed to the combination of methyl ethyl ketone and methyl n-butyl ketone developed paralysis after 25 days, and exposure to 225 ppm methyl n-butyl ketone alone produced paralysis after 66 days (suggesting that methyl ethyl ketone shortened the latency period for the onset of methyl n-butyl ketone-induced neuropathy.

Reproductive Effects

- Data reported by Schwetz and co-workers (1974) implicate MEK to be an embryotoxic, fetotoxic and teratogenic agent in the rat. Pregnant rats (Sprague-Dawley) were exposed to MEK vapor at a concentration of 1,126 ppm (3.3 g/$m^3$) or 2,618 ppm (7.7 g/$m^3$) for 7 hours/day on days 6 through 15 of gestation. The following parameters were evaluated: maternal mortality, liver weight and behavior, number of corpora lutea/dam, number of resorptions, number of implantations, fetal mortality, fetal weight and size, and skeletal and visceral anomalies among the fetuses. MEK exposure at either dose level did not appear to affect adversely the number of implantation sites, the number of live fetuses/litter, or the number of corpora lutea/dam. There was evidence of fetotoxicity as indicated by a marked decrease in fetal body weights following exposure to 1,126 ppm (3.3 g/$m^3$). Decreased fetal weight was not observed after exposure to 2,618 ppm (7.7 g/$m^3$) of MEK. Skeletal and visceral anomalies were noted after exposure to MEK. The total incidence of skeletal anomalies (skull, vertebral, and sternebral) was increased significantly ($P<0.05$) in the 1126 ppm exposure group compared to the controls. A significant difference ($P<0.05$) also was observed in the incidence of skeletal defects of the sternum of the high-dose group and controls. The occurrence of visceral anomalies, including dilated ureters and subcutaneous edema, was significantly ($P<0.05$) increased in the offspring of rats treated at the high level (2,618 ppm, 7.7 g/$m^3$).

Developmental Effects

- The results of another study of embryo- and fetotoxicity of inhaled MEK in rats were reported by Deacon and co-workers (1981). In this study, pregnant Sprague-Dawley rats were exposed to 0, 400 ppm (1.2 g/$m^3$), 1,000 ppm (2.9 g/$m^3$) or 3,000 ppm (8.8 g/$m^3$) MEK for 7 hours/day on days 6 through 15 of gestation. Maternal toxicity, as evidenced by decreased body weight gain and increased food consumption, was observed among rats exposed to 3,000 ppm (8.8 g/$m^3$); slight fetotoxicity was observed among litters of rats exposed to this level as evidenced by an increased incidence of two minor skeletal variants. The results of this study verify the observation of an increased incidence of skeletal variants observed in the earlier study by Schwetz and co-workers (1974).

Mutagenicity

- The mutagenic potential of MEK was investigated in a testing of microbial mutagenicity of pesticides (Smirasu, 1976). In this study, MEK was used as one of several solvents for the mutagenicity screening. The test systems used were *Escherichia coli* WP2 and *Salmonella typhimurium* strains TA1535, TA1537, TA1536 and TA1538 to detect base-pair substitutions and frameshift mutations. There was no increase in the number of revertants observed in any of the test systems following exposure to MEK. However, it should be noted that MEK was tested as a solvent control at a single concentration.

Carcinogenicity

° No information was found in the available literature on the carcinogenic effects of MEK exposure to humans or animals.

## V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for One-day, Ten-day, Longer-term (approximately 7 years) and Lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(NOAEL \text{ or } LOAEL) \times (BW)}{(UF) \times (\_\_\_ \text{ L/day})} = \_\_\_ \text{ mg/L } (\_\_\_ \text{ ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect-Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100 or 1,000), in accordance with NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

A One-day HA for MEK is calculated based upon findings reported by DiVincenzo and Krasavage (1974). Guinea pigs were administered MEK at a single intraperitoneal dose of 750, 1,500 or 2,000 mg/kg. Hepatotoxicity in guinea pigs was measured in terms of increased serum ornithine carbamyl transferase activity and lipid accumulation in the liver. Elevated serum ornithine carbamyl transferase activity was observed 24 hours after administration of 2,000 mg/kg of MEK. Lipid accumulation in liver cells of animals was noted also at the two higher doses (1,500 and 2,000 mg/kg). Therefore, in view of demonstrated hepatotoxicity in terms of increased serum enzyme activity (at dose level of 2,000 mg/kg) and lipid accumulation in the liver cells at dose levels of 1,500 and 2,000 mg/kg of MEK, the lowest dose level, 750 mg/kg as the NOAEL will be used in the development of a One-day HA.

The One-day HA for a 10 kg child is calculated as follows:

$$\text{One-day HA} = \frac{(750 \text{ mg/kg day}) (10 \text{ kg})}{(100)(1 \text{ L/day})} = 75 \text{ mg/L} = 75000 \text{ ug/L}$$

where:

750 mg/kg day = NOAEL based on absence of increase in enzyme activity in guinea pigs.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

Ten-day Health Advisory

There are no data from which to derive a Ten-day HA directly. Therefore, it is recommended that the HA can be determined by dividing the One-day HA by 10, resulting in a HA of 7500 ug/L for a 10 kg child.

Longer-term Health Advisory

Adequate duration-specific oral data are not available from which to derive the Longer-term HA. However, the LaBelle and Brieger (1955) inhalation study in rats may be considered for a longer-term HA. In this study, a group of 25 rats was exposed to 235 ppm (693 mg/$m^3$) MEK for 7 hours/day, 5 days/week for 12 weeks. Without indicating the specific organs examined, the authors reported that no significant pathological changes were observed either macroscopically or microscopically. The Longer-term HA is derived as follows:

Step 1: Determination of the Total Absorbed Dose (TAD)

$$TAD = \frac{(693\ mg/m^3)(1\ m^3/hr)(7\ hr/day)(5/7)(0.5)}{70\ kg} = 24.7\ mg/kg/day$$

where:

693 mg/$m^3$ = NOAEL of 235 ppm based on absence of pathological change in rats.

1 $m^3$/hr = respiratory rate of adult human (pulmonary rate/body weight ratio) assumed to be the same for humans and test animals.

7 hr/day = exposure duration.

5/7 = conversion from 5 days exposure to 7 days exposure.

0.5 = assumed fraction of MEK absorbed.

70 kg = assumed body weight of an adult.

Step 2: Determination of the Longer-Term HA

Longer-term HA for a 10-kg child:

$$\frac{(24.7\ mg/kg/day)\ (10\ kg)}{(100)\ (1\ L/day)} = 2.5\ mg/L\ (or\ 2500\ ug/L)$$

where:

24.7 mg/kg/day = TAD.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

Longer-term HA for a 70-kg adult:

$$\frac{(24.7 \text{ mg/kg/day})\ (70 \text{ kg})}{(100)\ (2 \text{ L/day})} = 8.6 \text{ mg/L (or 8600 ug/L)}$$

where:

24.7 mg/kg/day = TAD.

70 kg = assumed body weight of an adult.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

2 L/day = assumed daily water consumption of an adult.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed for synthetic organic chemicals and a value of 10% is assumed for inorganic chemicals. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

Lifetime HA for MEK may be derived based on LaBelle and Brieger (1955) inhalation study in rats for 12 weeks. In this study, a NOAEL of 693 mg/m$^3$

was identified. Animals were exposed to MEK for 7 hours/day, 5 days/week for 12 weeks. The Lifetime HA is derived as follows:

Total absorbed dose (TAD) of 24.7 mg/kg/day was determined as described under Longer-term HA.

Step 1: Determination of the Reference Dose (RfD)

$$RfD = \frac{24.7 \text{ mg/kg/day}}{(1,000)} = 0.0247 \text{ mg/kg/day}$$

where:

24.7 mg/kg/day = TAD (NOAEL) based on absence of pathological changes.

1,000 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study of less-than-lifetime duration.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$DWEL = \frac{(0.0247 \text{ mg/kg/day}) (70 \text{ kg})}{2 \text{ L/day}} = 0.86 \text{ mg/L or } 860 \text{ ug/L}$$

where:

0.0247 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

Lifetime HA = 0.86 mg/L x 20% = 0.17 mg/L (170 ug/L)

where:

0.86 mg/L = DWEL.

20% = assumed relative source contribution from water.

Evaluation of Carcinogenic Potential

- No studies on the carcinogenic effects in animals to MEK have been found in the available literature.
- IARC has not made an assessment of MEK's carcinogenic potential.
- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986), methyl ethyl ketone may be

classified in Group D: Not classified. This category is for agents with inadequate animal evidence of carcinogenicity.

## VI. OTHER CRITERIA, GUIDELINES AND STANDARDS

- An occupational threshold limit value (TLV) of 200 ppm was set by ACGIH (1980).

## VII. ANALYTICAL METHODS

- There is no standardized method for the determination of methyl ethyl ketone in drinking water samples. However, methyl ethyl ketone may be determined by purge and trap gas chromatographic-mass spectrometric (GC-MS) procedure used for determination of volatile organic compounds in industrial and municipal discharges (U.S. EPA, 1984). In this method, a 5 mL water sample is spiked with an internal standard of an isotopically stable analog of methyl ethyl ketone and purged with an inert gas. The volatile compounds are transferred from the aqueous phase into the gaseous phase where they are passed into a sorbent column and trapped. After purging is completed, the trap is backflushed and heated to desorb the compounds on to a gas chromatograph (GC). The compounds are separated by the GC and detected by a mass spectrometer (MS). The labeled compound serves to correct the variability of the analytical technique. The method detection limit is dependent upon the nature of interferences, but it is estimated to be 50 ug/L.

## VIII. TREATMENT TECHNOLOGIES

- Because of its polarity and resulting miscibility in water, MEK is a difficult compound to remove from contaminated potable water. The conventional water treatment techniques of coagulation and sand filtration are ineffective in MEK removal (McGuire et al., 1978).

- Chlorination does cause some oxidative degradation of MEK. Treatment with 100 mg/L chlorine for 12 hours reduced MEK by 5% (McGuire et al., 1978). However, such treatment leads to the formation of trihalomethanol which makes chlorination an undesirable treatment. Oxidative treatment with 100 mg/L potassium permanganate for 3 hours was completely ineffective in reducing MEK concentrations (McGuire, 1978).
- MEK also is not a good candidate for removal by air stripping. It has a low Henry's Law Constant of $3.4 \times 10^{-5}$ atm $m^3$/mole (McGuire et al., 1978).

- Adsorption to granular activated carbon (GAC) offers the best potential for MEK removal. McGuire et al. (1978) reported a 95% removal efficiency using a 1.1 min detention time over a 1.2 hr treatment period. However, in another laboratory investigation of removal of MEK (7.2 mg/L) by Filtrasorb 400, breakthrough occurred after 3 hours of treatment at a flow rate of 23 ml/min and a detention time of 2.1 min (McGuire et al., 1978).

- McGuire et al. (1978) also attempted laboratory isotherm studies using GAC and 0.2 mm ortho-phosphate buffered glass distilled water as a solvent for the MEK. These results also indicate that treatment with GAC can be used to remove MEK.

- Treatment with powdered activated carbon (PAC) however, does not seem to be as effective (McGuire et al., 1978; Kuo et al., 1977).

- Treatment technologies for the removal of methyl ethyl ketone from water are available and have been reported to be effective. Selection of individual or combinations of technologies to achieve methyl ethyl ketone reduction must be based on a case-by-case technical evaluation, and an assessment of the economics involved.

- Positioning the chlorination step in water treatment so that it occurs after MEK removal also should be considered since MEK can serve as a precursor for THM formation.

## IX. REFERENCES

ACGIH. 1980. American Conference of Governmental Industrial Hygienists. TLVs - Threshold limit values for chemical substances in workroom air, adopted by ACGIH for 1980. Cincinnati, OH.

Carpenter, C.P., H.F. Smyth and U.C. Pozzani. 1949. The assay of acute vapor toxicity, and the grading and interpretation of results on 96 chemical compounds. J. Ind. Hyg. Tox. 31(6):343-346.

Cavender, F.L., H.W. Casey, H. Salem, J.A. Swenberg and E.J. Gralla. 1983. A 90-day vapor inhalation toxicity study of methyl ethyl ketone. Fund. Appl. Toxicol. 3:264-270.

Chain, E.S.K. 1982. Oxidation of particular organics. Personal communication.

Coleman, W.E., R.D. Lingg, R.G. Melton and F.C. Kopfler. 1976. The occurrence of volatile organics in five drinking water supplies using gas chromatography/mass spectrometry. Chapter 21. In: L.H. Keith, ed. Identification and analysis of organic pollutants in water. Ann Arbor, MI: Ann Arbor Science Publications, Inc.

Deacon, M.M., M.D. Pilny, J.A. John, B.A. Schwetz, F.J. Murray, H.O. Yakel and R.A. Kuna. 1981. Embryo- and fetotoxicity of inhaled methyl ethyl ketone in rats. Toxicol. Appl. Pharmacol. 59:617-619.

Dietz, F.K., and G.J. Traiger. 1979. Potentiation of $CCl_4$ of hepatotoxicity in rats by a metabolite of 2-butanone: 2,3-butanediol. Toxicology. 14:209-215.

DiVincenzo, G.D., and N.J. Krasavage. 1974. Serum ornithine carbamyl transferase as a liver response test for exposure to organic solvents. Am. Ind. Hyg. Assoc. J. 35:21-29.

Duckett, S., N. Williams and S. Francis. 1974. Peripheral neuropathy associated with inhalation of methyl n-butyl ketone. Experientia. 30:1283.

Hites, R.A., G.A. Jungclaus, V. Lopez-Avila and L.S. Sheldon. 1979. Potentially toxic organic compounds in industrial wastewater and river systems: two case studies. ACS Symp. Ser. 94:63-90. D. Schuetzle, ed., Monitoring Toxic Substances.

Kimura, E.T., D.E. Ebert and P.W. Dodge. 1971. Acute toxicity and limits of solvent residue for sixteen organic solvents. Toxicol. Appl. Pharmacol. 19:699-704.

Kuo, P.P.K., E.S.K. Chain, F.B. DeWalle and J.H. Kim. 1977. Gas stripping, sorption, and thermal desorption procedures for preconcentrating volatile polar water-soluble organics from water samples for analysis by gas chromatography. Analytical Chemistry. 6:1023-1029.

LaBelle, C.W., and H. Brieger. 1955. The vapor toxicity of a composite solvent and its principal components. Arch. Ind. Health. 12:623-627.

Love, O.T., and R.G. Eilers. 1981. Treatment for the control of trichloroethylene and related industrial solvents in drinking water. U.S. Environmental Protection Agency, Drinking Water Research Division. Cincinnati, Ohio.

McGuire, M.J., I.H. Suffet and J.V. Radziul. 1978. Assessment of unit processes for the removal of trace organic compounds from drinking water. JAWWA. 10:565-572.

Munies, R., and D.E. Wurster. 1965. Investigation of some factors influencing percutaneous absorption. Absorption of methyl ethyl ketone. J. Pharm. Sci. 54:1281-1284.

NIOSH. 1980. National Institute for Occupational Safety and Health. 2-Butanone (MEK). In: Quarterly hazard summary report. Cincinnati, OH: National Institute for Occupational Safety and Health.

Patty, F.A., H.H. Schrink and W.P. Yant. 1935. Acute response of guinea pigs to vapors of some new commercial organic compounds. U.S. Public Health Reports. Vol. 50, pp. 1217-1228.

Saida, K., J.R. Mendell and H.S. Weiss. 1976. Peripheral nerve changes induced by methyl n-butyl ketone and potentiation by methyl ethyl ketone. J. Neuropath. Exp. Neurol. 35(3):207-225.

Scheiman, M.A., R.A. Saunders and F.E. Sallfeld. 1974. Organic contaminants of the District of Columbia water supply. BioMedical Mass Spectrometry. Vol. 1. pp 209.

Schwetz, B.A., B.K.J. Leong and P.J. Gehring. 1974. Embryo- and fetotoxicity of inhaled carbon tetrachloride, 1,1-dichloroethane and methyl ethyl ketone in rats. Toxicol. Appl. Pharmacol. 28:452-464.

Shackelford, W., and L.H. Keith. 1976. Frequency of organic compounds identified in water. Athens, GA: U.S. Environmental Protection Agency, Environmental Research Laboratory. (EPA-600/4-76-062)

Singley, J.E., and L.J. Bilello. 1981. Advances in the development of design criteria for packed column aeration. Submitted to Journal AWWA, 1981.

Smirasu, Y. 1976. Mutagenicity testing of pesticides. Kogia to Taisaku. J. Environ. Pollu. Control. 12:407-412.

Smith, A.R., and M.R. Mayers. 1944. Poisoning and fire hazards of butanone and acetone. Indust. Hyg. Bull., New York State Dept. Labor. 23:174. (Cited in LaBelle, C.W., and Brieger, H., 1955 paper)

Smyth, H.F., C.P. Carpenter, C.S. Weil, U.O. Pozzani and J.A. Striegel. 1962. Range-finding toxicity data: List VI. Am. Ind. Hyg. Assoc. J. 23:95-107.

Spencer, P.S., and H.H. Schaumburg. 1976. Feline nervous system response to chronic intoxication with commercial grades of methyl n-butyl ketone, methyl iso-butyl ketone, methyl ethyl ketone. Toxicol. Appl. Pharmacol. 30:301-311.

Takeuchi, Y., Y. Ono, N. Hisanga, M. Iwata, M. Aoyama, J. Kitoh, and Y. Sugiura. 1983. An experimental study of the combined effects of n-hexane and methyl ethyl ketone. Brit. J. Ind. Med. 40:199-203.

Traiger, G.J., and J.V. Bruckner. 1976. The participation of 2-butanone in 2-butanol-induced potentiation of carbon tetrachloride hepatotoxicity. J. Pharmacol. Exper. Therap. 196(2):493-500.

U.S. EPA. 1976. U.S. Environmental Protection Agency. Frequency of organic compounds identified in water. Environmental Research Lab, Athens, GA., PB-265 470.

U.S. EPA. 1984. U.S. Environmental Protection Agency. Method 1624 Revision B. Volatile Organic Compounds by Isotope Dilution GC/MS. Federal Register. 49(209):433407-433415, October 26.

U.S. EPA. 1986. U.S. Environmental Protection Agency. Final guidelines for carcinogen risk assessment. Federal Register. 51(185) 33992-34003. September 24.

U.S. ITC. 1981. United States International Trade Commission. Synthetic organic chemicals United States production. USITC Publication 1183. Washington, D.C. 20436.

Wang, T.C., and J.C. Bricker. 1979. 2-Butanone and tetrahydrofuran contamination in the water supply. Bull. Environ. Contam. Toxicol. 23:620-623.

Windholz, M., ed. 1976. The Merck Index, 9th ed. Merck and Co., Inc. Rahway, N.J. p. 5937.

Zakhari, S., P. Levy, M. Leibowitz and D.M. Aviado. 1977. Review of the literature on methyl ethyl ketone. In: Isopropanol and ketones in the environment. Cleveland, OH: CRC Press, Inc.

# STYRENE

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

## I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

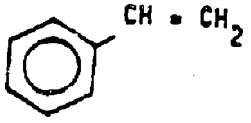
Health Advisories are developed for One-day, Ten-day, Longer-term (approximately 7 years, or 10% of an individual's lifetime) and Lifetime exposures based on data describing noncarcinogenic end points of toxicity. Health Advisories do not quantitatively incorporate any potential carcinogenic risk from such exposure. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

This Health Advisory (HA) is based on information presented in the Office of Drinking Water's Health Effects Criteria Document (CD) for Styrene (U.S. EPA, 1985a). The HA and CD formats are similar for easy reference. Individuals desiring further information on the toxicological data base or rationale for risk characterization should consult the CD. The CD is available for review at each EPA Regional Office of Drinking Water counterpart (e.g., Water Supply Branch or Drinking Water Branch), or for a fee from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Rd., Springfield, VA 22161, PB # 86-118056/AS. The toll-free number is (800) 336-4700; in the Washington. D.C. area: (703) 487-4650.

## II. GENERAL INFORMATION AND PROPERTIES

CAS No. 100-42-5

Structural Formula




Synonyms

Vinyl benzene, cinnamene, phenylethylene, ethenylbenzene

Use

Styrene plastics .

Properties (Hansch and Leo, 1979; Lewis et al., 1983)

| | |
|---|---|
| Chemical Formula | $C_8H_8$ |
| Molecular Weight | 104.16 |
| Physical State | Clear, colorless liquid with a characteristically sweet and pleasant odor |
| Melting Point | 145°C |
| Density (20°C) | 30.86 g/cm$^3$ |
| Vapor Pressure (20°C) | 4.53 torr |
| (25°C) | 6.18 torr |
| Water Solubility | 320 mg/L |
| Log Octanol/Water Partition Coefficient | 2.95 |
| Conversion Factors | 1 mg/m$^3$ = 0.235 ppm<br>1 ppm = 4.26 mg/m$^3$ |

Occurrence

- Styrene is produced primarily from the dehydrogenation of ethylbenzene. In 1982, the U.S production of styrene totaled 5.9 billion pounds.

- National drinking water surveys indicate that styrene is an infrequent contaminant. To date, the testing of 941 ground water supplies and 102 surface water supplies has failed to result in the detection of a single positive occurrence (Boland, 1981).

- Contamination of drinking water by styrene, however, has been reported occasionally by State programs.

## III. PHARMACOKINETICS

### Absorption

- Available data indicate that the absorption of styrene from the gastrointestinal tract of rats is rapid and virtually complete (Plotnick and Weigel, 1979).

- Styrene uptake and absorption has been the subject of a number of human inhalation studies (Fiserova-Bergerova and Teisinger, 1965; Teramoto and Horiguchi, 1979). The findings of these studies indicate that pulmonary retention of styrene is approximately 2/3 of the administered concentration with considerable variation in measured uptake between individuals and studies (mean uptakes ranged from 59 to 89%).

### Distribution

- The distribution of styrene following oral administration was studied in rats given single doses of 20 mg/kg $^{14}$C-styrene in corn oil by gavage (Plotnick and Weigel, 1979). Peak tissue levels were reached within 2 to 4 hours. The organs with the highest concentrations were kidney (46 ug/g in males; 25 ug/g in females), liver (13 ug/g in males; 7 ug/g in females) and pancreas (10 ug/g in males; 6 ug/g in females) with lower concentration levels in lungs, heart, spleen, adrenals, brain, testes and ovaries.

- Results from inhalation studies in rats indicate that distribution of styrene is widespread with relatively high concentrations in adipose tissue (Withey and Collins, 1979).

- In humans, Dowty et al. (1976) found concentrations of transplacentally transferred styrene to be somewhat higher than those of maternal blood, which suggests a selective one-way transplacental transfer.

- Pellizzari et al. (1982) detected styrene in each of 8 milk samples collected from lactating women residing in various cities.

### Metabolism

- The metabolic fate of styrene in mammals has been studied extensively. There is limited information from human studies, but similarities to the process in other mammals have been identified.

- Based on studies in rats administered styrene-7,8-oxide or styrene glycol by intraperitoneal injection, Ohtsuji and Ikeda (1971) have proposed that the metabolism of styrene proceeds via P-450 microsomal oxidations to styrene oxide, styrene glycol, and then to mandelic acid which is metabolized to either phenylglyoxylic acid or to benzoic the hippuric acid.

Excretion

- Results from a number of studies in rats (Withey and Collins, 1977, 1979; Ramsey and Young, 1978, 1980; Teramoto and Horiguchi, 1979) indicate that styrene is eliminated relatively rapidly from all tissues in test animals.

- Twenty-four hours following oral administration of 20 mg/kg $^{14}C$-styrene to rats, concentrations in all tissues and organs examined were less than 1 ug/g (Plotnick and Weigel, 1979).

- The elimination of styrene from the heart, brain, liver, spleen and kidney of rats was described by biphasic log-linear kinetics after intravenous injection of 4.0 mg/kg (Withey and Collins, 1977). Half-lives ranged from 3.8 to 7.1 minutes for the alpha (fast) phase and from 20 to 37 minutes for the beta (slow) phase.

- Predictions based on a toxicokinetic model (parameters estimated from a human inhalation study) indicated that maximum concentrations of styrene in both blood and fat of humans were reached after a few repeated 8-hour daily exposures to 80 ppm styrene, suggesting no tendency for long-term accumulation (Ramsey et al., 1980; Ramsey and Young, 1978, 1980).

## IV. HEALTH EFFECTS

Humans

- Results of controlled experiments using human volunteers indicate that styrene administered by inhalation at relatively high doses results in central nervous system (CNS) effects.

- Drowsiness, listlessness and an altered sense of balance were reported during a 4-hour exposure of two male subjects to styrene at 3,407 mg/m$^3$ (800 ppm) (Carpenter et al., 1944).

- Stewart et al. (1968) reported that volunteers exposed to styrene by inhalation at 217 mg/m$^3$ (50 ppm) and 499 mg/m$^3$ (117 ppm) for 1 and 2 hours, respectively, showed no signs of toxicity. The moderately strong initial styrene odor diminished after 5 minutes. At 921 mg/m$^3$ (216 ppm) nasal irritation resulted after 20 minutes. Eye and nose irritation, strong odor and altered neurological function were reported for volunteers exposed to styrene at 1,600 mg/m$^3$ (376 ppm) for 1 hour. Most volunteers exposed to this level exhibited reduced performance in the Crawford Manual Dexterity Collar and Pin Test, the modified Romberg Test and the Flannagan Coordination Test. Six subjects were exposed to 422 mg/m$^3$ (99 ppm) styrene vapor for seven hours. No serious untowed effects were noted.

- Gamberale and Hultengren (1974) exposed 12 subjects to styrene by inhalation at concentrations of 213, 639, 1,065 and 1,491 mg/m$^3$ (50, 150, 250 and 350 ppm) during four consecutive 30-minute intervals. A dose-related increase in single reaction time was evident. Reaction time recorded during the final 30-minute exposure was significantly increased ($p < 0.05$).

- Odkvist et al. (1982) studied the effects of styrene on the vestibulo-oculomotor functions in 10 subjects exposed to styrene by inhalation at 370 to 591 mg/m$^3$ (88-140 ppm) for approximately 80 minutes. The rate of movement of the eyes between two alternating light sources (saccade) increased significantly ($p < 0.05$) after exposure. Suppression of the vestibulo-oculomotor reflex was also affected.

- There is suggestive evidence that the human fetus is more sensitive than the adult to the toxic effects of styrene (Holmberg, 1977; Hemminki et al., 1980).

- The frequency of spontaneous abortions among Finnish chemical workers was analyzed by Hemminki et al. (1980). Information on spontaneous abortions (15,482 cases), induced abortions (71,235 cases) and births (193,897 cases) for 1973-1976 was obtained from the Hospital Discharge Registry of the Finnish National Board of Health and linked by social security number to the membership of the Finnish Union of Chemical Workers (approximately 900 female members). About 85% of the total number of spontaneous abortions in Finland were reportedly listed in the registry. The rate of spontaneous abortion was defined as the number of spontaneous abortions x 100/number of births. The rates of spontaneous abortion were 8.54% (N = 52) and 15.0% (N = 6) among the female union members and a subgroup in the styrene industry, respectively. These rates were significantly higher ($p<0.01$) than the rate among all Finnish women (5.52%, 15,482 spontaneous abortions). The ratios of spontaneous abortion were 16 and 32 in the female union workers and female styrene industry workers, respectively, which were significantly higher ($p<0.001$) than the rate among all Finnish women (8%).

- The information on the work histories of 43 Finnish mothers of children born with central nervous system (CNS) defects from June 1, 1976 to March 1, 1977 were obtained through personal interviews (Holmberg, 1977). Two of these mothers had been employed in the reinforced plastics industry with regular exposure to styrene, polyester resin, organic peroxides and acetone during pregnancy. The defects in their two children were anencephaly and congenital hydrocephaly. The overall rates of anencephaly and congenital hydrocephaly were reported to be 0.2 and 0.3, respectively, per 1000 live births in Finland. Based on these estimates, there appeared to be more than a 300 fold increased rate of these malformations in the reinforced plastics industry during the 9-month study period compared with the general population (2/12 vs 0.5/1000).

Animals

Short-term Exposure

- Wolf et al. (1956) reported an acute oral $LD_{50}$ of greater than 5,000 mg/kg for rats treated with styrene by gavage. This indicates that the acute toxicity of styrene is relatively low.

- The lowest single oral dose of styrene (administered by oral intubation) causing 100% mortality in rats within two weeks of treatment was 8,000 mg/kg, while 1,600 mg/kg was the maximum dose resulting in no deaths (Spencer et al., 1942).

- The effects of styrene administration at 250, 450 or 900 mg/kg orally (method not stated) for 7 consecutive days on hepatic mixed function oxidase (MFO) enzyme activities, glutathione content and glutathione-S-transferase activity were reported by Das et al. (1981). Activities of aryl hydrocarbon hydroxylase and aniline hydroxylase were significantly enhanced at higher doses of styrene (450 and 900 mg/kg). A significant lowering of glutathione content accompanied with the inhibition of glutathione-S-transferase activity was also noted at the highest dose of styrene (900 mg/kg). Therefore, the NOAEL for effects on hepatic enzymes in this study was 250 mg/kg/day.

- Agrawal et al. (1982) studied the effects of styrene on dopamine receptor binding in rats. Styrene was administered at 200 or 400 mg/kg/day by gavage to groups of 6 eight-week old ITRC male albino rats. Styrene was administered in a single dose or in up to 90 daily doses over 90 days. Significant increases in the specific binding of $^3$H-spiroperidol to dopamine receptors in the corpus stratum were noted at both levels after single or repeated exposure to styrene. The LOAEL for this study was identified as 200 mg/kg/day.

Long-term Exposure

- Changes in hepatic enzyme activity following oral exposure to styrene have been demonstrated by a number of investigators.

- Srivastava et al. (1982) administered styrene by gavage (at 200 or 400 mg/kg/day) to groups of 5 adult male albino ITRC rats, 6 days per week for 100 days. These animals did not exhibit any changes in weight gain or other overt signs of toxicity. There were significant dose-dependent increases in hepatic enzymes (benzo[a]pyrene hydroxylase and aminopyrine-N-demethylase) as well as decreases (glutathione-S-transferase). There were significant decreases in some mitochondrial enzymes as well. Histopathological changes were seen only at the high dose and these consisted of tiny areas of focal liver necrosis, consisting of a few degenerated hepatocytes and inflammatory cells. Therefore, the LOAEL for hepatic effects was 200 mg/kg/day.

- Groups of ten female rats were administered styrene at 66.7, 133, 400 or 667 mg/kg/day by intubation, five days a week for six months (Wolf

et al., 1956). At the two higher dose levels, decreased growth weights and increased liver and kidney weights were observed without hematologic or histopathologic effects. At the two lower dose levels, no effects were noted on body weight, organ weight or pathology. Therefore, the NOAEL for this study was 133 mg/kg/day and the LOAEL was 400 mg/kg/day.

- Beagle dogs were given styrene in a peanut oil suspension by gavage 7 days per week for 560 days (Quast et al., 1978). Dose levels were 200, 400 or 600 mg/kg bw/day. The controls received peanut oil only. At the two higher dose levels, minimal histopathologic effects were noted in the liver (increased iron deposits within the reticulo-endothelial cells) as well as hematologic effects that included increased Heinz bodies in erythrocytes and a decreased packed cell volume. At the lowest dose level, these effects were not noted. Therefore, 200 mg/kg/day was identified as the NOAEL for this study and 400 mg/kg/day can be designated as the LOAEL.

Reproductive Effects

- The reproductive/teratogenic effects of styrene oxide were assessed in Wistar rats (Sikov et al. 1981). The percentage of pregnant rats was reduced significantly.

Developmental Effects

- Investigators at the Dow Chemical Company administered styrene in peanut oil to pregnant Sprague-Dawley rats (29 to 39 dams per group) by gavage at dose levels of 0, 180 or 300 mg/kg/day (0, 90, 150 mg/kg twice daily) on days 6 through 15 of gestation (Murray et al., 1976; 1978). Maternal toxicity was indicated by significantly reduced ($p < 0.05$) body weight gain and food consumption at the higher dose level. There were no significant effects observed on maternal mortality or percent pregnancy. No teratogenic or fetotoxic effects were observed. Therefore, the NOAEL for maternal toxicity was 180 mg/kg/day.

Mutagenicity

- Results were negative for six mutagenicity tests using Salmonella typhimurium test systems, both with and without S-9 metabolic activating system. Styrene was tested using the bacterial strains TA1535, TA1537, TA98 and TA100. De Meester et al. (1977, 1981) and Vainio et al. (1976) obtained positive results with mutant strains sensitive to base pair substitution while all tests were negative in strains sensitive to frameshift mutagens.

- Styrene oxide, a major metabolite of styrene, has been demonstrated consistently to be mutagenic in S. typhimurium TA1535 and TA100, in the presence and absence of a mammalian metabolic activating system (De Meester et al., 1977; 1981).

Carcinogenicity

- Both positive and negative results have been reported in bioassays of the potential carcinogenicity of styrene in experimental animals. Most of the long-term bioassay results, however, are characterized by inconsistent observations of elevated tumor formation and excessive mortality among treated animals (Jersey et al., 1978; Ponomarkov and Tomatis, 1978; NTP, 1979; Maltoni et al., 1982).

- Retrospective cohort mortality and case-control studies have been conducted on workers exposed to styrene in the styrene-polystyrene manufacturing industry and in the styrene-butadiene synthetic rubber industry (McMichael et al., 1976; Smith and Ellis, 1977; Meinhardt et al., 1978). There are inadequate data at present to indicate that styrene is a human carcinogen. However, an elevated incidence of tumors of the hematopoietic and lymphatic tissues have been observed. The available studies are limited because of relatively small cohort sizes or multiple chemical exposures of workers (including exposure to benzene).

## V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for One-day, Ten-day, Longer-term (approximately 7 years) and Lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(NOAEL \text{ or } LOAEL) \times (BW)}{(UF) \times (\_\_\_ \text{ L/day})} = \_\_\_ \text{ mg/L } (\_\_\_ \text{ ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect-Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100 or 1,000), in accordance with NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

The study of Stewart et al. (1968) was seleted as the basis for calculating the One-day HA. The study invloved a controlled styrene inhalation exposure using nine healthy human male volunteers. No subjective or objective signs of toxicity were noted following one and two hour exposures to 51 ppm (217 $mg/m^3$) or 117 ppm (449 $mg/m^3$) styrene respectively. To simluate a work day, six subjects were exposed to 99 ppm (422 $mg/m^3$) styrene vapor for seven

hours. From a subjective standpoint, no serious untoward effects were noted except mild eye and throat irritation in three subjects. There were no objective signs of impairment of balance or coordination; however, three of the six subjects did report that they were having intermittent difficulty in performing the modified Romberg Test. In contrast, exposure to 376 ppm (1602 mg/$m^3$) styrene vapor for one hour resulted in abnormal neurological findings and complaints of nausea and inebriation. The result of urinalysis, hematology and blood chemistry studies were normal and unchanged from pre-exposure values.

The results of another study (Odkvist et al., 1982) using human volunteers exposed to similar styrene levels, indicate that the mean pulmonary styrene uptake was 64% of the inspired amount. Using a NOAEL of 99 ppm (422 mg/$m^3$) from a 7-hour exposure, the One-day Health Advisory for a 10-kg child can be derived. First the total absorbed dose (TAD) is determined.

$$TAD^* = \frac{(422\ mg/m^3)\ (20\ m^3/day)\ (7\ hours/24\ hours)\ (0.64)}{70\ kg} = 22.5\ mg/kg/day$$

where:

TAD = total absorbed dose.

442 mg/$m^3$ = NOAEL, based on the absence of adverse effects in humans exposed to styrene by inhalation.

7 hours/24 hours = duration of exposure.

20 $m^3$/day = assumed ventilation volume for 70-kg adult.

0.64 = estimated ratio of absorbed dose (Odkvist et al., 1982).

70 kg = weight of exposed individual (adult).

Therefore the One-day Health Advisory for a 10-kg child is as follows:

$$\text{One-day HA} = \frac{(22.5\ mg/kg/day)\ (10\ kg)}{(10)\ \ (1\ L/day)} = 22.5\ mg/L$$

where:

22.5 mg/kg/day = TAD.

10 kg = assumed body weight of a child.

10 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from a study in humans.

1 L/day = assumed daily water consumption of a child.

Ten-day Health Advisory

No information was found in the available literature that was suitable for deriving a Ten-day HA value for styrene. It is therefore recommended that the Longer-term HA for a 10-kg child (2 mg/L, calculated below) be used at this time as a conservative estimate of the Ten-day HA value.

Longer-term Health Advisory

The Quast et al. (1978) study in dogs has been chosen to serve as the basis for calculating the Longer-term HAs for styrene. In this study, beagle dogs were administered styrene by gavage at 0, 200, 400 or 600 mg/kg/day, 7 days per week, for 560 days. At the two higher doses, minimal histopathologic effects were noted in the liver (increased iron deposits within the reticulo-endothelial cells) as well as hematologic effects that included increased Heinz bodies in erythrocytes and a decreased packed cell volume. At the lowest dose level, these effects were not noted with the possible exception of the equivocal observation of low level occurrence of Heinz bodies in a single female from this group.

Based on the NOAEL of 200 mg/kg/day determined in this study, the Longer-term HAs are calculated as follows:

For a 10-kg child:

$$\text{Longer-term HA} = \frac{(200 \text{ mg/kg/day})\ (10 \text{ kg})}{(100)\ (10)\ (1 \text{ L/day})} = 2 \text{ mg/L } (2000 \text{ ug/L})$$

where:

200 mg/kg/day = NOAEL at which no decreased growth weights or increased liver and kidney weights were observed in dogs.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

10 = modifying factor for small group size (4 dogs per treatment).

1 L/day = assumed daily water consumption of a child.

For a 70-kg adult:

$$\text{Longer-term HA} = \frac{(200 \text{ mg/kg/day})\ (70 \text{ kg})}{(100)\ (10)\ (2 \text{ L/day})} = 7 \text{ mg/L } (7000 \text{ ug/L})$$

where all factors are the same except:

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed for synthetic organic chemicals and a value of 10% is assumed for inorganic chemicals. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical. For Group C carcinogens, an additional safety factor of 10 is added to the DWEL.

The Lifetime HA for a 70-kg adult has been determined on the basis of the study in dogs by Quast et al. (1978) as described above.

Using the NOAEL of 200 mg/kg/day, as determined in that study, the Lifetime HA is calculated as follows:

Step 1: Determination of the Reference Dose (RfD)

$$RfD = \frac{(200 \text{ mg/kg/day})}{(1{,}000)} = 0.2 \text{ mg/kg/day}$$

where:

200 mg/kg/day = NOAEL at which no decreased growth weights or increased liver and kidney weights were observed in dogs.

1,000 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study of less-than-lifetime duration.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$DWEL = \frac{(0.2 \text{ mg/kg/day})\ (70 \text{ kg})}{(2 \text{ L/day})} = 7 \text{ mg/L } (7000 \text{ ug/L})$$

where:

0.2 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

$$\text{Lifetime HA} = \frac{(7\ \text{mg/L})\ (20\%)}{(10)} = 0.14\ \text{mg/L}\ (140\ \text{ug/L})$$

where:

7 mg/L = DWEL.

20% = assumed relative source contribution from water.

10 = additional uncertainty factor per ODW policy to account for possible carcinogenicity.

Evaluation of Carcinogenic Potential

- Data on an increased incidence of lung tumors (adenomas and carcinomas) in $O_{20}$ strain mice (Ponomarkov and Tomatis, 1978) were used for the quantitative assessment of cancer risk due to styrene. Based on the data from this study and using the linearized multistage model, a carcinogenic potency factor ($q_1^*$) for humans of 1.34 $(mg/kg/day)^{-1}$ was calculated from the data for male mice and a $q_1^*$ of 2.47 $(mg/kg/day)^{-1}$ was calculated from the data for female mice (Ponomarkov and Tomatis, 1978). Because the data cannot accommodate a tumor incidence of 100% when only a single dose is tested, the tumor response for female mice was adjusted from 32/32 and the transformed dose reduced by multiplying the calculated transformed dose, 25.7 mg/kg/day, by the ratio 31/32 to arrive at an adjusted transformed dose of 24.9 mg/kg/day. The higher of the two $q_1^*$ values is the basis for the estimation of cancer risk levels. The doses corresponding to increased lifetime cancer risks of $10^{-4}$, $10^{-5}$ and $10^{-6}$ for a 70-kg adult are $3 \times 10^{-3}$, $3 \times 10^{-4}$, $3 \times 10^{-5}$ mg/kg/day, respectively. Assuming a water consumption of 2 liters/day, the corresponding concentrations of styrene in water are 1.4, $1.4 \times 10^{-1}$ and $1.4 \times 10^{-2}$ ug/L, respectively. These criteria, which reflect lifetime exposure, are uncertain because of short exposure duration (13% of lifetime) and the small number of animals in each dose group.

- IARC evaluated styrene in February of 1979 and found insufficient evidence to reach a conclusion as to its carcinogenicity rating (IARC, 1979).

- Applying the criteria described in EPA's guideline for assessment of carcinogenic risk (U.S. EPA, 1986), styrene may be classified in Group C: Possible human carcinogen. This category is for agents with limited evidence of carcinogenicity in animals in the absence of human data.

## VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- The OSHA Standard for styrene is an 8-hour TWA concentration of 100 ppm, a ceiling concentration of 200 ppm and a maximum peak concentration (29 CFR 1910.1000; Table Z-2) of 600 ppm for 5 minutes or less in any 3-hour period.

- The ACGIH (1982) has established the TWA-TLV for styrene in workroom air as 50 ppm with an STEL of 100 ppm. The TLV was reduced from 100 ppm in 1981 (ACGIH, 1981).

- NIOSH (1983) recommended a styrene concentration limit in workplace air of 50 ppm TWA for up to a 10-hour day, 40 hour work-week and a ceiling concentration 100 ppm determined during any 15 minute sampling period.

## VII. ANALYTICAL METHODS

- Styrene content is determined by a purge-and-trap gas chromatographic procedure used for the determination of volatile aromatic and unsaturated organic compounds in water (U.S. EPA, 1985b). This method calls for the bubbling of an inert gas through the sample and trapping styrene on an adsorbant material. The adsorbant material is heated to drive off styrene onto a gas chromatographic column which is temperature programmed to separate the method analytes which are then detected by the photoionization detector. This method is applicable to the measurement of styrene over a concentration range of 0.05 to 1,500 ug/L. Confirmatory analysis for styrene is by mass spectrometry which has a detection limit of 0.3 ug/L (U.S. EPA, 1985c).

## VIII. TREATMENT TECHNOLOGIES

- Information is available on the removal of styrene from water by air stripping, adsorption and oxidation. Styrene has a Henry's Law Constant of 12 atm which makes it suitable for removal from water by air stripping (U.S. EPA, 1985d).
- Decarbonaters which have some aeration function have been evaluated for their efficacy in styrene removal. When the influent styrene concentration was 0.076 ug/L, the decarbonators tested were able to remove 51.3% (U.S. EPA, 1985d).

- Tests evaluating adsorption of styrene by granular activated carbon showed that an average of 40% was removed over a 10-month period (U.S. EPA, 1985d). The influent styrene concentration was 0.03 ug/L.

- The ethenyl double bond found in the styrene molecule makes it amendable to oxidation. It is, therefore, possible that oxidative techniques may be effective in removing styrene from potable water. Bench scale evaluations of ozone treatment of styrene-contaminated water conducted by Avigne (1983, as cited by U.S. EPA, 1985b) indicate that the reaction rate constant for a 0.007 mM styrene solution (pH 2) is 300,000 L/mole-sec. The pH was maintained at 2 to inhibit the

decomposition of ozone. Oxidation of styrene to benzaldehyde and hydrogen peroxide was reported by Legube (1983, as cited by U.S. EPA, 1985b). Using an ozone application rate of $10^7$ mg/hr at 12 L/hr 0.9 moles ozone per mole of styrene was required to completely oxidize the styrene. The initial styrene concentration was $1.1 \times 10^{-4}$ mole/L. It was suggested that further oxidation of benzaldehyde to benzoic acid might occur.

- It is possible that other oxidizing agents such as permanganate could be effective in oxidizing styrene. However, no studies of tests of these alternative oxidizing situations were available.

## IX. REFERENCES

ACGIH. 1981. American Conference of Governmental Hygienists. TLVs. Threshold limit values for chemical substances and physical agents in the workroom environment with intended changes for 1981. Cincinnati, OH. p. 50.

ACGIH. 1982. American Conference of Governmental Hygienists. TLVs. Threshold limit values for chemical substances and physical agents in the Workroom environment with intended changes for 1982. Cincinnati, OH. p. 29.

Agrawal, A.K., S.P. Srivastava and P.K. Seth. 1982. Effect of styrene on dopamine receptors. Bull. Environ. Contam. Toxicol. 29(4):400-403.

Boland, P.A. 1981. National screening program for organics in drinking water. EPA contract 68-01-4666. SRI International.

Carpenter, C.P., C.B. Shaffer, C.S. Weil and H.F. Smyth. 1944. Studies on the inhalation of 1,3-butadiene with a comparison to its narcotic effect with benzol, toluol and styrene, and a note on the elimination of styrene by the human. J. Ind. Hyg. Toxicol. 26(3):69-78.

Das, M., R. Dixit, M. Mushtaq, S.P. Srivastava and P.K. Seth. 1981. Effect of styrene on hepatic mixed function oxidasaes, glutathione content and glutathione-S-transferase activity in rats. Drug Chem. Toxicol. 4(3):219-227.

De Meester, C., F. Poncelet, M. Roberfroid, J. Rondelet and M. Mercier. 1977. Mutagenicity of styrene and styrene oxide. Mutat. Res. 56(2):147-152.

De Meester, C., M. Durverger-Van Bogaert, M. Lambotte-Vandepaer, M. Mercier and F. Poncelet. 1981. Mutagenicity of styrene in the Salmonella typhimurium test system. Chem. Biol. Interact. 20(2):163-170.

Dowty, B.J., J.L. Laseter and J. Storer. 1976. Transplacental migration and accumulation in blood of volatile organic constituents. Pediatr. Res. 10:696-701.

Fiserova-Bergerova, V., and Teisinger. 1965. Pulmonary styrene vapor retention. Ind. Med. Surg. 34:620-622.

Gamberale, F., and M. Hultengren. 1974. Exposure to styrene. II. Psychological functions. Work Environ. Health 11(2):86-93.

Hansch, C., and A.J. Leo. 1979. Substituent constants for correlation analysis in chemistry and biology. John Wiley and Sons, New York, NY.

Hemminki, K., E. Pranssila and H. Vainio. 1980. Spontaneous abortion among female chemical workers in Finland. Int. Arch. Occup. Health 45:123-126.

Holmberg, P.C. 1977. Central nervous defects in two children of mothers exposed to chemicals in the reinforced plastics industry. Scand. J. Work Environ. Health 5:333-335.

IARC. 1979. International Agency for Research on Cancer. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Some monomers, plastics and synthetic elastomers, and acrolein. 19, 97-115.

Jersey, G., M. Balmer, J. Quast et al. 1978. Two year chronic inhalation toxicity and carcinogenicity study on monomeric styrene in rats. Dow Chemical study for Manufacturing Chemical Association. December 6.

Lewis, P.J., C. Hagopian and P. Koch. 1983. Styrene. In: Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed. M. Grayson and D. Eckroth, eds. John Wiley and Sons, Inc. New York. Vol. 21, pp. 770-801.

Maltoni, C., A. Cilberti and D. Carrietti. 1982. Experimental contributions in identifying brain potential carcinogens in the petrochemical industry. Ann. New York Acad. Sci. 381:216-249.

McMichael, A.J., R. Spirtas, J.F. Gamble and P.M. Tousey. 1976. Mortality among rubber workers: Relationship to specific jobs. J. Occup. Med. 18:178-185.

Meinhardt, T., R. Young and R. Hartle. 1978. Epidemiologic investigations of styrene-butadiene rubber production and reinforced plastic production. Scand. J. Work Environ. Health. 8(4):250-259.

Murray, F.J., J.A. John, H.D. Haberstoh et al. 1976. Teratologic evaluation of styrene monomers administered rats by gavage. Dow Chemical Study for Manufacturing Chemical Association. August 26.

Murray, F.J., J.A. John, M.F. Balmer and B.A. Schwetz. 1978. Teratologic evaluation of styrene given to rats and rabbits by inhalation or by gavage. Toxicology 11(4):335-343.

NIOSH. 1983. National Institute for Occupational Safety and Health. Criteria for a recommended standard ... occupational exposure to styrene. DHHS (NIOSH) Publ. No. 83-119. U.S. DHHS, Cincinnati, OH.

NTP. 1979. National Toxicology Program. National Cancer Institute Carcinogenesis Technical Report Series No. 185. Bioassay of styrene for possible carcinogenicity.

Odkvist, L.M., B. Larsby, R. Tham et al. 1982. Vestibulo-oculomotor disturbances in humans exposed to styrene. Acta Oto-Laryngol. 94(5-6):487-493.

Ohtsuji, M., and M. Ikeda. 1971. Metabolism of styrene in the rat and the stimulatory effect of phenobarbital. Toxicol. Appl. Pharmacol. 18(2):321-328.

Pellizzari, E.D., T.D. Hartwell, B.S.H. Harris, R.D. Waddell, D.A. Whitaker and M.D. Erickson. 1982. Purgeable organic compounds in mother's milk. Bull. Environ. Contam. Toxicol. 28(3):322-328.

Plotnick, H.B., and W.W. Weigel. 1979. Tissue distribution and excretion of $^{14}$-C-styrene in male and female rats. Res. Commun. Chem. Pathol. Pharmacol. 24(3):515-524.

Ponomarkov, V.I., and L. Tomatis. 1978. Effects of long-term oral administration of styrene to mice and rats. Scand. J. Work Environ. Health. 4(Suppl.2):127-135.

Quast, J.F., R.P. Kalnins, K.J. Olson, et. al. 1978. Results of a toxicity study in dogs and teratogenicity studies in rabbits and rats administered monomeric styrene. Toxicol. Appl. Pharmacol. 45:293-294.

Ramsey, J.C., and J.D. Young. 1978. Pharmacokinetics of inhaled styrene in rats and humans. Scand. J. Work and Health 4(Suppl.2):84-91.

Ramsey, J.C., and J.D. Young. 1980. Comparative pharmacokinetics of inhaled styrene in rats and humans. In: Proc. 10th Conference on Environmental Toxicology, OH. November, 1979. AFAMRL-TR-79-121. Wright Patterson Air Force Base, OH. pp. 103-117.

Ramsey, J.C., J.D. Young, R.J. Karbowski, M.B. Chenoweth, L.P. McCarty and W.H. Braun. 1980. Pharmacokinetics of inhaled styrene in human volunteers. Toxicol. Appl. Pharmacol. 53(1):54-63.

Sikov, M.R., W.C. Cannon, D.B. Carr, R.A. Miller, L.F. Montgomery and D.W. Phelps. 1981. Teratologic Assessment of butylene oxide, styrene oxide and methyl bromide. Study performed by Battelle Pacific Northwest Laboratory, Richland, W.A. for National Institute of Occupational Safety and Health, Division of Biochemical and Behavioral Science, Experimental Toxicol. Branch, Cincinnati, OH. DHHS (NIOSH) Publ. No. 81-124.

Smith, A.H., and L. Ellis. 1977. Styrene butadiene rubber synthetic plants and leukemia (letter to the editor). J. Occup. Med. 19(7):441.

Spencer, H.C., D.D. Irish, E.M. Adams and V.K. Rowe. 1942. The response of laboratory animals to monomeric styrene. J. Ind. Toxicol. 24(10):295-301.

Srivastava, S.P., M. Das, M. Mushtaq, S.V. Chandra and P.K. Seth. 1982. Hepatic effects of orally administered styrene in rats. J. Appl. Toxicol. 2(4):219-222.

Stewart, R.D., H.C. Dodd, E.D. Baretta and A.W. Schaffer. 1968. Human exposure to styrene vapor. Arch. Environ. Health 16(5):656-662.

Teramoto, K., and S. Horiguchi. 1979. Absorption, distribution and elimination of styrene in man and experimental animals. Arch. Hig. Rada Toksikol. 30(Suppl):431-439.

U.S. EPA. 1985a. U.S. Environmental Protection Agency. Draft health effects criteria document for styrene. Office of Drinking Water.

U.S. EPA. 1985b. U.S. Environmental Protection Agency. Method 503.1. Volatile aromatic organic compounds in water by purge and trap gas chromatography. Environmental Monitoring and Support Laboratory, Cincinnati, Ohio 45268.

U.S. EPA. 1985c. U.S. Environmental Protection Agency. Method 524.1. Volatile organic compounds in water by purge and trap gas chromatography/mass spectrometry. Environmental Monitoring and Support Laboratory, Cincinnati, Ohio 45268.

U.S. EPA. 1985d. U.S. Environmental Protection Agency. Draft technologies and costs for removal of synthetic organic chemicals from portable water supplies. Science and Technology Branch, CSD, ODW, U.S. EPA Washington, D.C.

U.S. EPA. 1986. U.S. Environmental Protection Agency. Guidelines for carcinogen risk assessment. Federal Register. 51(185):33992-34003. September 24.

Vainio, H., R. Paakonen, K. Ronnholm, V. Raunio and O Pelkonen. 1976. A study on the mutagenic activity of styrene and styrene oxide. Scand. J. Work Environ. 3:147-151.

Withey, J.R., and P.G. Collins. 1977. Pharmacokinetics and distribution of styrene monomer in rats after intravenous administration. J. Toxicol. Environ. Health 3(5-6):1011-1120.

Withey, J.R., and P.G. Collins. 1979. The distribution and pharmacokinetics of styrene monomer in rats by the pulmonary route. J. Environ. Pathol. Toxicol. 2(6):1329-1342.

Wolf, M.A., V.K. Rowe, D.D. McCollister, R.L. Hollingsworth and F. Oyen. 1956. Toxicological studies of certain alkylated benzene and benzene. Arch. Ind. Health 14:387-398.

March 31, 1987

# TETRACHLOROETHYLENE (PCE)

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

## I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

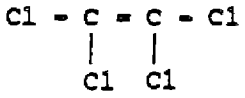
Health Advisories are developed for One-day, Ten-day, Longer-term (approximately 7 years, or 10% of an individual's lifetime) and Lifetime exposures based on data describing noncarcinogenic end points of toxicity. Health Advisories do not quantitatively incorporate any potential carcinogenic risk from such exposure. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

This Health Advisory (HA) is based on information presented in the Office of Health and Environmental Assessment Criteria Document (CD) for Tetrachloroethylene (U.S. EPA, 1985a). Individuals desiring further information on the toxicological data base or rationale for risk characterization should consult the CD. The CD is available for a fee from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Rd., Springfield, VA, 22161. The toll-free number is (800) 336-4700; in the Washington, D.C. area: (703) 487-4650.

## II. GENERAL INFORMATION AND PROPERTIES

CAS No. 127-18-4

Structural Formula



Synonyms

PCE, Perchloroethylene, 1,1,2,2-Tetrachloroethylene, Perc

Uses

Solvent for many organic substances
In drycleaning processes
Metal degreaser
Intermediate in the synthesis of certain fluorocarbons
In the textile industry (Fuller, 1976)

Properties (Verschueren, 1977; Torkelsen and Rowe, 1981; Windholz, 1983)

| | |
|---|---|
| Chemical Formula | $C_2Cl_4$ |
| Molecular Weight | 165.85 |
| Physical State | liquid |
| Boiling Point | 121.2°C |
| Melting Point | -- |
| Density | -- |
| Vapor Pressure | 19 mm Hg |
| Specific Gravity | 1.623 |
| Water Solubility | 150 mg/L (25°C) |
| Log Octanol/Water Partition Coefficient | 2.86 |
| Taste Threshold | -- |
| Odor Threshold (water) | 300 ug/L |
| 1 ppm in air | 6.78 mg/$m^3$ |
| Conversion Factor | -- |

Occurrence

- Tetrachloroethylene (PCE) is a synthetic chemical with no natural sources.
- Production of PCE was 550 million pounds in 1982 (U.S. ITC, 1983).
- The majority of PCE is not consumed during its various uses, but is released directly to the atmosphere. Tetrachloroethylene that does not evaporate during use becomes heavily contaminated with grease and oil and is disposed of in the forms of solid and liquid wastes. During disposal, PCE is dischrarged directly to land and surface water. Because metal and fabric cleaning industries are widely dispersed, PCE releases occur nationwide.
- PCE released to air degrades in a matter of days or weeks. PCE released to water degrades slowly; volatilization appears to be the major transport process for removal of PCE from aquatic systems (U.S. EPA, 1979). It is very mobile in soil and readily migrates to ground water. In ground water, where volatilization does not occur, PCE remains for months or years. Under certain conditions, PCE in ground water has been reported to degrade to trichloroethylene and then to dichloroethylene and vinyl chloride (Parsons et al., 1984; Vogel and McCarty, 1985).
- Tetrachloroethylene is ubiquitous in the air with levels in the ppt to ppb range. It is also a common contaminant in ground and surface waters with higher levels found in ground water. Surveys of drinking water supplies have found that 3% of all public systems derived from well water contain PCE levels of 0.5 ug/L or higher. A small number of systems (0.7%) have levels higher than 5 ug/L. Public systems derived from surface water have also been found to contain tetrachlorethylene but at lower levels.
- The major sources of exposure to tetrachloroethylene are from contaminated water and to a lesser extent air. Tetrachloroethylene has been reported to occur in some foods in the ppm range, but food is considered only a minor source of exposure (U.S. EPA, 1983).

## III. PHARMACOKINETICS

Absorption

- Single oral doses of ($^{36}$Cl)-PCE were absorbed completely when administered to rats at a concentration of 189 mg/kg (Daniel, 1963) as were doses of ($^{14}$C)-PCE administered to mice at a dose of 500 mg/kg (Schumann et al., 1980).
- Human volunteers at rest absorbed about 25 percent of PCE administered by inhalation exposure at 72 or 144 ppm over a four-hour period. The compound initially was absorbed rapidly, with decreasing uptake as exposure continued. Absorption was determined by measuring PCE and its metabolites (trichloroethanol, trichloroacetic acid) in exhaled air, blood and urine (Monster, 1979; Monster et al., 1979; Monster and Houtkooper, 1979).

Distribution

- Once in the bloodstream, PCE tends to distribute to body fat. In human tissue at autopsy, ratios of fat to liver concentrations are greater than 6:1 (McConnell et al., 1975). The fat to blood ratio is about 90 and the half-life for saturation of the fat to 50% of its equilibrium concentration is about 25 hours (Monster, 1979).

- In rats exposed via inhalation, PCE levels rise more or less continuously with duration of exposure in brain, lungs, and fat, but tend to level off in blood and liver after a 3-hour exposure. Brain cerebrum concentrations of PCE exceed blood levels by about four-fold, and brain cerebellum by about three-fold, independent of the duration of exposure (Savolainen et al., 1977).

Metabolism

- Only small amounts of PCE (less than 4% of the estimated absorbed dose) are metabolized and excreted as trichloroacetic acid in humans (Ogata et al., 1971; Fernandez et al., 1976).

- Oxidative metabolism is proposed to proceed via an epoxide intermediate which can lead to the major metabolite, trichloroacetic acid. (U.S. EPA, 1985a). In humans, PCE is metabolized to trichloroethanol, trichloroacetic acid and unidentified chlorinated products (Ikeda and Ohtsuji, 1972; Ikeda, 1977).

- Workers exposed occupationally reached a plateau rate of urinary metabolite excretion (measured as total trichloro-compounds) when the workplace air concentrations of PCE approached 100 ppm. Metabolite excretion did not increase when air concentrations rose to 400 ppm (Ikeda et al., 1972).

Excretion

- PCE itself is eliminated primarily via the lungs. The respiratory half-life for PCE elimination has been estimated at 65 to 70 hours (Stewart et al., 1970; Ikeda and Imamura, 1973).

- Trichloroacetic acid, as a metabolite of PCE, is eliminated with a half-life of 144 hours via the urine (Ikeda and Imamura, 1973).

## IV. HEALTH EFFECTS

Humans

- Liver, kidney, and CNS effects have been observed in humans occupationally exposed to tetrachloroethylene (U.S. EPA, 1985a).

- Hookworm treatment with oral PCE was prevalent in the 1920s and 1930s in India and the Pacific Islands. Thousands of individuals received oral doses of approximately 0.15 mL/kg (Kendrick, 1929) or a total dose of about 4 mL for adults (Fernando et al., 1939). No-effect levels for oral exposure cannot be derived from these clinical reports,

although they suggest that PCE is relatively nontoxic by the oral route at these doses.

- Stewart et al. (1974) exposed 19 volunteers to PCE (20 to 150 ppm) for a 5-week period and noted deleterious effects (decreased odor perception, diminished response on the modified Romberg test) at 100 ppm but not at 20 ppm.

Animals

Short-term Exposure

- In mice, the 24-hour $LD_{50}$s/$LC_{50}$s are: 8.8 to 10.8 g/kg by the oral route (Wenzel and Gibson, 1951), 5,200 ppm with 4 hours inhalation exposure (Friberg et al., 1953) and 4.7 g/kg intraperitoneal (Klaassen and Plaa, 1966).

- In rats, the 24-hour $LD_{50}$s/$LC_{50}$s are 13 g/kg oral (Smyth et al., 1969) and 4,000 ppm with four hours inhalation exposure (Carpenter et al., 1949).

- Single oral gavage doses of 2,158 mg/kg PCE to rabbits resulted in a 50% increase in serum lipoprotein levels and mild transient elevations of serum enzymes (alkaline phosphatase, SGOT, SGPT) which were indicative of liver damage (Fujii, 1975).

- A dose-response related increase in fatty infiltration of the livers of mice was observed after four hours of exposure to 200 to 3,000 ppm (1400 to 20,000 mg/m$^3$) via inhalation (Kylin et al., 1963). Decreased hepatic ATP and increased total lipid and triglyceride levels were observed in mice exposed to 800 ppm PCE in air for three hours (Ogata et al., 1968).

- Schumann, et al. (1980) administered tetrachloroethylene in corn oil to rats and mice via gavage for 11 consecutive days at does of 100, 250, 500 and 1000 mg/kg. For mice, histopathological changes (centrilobular swelling) were observed at all dose levels and increased body weight/liver weight ratios were observed at doses of 250 mg/kg/day and higher. Rats were more resistant with toxicity (increased liver weight and serum enzyme levels) apparent only at the highest dose. A LOAEL of 100 mg/kg/day was identified based on histopathological changes in mice.

Longer-term Exposure

- Rats were exposed to 70, 230 or 470 ppm PCE (470, 1600, or 3200 mg/m$^3$) by inhalation 8 hours/day, 5 days/week for 150 days. No significant changes were observed at 70 ppm; renal and liver congestion and swelling were observed at 230 and 470 ppm (Carpenter, 1937).

- Rats, rabbits and monkeys were exposed via inhalation to PCE at 400 ppm (2700 mg/m$^3$) 7 hours/day, 5 days/week for up to 179 days (Rowe, et al., 1952). Histopathological examination of the liver, kidney and spleen revealed no significant changes at this exposure level.

- Guinea pigs showed a dose dependent increase in liver weight and fatty infiltration of the liver when exposed to 100, 200 or 400 ppm (680, 1400, or 2700 mg/m$^3$) for up to 169 exposures over 236 days (Rowe et al., 1952).

- Kylin et al. (1965) observed fatty infiltration in livers of mice exposed to 200 ppm (1400 mg/m$^3$), 4 hours/day, 5 days/week for 8 months.

- In a study by Buben and O'Flaherty (1985), male Swiss-Cox mice were exposed to tetrachloroethylene in corn oil via gavage at doses of 0, 20, 100, 200, 500, 1000, 1500, and 2000 mg/kg, 5 days/week for 6 weeks. Liver toxicity was evaluated by several parameters including liver weight /body weight ratio, hepatic triglyceride concentrations, DNA content, histopathological evaluation and serum enzyme levels. Increased liver triglycerides were first observed in mice treated with 100 mg/kg. Liver weight/body weight ratios were significantly higher than controls for th 100 mg/kg group, and slightly higher than controls in the 20 mg/kg group. A NOAEL of 20 mg/kg/day was identified based on the absence of hepatotoxic effects.

- Toxic nephropathy was observed in mice exposed to 386 and 1072 mg/kg in corn oil via gavage, 5 days/week, for 78 weeks (NCI, 1977).

Reproductive Effects

- Rabbits showed liver enzyme changes and renal function alterations following 200 to 300 ppm exposures (1400 to 20,000 mg/m$^3$), 4 hours/day, 5 days/week for 9 weeks (Brancaccio et al., 1971; Mazza, 1972).

- Pregnant rats exposed to 300 ppm PCE (20,000 mg/m$^3$) for 7 hours/day, on days 6 through 15 of gestation had 4 to 5% reduction in body weight and twice the number of resoprtions per implantation compared with controls (Schwetz et al. (1975).

Developmental Effects

- Schwetz et al. (1975) assayed for reproductive and developmental effects in rats and mice exposed to 300 ppm PCE (20,000 mg/m$^3$) by inhalation for 7 hours/day on gestational days 6 through 15. Pregnant mice exhibited a significant increase in the mean relative liver weights and their fetuses weighed significantly less than controls. In the mouse pups, significant subcutaneous edema, delayed skull ossification and the presence of split sternebrae were observed.

- Offspring of rats exposed to PCE (900 ppm [6100 mg/m$^3$], days 7-13 of gestation; 900 ppm, days 14-20 of gestation; 100 ppm [680 mg/m$^3$], days 14-20 of gestation) were evaluated with respect to brain histopathology and biochemistry and several behavioral parameters. No significant differences were found between controls and the 100 ppm dose group. Differences in neurotransmitter levels and some alterations on behavioral tests were noted in the 900 ppm dose groups.

Mutagenicity

- Several mutagenicity studies have been performed on PCE which employ the Ames Salmonella/microsome test or modifications of this test. Most tests reveal little or no evidence of mutagenic activity by PCE except at concentrations which result in greater than 90% bacterial toxicity (U.S. EPA, 1985a).

Carcinogenicity

- PCE containing stabilizers was concluded by NCI (1977) to be a liver carcinogen in B6C3F$_1$ mice administered 386 to 1,072 mg/kg by gavage for 78 weeks. No conclusion concerning the effects on Osborne-Mendel rats administered 471 to 949 mg/kg by gavage could be made because of high mortality rates (median survival for treated animals was less than 68 weeks compared to greater than 88 weeks for controls).

- In the NTP (1985) inhalation bioassay, rats and mice of both sexes were exposed to 0, 200 and 400 ppm (rats) and 0, 100 and 200 ppm (mice) tetrachloroethylene. Male rats exhibited a significantly increased incidence of mononuclear cell leukemia, and an increased incidence of renal tubular adenomas/carcinomas (combined). PCE induced hepatocellular carcinomas in male and female mice at both doses. Classification of PCE as carcinogenic in the rat is controversial. The Science Advisory Board's Halogenated Organics Subcommittee (U.S. EPA, 1987) has questioned the relevance of mononuclear leukemia to man, a species not susceptible to this type of leukemia, and the validity of combining renal adenomas/carcinomas to achieve statistical significance to the results.

## V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for One-day, Ten-day, Longer-term (approximately 7 years) and Lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(NOAEL \text{ or } LOAEL) \times (BW)}{(UF) \times (\_\_\_ L/day)} = \_\_\_ mg/L \ (\_\_\_ ug/L)$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect-Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100 or 1,000), in accordance with NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child

One-day Health Advisory

The available studies were not considered sufficient for derivation of a One-day HA. It is recommended that the value for the Ten-Day HA, 2 mg/l, be used at this time as a conservative estimate for the One-Day HA.

Ten-day Health Advisory

Hepatotoxicity in mice exposed to tetrachloroethylene was selected as the basis for calculating the Ten-day HA value. Schumann et al. (1980) administered PCE in corn oil to rats and mice via gavage for 11 consecutive days at doses of 0, 100, 250, 500 and 1000 mg/kg. For mice, histopathological changes (centrilobular hepatocellular swelling) were observed in all treated animals, and increased liver weight/body weight ratios were observed in animals exposed to doses of 250 mg/kg and higher. The lowest dose, 100 mg/kg/day, represents the LOAEL for the study. This value is consistent with the estimated LOAEL (based on altered hepatic lipid and triglyceride content) of 160 mg/kg/day for mice exposed to 200 ppm for 4 hours (Kylin et al, 1963; see appendix), and could be used as the basis for the Ten-Day Health Advisory with the application of an uncertainty factor of 1000. This uncertainty factor is in accordance with NAS/ODW guidelines for derivation of the HA based on a LOAEL from an animal study. Data from longer-term studies indicates that an uncertainty factor of 1000 may be overly conservative in this case.

Buben and O'Flaherty (1985) treated mice with doses ranging from 20 to 2000 mg/kg, 5 days/week for 6 weeks and observed a slight increase in liver weight in mice treated with 20 mg/kg; at 100 mg/kg, increases were significantly different from controls. From this study, a dose of 20 mg/kg was identified as a NOAEL and 100 mg/kg was identified as a LOAEL. Basing the Ten-day HA on the NOAEL of 20 mg/kg with an uncertainty factor of 100 is consistent with the protection of humans from the CNS effects observed by Stewart et al. (1980) at 100 ppm for 7 hours (approximately 20 mg/kg, see appendix).

The value was calculated as follows:

$$\text{Ten-day HA} = \frac{(20\ \text{mg/kg/day})\ (10\ \text{kg})}{(100)\ (1\ \text{L/day})} = 2.0\ \text{mg/L} = 2{,}000\ \text{ug/L}$$

where:

20 mg/kg/day = NOAEL based on the absence of effects on liver weight of mice exposed to tetrachloroethylene via gavage.

10 kg = assumed body weight of child.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use of a NOAEL from an animal study.

1 L/day = assumed daily water consumption for a child.

Longer-term Health Advisory

The study by Buben and O'Flaherty was also selected as the basis for the longer-term HA. Lifetime carcinogenicity bioassays did not provide an indication of toxicity at the low dose range (NCI, 1977; NTP, 1985). The NOAEL of 20 mg/kg/day and the LOAEL of 100 mg/kg/day identified in the study by Buben and O'Flaherty are consistent with estimates of LOAELs from inhalation studies. A LOAEL of 63 mg/kg/day (based on increased liver weight and fatty infiltration of the liver) was estimated from chronic exposure of guinea pigs to 100 ppm for 7 hours/day (Rowe et al., 1952; see appendix), and a LOAEL of 160 mg/kg/day (based on fatty infiltration of the liver) from mice exposed to 200 ppm for 4 hours (Kylin et al, 1965). The Longer-term HA value for a 10-kg child was calculated as follows:

$$\text{Longer-term HA} = \frac{(20\ \text{mg/kg/day})(5/7)(10\ \text{kg})}{(100)\ (1\ \text{L/day})} = 1.4\ \text{mg/L} = 1{,}400\ \text{ug/L}$$

where:

20 mg/kg/day = NOAEL based on the absence of effects on liver weight for mice exposed to tetrachloroethylene via gavage.

5/7 = factor to convert 5 day/week exposure to daily exposure.

10 kg = assumed weight of child.

100 = uncertainty factor chosen in accordance with NAS/ODW guidelines for used of a NOAEL from an animal study.

1 L/day = assumed water consumption for a 10 kg child.

The Longer-term HA value for a 70-kg adult was calculated as follows:

$$\text{Longer-term} = \frac{(20\ \text{mg/kg/day})(5/7)(70\ \text{kg})}{(100)\ (2\ \text{L/day})} = 5.0\ \text{mg/L} = 5{,}000\ \text{ug/L}$$

where:

20 mg/kg/day = NOAEL based on the absence of effects on liver weight for mice exposed to tetrachloroethylene via gavage.

5/7 = factor to convert 5 day/week exposure to daily exposure.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use of a NOAEL from an animal study.

70 kg = assumed weight of adult.

2 L/day = assumed water consumption for 70 kg adult.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed for synthetic organic chemicals and a value of 10% is assumed for inorganic chemicals. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

No suitable chronic oral or lifetime oral studies were located in the literature to serve as the basis for the Lifetime HA value. NOAELs were not identified in the NCI (1977) study in which LOAELs were identified at high doses (386 mg/kg/day, mice, 471 mg/kg/day, rats). The NTP (1983) study in which lower doses were tested has not been validated.

Approximate NOAELs and LOAELs calculated from chronic and lifetime inhalation studies give less conservative estimates of toxic doses than the six-week oral study of Buben and O'Flaherty (1985). LOAEL estimates of 63 mg/kg/day for guinea pigs exposed to 100 ppm, 7 hrs/day (Rowe et al., 1952), 400 mg/kg/day for rats exposed to 475 ppm for 7 hr/day (Carpenter, 1937) and 160 mg/kg/day for mice exposed to 100 ppm for 6 hr/day (NTP, 1985) are consistent with the NOAEL of 20 mg/kg/day and LOAEL of 100 mg/kg/day identified in the study by Buben and O'Flaherty. In this study, mice were treated with doses of 20 to 2000 mg/kg/day, 5 days/week for 6 weeks. A slight increase in liver weight was observed at 20 mg/kg; at 100 mg/kg, liver weight and hepatic triglyceride levels were significantly increased over controls. Using the NOAEL of 20 mg/kg/day and an uncertainty factor of 1000 consistent with the use of data from less than lifetime studies, the Reference dose and DWEL were calculated as follows:

Step 1: Determination of the Reference Dose (RfD)

$$\text{Reference Dose} = \frac{(20 \text{ mg/kg/day})\ (5/7)}{1000} = 0.0143 \text{ mg/kg/day}$$

where:

20 mg/kg/day = NOAEL based on the absence of effects in liver weight for mice exposed to tetrachloroethylene via gavage.

5/7 = factor to convert 5 day/week exposure to daily exposure.

1000 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study of less-than-lifetime duration.

Step 2: Determination of the Drinking Water Equivalent Level (DWEL)

$$DWEL = \frac{(0.0143 \text{ mg/kg/day})\ (70 \text{ kg})}{(2 \text{ L/day})} = 0.5 \text{ mg/L} = 500 \text{ ug/L}$$

where:

0.0143 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 3: Determination of the Lifetime Health Advisory

A lifetime HA is not recommended for PCE because of its classification as group B2: probable human carcinogen (US EPA, 1986). The estimated excess cancer risk associated with lifetime exposure to drinking water containing tetrachloroethylene at 500 ug/L is approximately $1 \times 10^{-3}$. This estimate represents the upper 95% confidence limit from extrapolations prepared by EPA's Carcinogen Assessment Group using the linearized, multistage model. The actual risk is unlikely to exceed this value, but there is considerable uncertainty as to the accuracy of risks calculated by this methodology.

Controversy surrounds the classification of PCE. The Science Advisory Board, Halogenated Organics Subcommittee has recommended a classification of Group C: possible human carcinogen (U.S. EPA, 1987). This committee concluded that the animal evidence of carcinogenicity was limited and questioned grouping rat renal adenomas/carcinomas for statistical analysis and extrapolating mouse mononuclear cell leukemia to man, a species which is not susceptible to this type of leukemia. In contrast to group B2 carcinogens for which no lifetime HA values are recommended, lifetime HA values are calculated for group C carcinogens as follows:

$$\text{Lifetime HA} = \frac{500 \text{ ug/L} \times 20\%}{10} = 10 \text{ ug/L}$$

where:

500 ug/L = DWEL.

20% = assumed relative source contribution from water.

10 = additional uncertainty factor per ODW policy to account for possible carcinogenicity.

Evaluation of Carcinogenic Potential

° The National Academy of Sciences (NAS, 1977, 1980) and EPA's Carcinogen Assessment Group (Anderson, 1983) have calculated drinking water concentrations that would be estimated to increase the risk by one excess cancer per million ($10^{-6}$) and per one hundred thousand ($10^{-5}$). Assuming consumption of 2 liters of water/day by a 70 kg adult over a 70 year lifetime, NAS calculated drinking water concentrations of 3.5 ug/L and 35 ug/L for $10^{-6}$ and $10^{-5}$ risks, respectively. CAG calculated concentrations of 66, 6.6 and 0.7 ug/L for $10^{-4}$, $10^{-5}$ and $10^{-6}$ risks, respectively. Each group employed the linearized, non-threshold multistage model, extrapolating from data obtained in the 1977 NCI bioassay in mice.

° The linear multistage model is only one method of estimating carcinogenic risk. It is possible to estimate carcinogenic risk with the probit, logit or Weibull models, but for PCE the data are inadequate for calculating reasonable risk estimates using these techniques. While recognized as statistically alternative approaches, the range of risks described by using any of these modelling approaches has little biological significance unless data can be used to support the selection of one model over another. In the interest of consistency of approach and in providing an upper bound on the potential cancer risk, the Agency has recommended use of the linearized multistage approach.

° IARC (1979) stated that there is limited evidence to conclude that it is a carcinogen in mice, and placed it in Group 3.

° The US EPA Carcinogen Assessment Group (CAG) classified tetrachloroethylene in Group B2: Probable human carcinogen (U.S. EPA, 1986). This classification has been questioned by the Science Advisory Board, Halogenated Organics Subcommittee, which has recommended a classification of Group C: Possible human carcinogen (U.S. EPA, 1987).

## VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

° The World Health Organization has recommended a tentative guideline value of 10 ug/L for PCE in drinking water, based on carcinogenic properties (WHO, 1984).

° The National Academy of Sciences (NAS, 1980) calculated 24-hour and 7-day SNARLS. The 24-hour SNARL was 172 mg/L, based on a 490 mg/kg LOAEL following i.p. administration, a 100-fold uncertainty factor, and a 70 kg adult drinking 2 L/day of drinking water. A 7-day SNARL of 24.5 mg/liter was calculated by dividing the 24-hour SNARL by seven.

## VII. ANALYTICAL METHODS

° Analysis of tetrachloroethylene is by a purge-and-trap gas chromatographic procedure used for the determination of volatile organohalides in drinking water (U.S. EPA, 1985b). This method calls for the

bubbling of an inert gas through the sample and trapping tetrachloroethylene on an adsorbant material. The adsorbant material is heated to drive off the tetrachloroethylene onto a gas chromatographic column. This method is applicable to the measurement of tetrachloroethylene over a concentration range of 0.03 to 1500 ug/L. Confirmatory analysis for tetrachloroethylene is by mass spectrometry (U.S. EPA, 1985c). The detection limit for confirmation by mass spectrometry is 0.3 ug/L.

## VIII. TREATMENT TECHNOLOGIES

- Treatment technologies which will remove tetrachloroethylene from water include granular activated carbon adsorption (GAC), aeration and boiling.

- Dobbs and Cohen (1980) developed adsorption curves for several organic chemicals including PCE. It was reported that Filtrasorb® 300 carbon exhibited adsorptive capacities of 51 mg, 14 mg, 3.9 mg and 1.1 mg PCE/gm carbon at equilibrium concentration of 1,000, 100, 10 and 1 mg/L respectively. USEPA-DWRD installed pilot-scale adsorptiion columns in New Jersey and Rhode Island. In Rhode Island, a Filtrasorb® 400 GAC column maintained a concentration of PCE below 0.1 mg/L for 11 weeks of operation and below for 20 weeks of operation in the effluent, given an influent concentration that ranged from 600 to 2,500 mg/L (Love and Eilers, 1982). In New Jersey, PCE concentration ranging from 60 to 205 mg/L were reduced to less than 0.1 mg/L by GAC over a 58-week study period (Love and Eilers, 1982).

- PCE is amenable to aeration on the basis of its Henry's Law Constant of 1,100 atm (Kavanaugh and Trussell, 1980). In a pilot-scale packed tower aeration study, removal efficiencies of 72 to 99.8% for PCE were achieved using air-to-water ratios of 5-80, respectively (ESE, 1985).

- In diffused-air aeration pilot-scale studies using either spiked Cincinnati tap water (17-1,025 mg/L PCE) or actual PCE contaminated New Jersey groundwater (94 mg/L PCE), diffused aeration removed 90% of PCE at an air-to-water ratio of 4 for the latter and 98+% for the Cincinnati water at air-to-water ratios of 8, 16 and 20 (Love and Eilers, 1982).

- Air stripping is an effective, simple and relatively inexpensive process for removing PCE and other volatile organics from water. However, use of this process then transfers the contaminant directly to the air stream. When considering use of air stripping as a treatment process, it is suggested that careful consideration be given to the overall environmental occurrence, fate, route of exposure and various other hazards associated with the chemical.

## IX. REFERENCES

Anderson, E.L. 1983. Draft memo to Frederic A. Eidsness, Jr., entitled "Latest Cancer Risk Rate Estimates." March 22.

Brancaccio, A., V. Mazza and R. DiPaolo. 1971. Renal function in experimental tetrachloroethylene poisoning. Folia Med. (Naples). 54:233-237.

Buben, J.A., and E. O'Flaherty. 1985. Delineation of the role of metabolism in the hepatotoxicity of trichloroethylene and perchloroethylene: a dose-effect study. Tox. Appl. Pharm. 78:105-122.

Carpenter, C.P. 1937. The chronic toxicity of tetrachloroethylene. J. Ind. Hyg. Toxicol. 19:323-326.

Carpenter, C.P., H.F. Smyth, Jr. and U.C. Pozzani. 1949. The assay of acute vapor toxicity and the grading and interpretation of results on 96 chemical compounds. J. Ind. Hyg. Toxicol. 31:343-346.

Cerna, N., and H. Kypenova. 1977. Mutagenic activity of chloroethylenes analyzed by screening system tests. Mut. Res. 46 (3):214-215.

Daniel, J.W. 1963. The metabolism of $^{36}Cl$-labelled trichloroethylene and tetrachloroethylene in the rat. Biochem. Pharmacol. 12:795-802.

Dobbs, R.A., and J.M. Cohen. 1980. Carbon adsorption isotherms for toxic organics. EPA 600/8-80-023. Office of Research and Development, MERL, Wastewater Treatment Division, Cincinnati, Ohio.

ESE. 1985. Environmental Science and Engineering. Draft technologies and costs for the removal of volatile organic chemicals from potable water supplies. No. 84-912-0300. Prepared for U.S. EPA, Science and Technology Branch, CSD, ODW, Washington, D.C.

Federal Register. 1986. Guidelines for carcinogen risk assessment. 51 (185): 33992 - 34003. September 24.

Fernandez, J., E. Guberan and J. Caperos. 1976. Experimental human exposures to tetrachloroethylene vapor and elimination in breath after inhalation. Am. Ind. Hyg. Assoc. J. 37:43-150.

Fernando, P.B., M. D'Silva, G.K.B. Stork and G.R. Sinnatamby. 1939. Tetrachloroethylene in the treatment of hookworm disease, with special reference to toxicity. Indian J. Med. Res. 26:759-783.

Friberg, L., B. Kylin and A. Nystrom. 1953. Toxicities of trichloroethylene and tetrachloroethylene and Fujiwara's pyridine-alkali reaction. Acta Pharmacol. et Toxicol. 9:303-312.

Fujii, T. 1975. The variation in the liver function of rabbits after administration of chlorinated hydrocarbons. Jap. J. Ind. Health. 17:81-88.

Fuller, B.B. 1976. Air pollution assessment of tetrachloroethylene MTR-7143, McLean, Virginia, Mitre Corporation. EPA Contract No. 68-02-1495.

Hake, C.L., and R.D. Stewart. 1977. Human exposure to tetrachloroethylene: Inhalation and skin contact. Environ. Health Perspect. 21:231-238.

Ikeda, M. 1977. Metabolism of trichloroethylene and tetrachloroethylene in human subjects. Environ. Health Perspect. 21:239-245.

Ikeda, M., and T. Imamura. 1973. Biological half-life of trichloroethylene and tetrachloroethylene in human subjects. Int. Arch. Arbeitsmed. 31:209-224.

Ikeda, M., and H. Ohtsuji. 1972. A comparative study of the excretion of Fujiwara reaction-positive substances in urine of humans and rodents given trichloro- or tetrachloro- derivatives of ethane and ethylene. Brit. J. Ind. Med. 29:99-104.

Ikeda, M., H. Ohtsuji, T. Imamura and Y. Komoike. 1972. Urinary excretion of total trichloro compounds, trichloroethanol and trichloroacetic acid as a measure of exposure to trichloroethylene and tetrachloroethylene. Brit. J. Ind. Med. 29:328-333.

IARC. 1979. International Agency for Research on Cancer. IARC monographs on the evaluation of the carcinogenic risk of chemicals to man. Some monomer, plastic and synthetic elastomes and acrolein. 19:377-401.

Kavanaugh, M.C., and R.R. Trussell. 1980. Design of aeration towers to strip volatile contaminants from drinking water. JAWWA.

Kendrick, J.F. 1929. The treatment of hookworm disease with tetrachloroethylene. Amer. J. Trop. Med. 9:483-488.

Klaassen, C.D., and G.L. Plaa. 1966. Relative effects of various chlorinated hydrocarbons on liver and kidney function in mice. Toxicol. Appl. Pharmacol. 9:139-151.

Kylin, B., H. Reichard, I. Sumegi and S. Yllner. 1963. Hepatotoxicity of inhaled trichloroethylene, tetrachloroethylene and chloroform. Single exposure. Acta Pharmacol. Toxicol. 20:16-26.

Kylin, B., I. Sumegi and S. Yllner. 1965. Hepatotoxicity of inhaled trichloroethylene and tetrachloroethylene. Long-term exposure. Acta Pharmacol. Toxicol. 22:379-385.

Love, O.T., Jr., and R.G. Eilers. 1982. Treatment of drinking water containing trichloroethylene and related industrial solvents. JAWWA.

Margard, W. 1978. In vitro bioassay of chlorinated hydrocarbon solvents. Battelle Laboratories. Unpublished proprietary document for Detrex Chemical Industries. July.

Mazza, V. 1972. Enzymatic changes in experimental tetrachloroethylene poisoning. Folia Med. 55(9-10):373-381.

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

Monster, A.C. 1979. Difference in uptake, elimination and metabolism in exposure to trichloroethylene, 1,1,1-trichloroethane, and tetrachloroethylene. Int. Arch. Occup. Environ. Health. 42:311-317.

Monster, A.C., G. Boersma and H. Steenweg. 1979. Kinetics of tetrachloroethylene in volunteers: Influence of exposure concentration and work load. Int. Arch. Occup. Environ, Health. 42:303-309.

Monster, A.C., and J.M. Houtkooper. 1979. Estimation of individual uptake of trichloroethylene, 1,1,1-trichloroethane and tetrachloroethylene from biological parameters. Int. Arch. Occup. Environ. Health. 42:319-323.

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

NAS. 1980. National Academy of Sciences. Drinking Water and Health. Volume 3. National Academy Press. Washington, D.C.

NCI. 1977. National Cancer Institute. Bioassay of tetrachloroethylene for possible carcinogenicity. DHEW Publication No. NIH 77-813, U.S. Department of HEW, PHS, National Institute of Health, National Cancer Institute PB-272 950, NTIS.

NTP. 1983. Bioassay on tetrachloroethylene in female B6C3F$_1$ mice. Draft.

NTP. 1985. NTP technical report on the toxicology and carcinogenesis studies on tetrachloroethylene (perchloroethylene). NTP, Research Triangle Park, NC.

Nelson, B.K., B.J. Taylor, J.V. Setzer and R.W. Hornung. 1979. Behavioral teratology of perchloroethylene in rats. J. Environ. Pathol. Toxicol. 3:233-250.

Ogata, M., Y. Takatsuka, K. Tomokuni and K. Muroi. 1971. Excretion of organic chlorine compounds in the urine of persons exposed to vapors of trichloroethylene and tetrachloroethylene. Brit. J. Ind. Med. 28:386-391.

Ogata, M., K. Tomokuni and S. Watanabe. 1968. ATP and lipid contents in the liver of mice after inhalation of chlorinated hydrocarbons. Ind. Health. 6:116-119.

Parsons, F., P.R. Wood and J. DeMarco. 1984. Transformation of tetrachloroethene and trichloroethene in microcosms and groundwater, JAWWA. 26(2):56f.

Rowe, V.K., D.D. McCollister, H.C. Spencer, E.M. Adams and D.D. Irish. 1952. Vapor toxicity of tetrachloroethylene for laboratory animals and human subjects. AMA Arch. Ind. Hyg. Occup. Med. 5:566-579.

Savolainen, H., P. Pfaffli, M. Tengen and H. Vainio. 1977. Biochemical and behavioral effects of inhalation exposure to tetrachloroethylene and dichloromethane. J. Neuropathol. Exp. Neurol. 36(6):941-949.

Schumann, A.M., J.F. Quast and P.G. Watanabe. 1980. The pharmacokinetics and macromolecular interactions of perchloroethylene in mice and rats as related to oncogenicity. Toxicol. Appl. Pharmacol. 55:207-219.

Schwetz, B.A., B.K.J. Leong and P.J. Gehring. 1975. The effect of maternally inhaled trichloroethylene, perchloroethylene, methyl chloroform, and methylene chloride on embryonal and fetal development in mice and rats. Toxicol. Appl. Pharmacol. 32:84-96.

Smyth, H.F., Jr., C.S. Weil, J.S. West and C.P. Carpenter. 1969. An exploration of joint toxic action: Twenty-seven industrial chemicals intubated in rats in all possible pairs. Toxicol. Appl. Pharmacol. 14:340-347.

Stewart, R.D., E.D. Barretta, H.C. Dodd and T.R. Torkelson. 1970. Experimental human exposure to tetrachloroethylene. Arch. Environ. Health. 20:224-229.

Stewart, R.D., H.H. Gay, D.S. Erley, C.L. Hake and A.W. Schaffer. 1961. Human exposure to tetrachloroethylene vapor. Arch. Environ. Health. 20:516-522.

Stewart, R.D., C.L. Hake, H.V. Forster, A.J. Lebrun, J.F. Peterson and A. Wu. 1974. Tetrachloroethylene: Development of a biologic standard for the industrial worker by breath analysis. Report No. NIOSH-MCOW-ENUM-PCE-74-6, Medical College of Wisconsin, Milwaukee, Wisconsin.

Torkelson, T.R., and V.K. Rowe. 1981. Halogenated aliphatic hydrocarbons. In: Industrial Hygiene and Toxicology. 3rd ed. Vol. 2B. John Wiley and Sons, New York. p. 3561.

U.S. EPA. 1979. U.S. Environmental Protection Agency. Water Related Environmental Fate of 129 Priority Pollutants, Office of Water Planning and Standards, EPA-440/4-79-029, December 1979.

U.S. EPA. 1983. U.S. Environmental Protection Agency. Tetrachloroethylene occurrence in drinking water, food, and air. Office of Drinking Water.

U.S. EPA. 1985a. U.S. Environmental Protection Agency. Health Effects Criteria Document for Tetrachloroethylene. Criteria and Standards Division, Office of Drinking Water. Washington, D.C. April.

U.S. EPA. 1985b. U.S. Environmental Protection Agency. Method 502.1. Volatile Halogenated Organic Compounds in Water by Purge and Trap Gas Chromatography. Environmental Monitoring and Support Laboratory, Cincinnati, Ohio 45268.

U.S. EPA. 1985c. U.S. Environmental Protection Agency. Method 524.1. Volatile Organic Compounds in Water by Purge and Trap Gas Chromatography/Mass Spectrometry. Environmental Monitoring and Support Laboratory, Cincinnati, Ohio 45268.

U.S. EPA. 1986. U.S. Environmental Protection Agency. Addendum to the Health Assessment Document for Tetrachloroethylene (Perchloroethylene). Office of Health and Environmental Assessment. External Review Draft. April.

U.S. EPA. 1987. U.S. Environmental Protection Agency. Science Advisory Board's Environmental Health Committee, Halogenated Organics Subcommittee Report. Memo from N. Nelson and R.A. Griesemer to Lee M. Thomas, January 27, 1987.

U.S. ITC. 1983. U.S. International Trade Commission. Synthetic organic chemicals United States production, 1983. USITC Publication 1422. Washington, D.C. 20436.

Verschueren, K. 1977. Handbook of Environmental Data on Organic Chemicals. 2nd ed. Van Nostrand Reinhold Company. New York. p. 580-582.

Vogel, T., and P. McCarty. 1985. Biotransformation of tetrachloroethylene to trichloroethylene, dichloroethylene, vinyl chloride, and carbon dioxide under methanogenic conditions. Appl. Environ. Microbiol. 49(5).

Wenzel, D.G., and R.D. Gibson. 1951. A study of the toxicity and anthelminthic activity of n-butylidene chloride. J. Pharm. Pharmacol. 3:169-176.

WHO. 1984. World Health Organization. Guidelines for Drinking Water Quality. Volume I. Geneva. ISBN 9241541687.

Windholz, M. 1983. The Merck Index, 10th ed. Merck and Co., Inc. Rahway, New Jersey. p. 1315.

## Appendix

Estimation of absorbed dose based on inhalation exposure

| Species | Approx. weight (kg) | Approximate minute vol. (liter/min) | [PCE] (ppm) | Time of Exposure (hr/day) | Approximate dose (mg/kg/day)[a] | Reference |
|---|---|---|---|---|---|---|
| Human | 70.0 | 10.0 | 100 | 7 | 20 | Stewart et al, 1977 |
| Guinea pig | 0.50 | 0.222 | 100 | 7 | 63 | Rowe et al, 1952 |
| Rat | 0.25 | 0.132 | 200 | 6 | 130 | Savolainen et al, 1977 |
| | | | 400 | 6 | 260 | Savolainen et al, 1977 |
| | | | 230 | 8 | 200 | Carpenter, 1937 |
| | | | 470 | 8 | 400 | Carpenter, 1937 |
| Mouse | 0.025 | 0.024 | 100 | 6 | 120 | NTP, 1985 |
| | | | 200 | 6 | 230 | NTP, 1985 |
| | | | 200 | 4 | 160 | Kylin, 1963, 1965 |

[a]Dose = [PCE(mg/L)][min. vol.(L/hr)][Time(hr/day)][50% absorption]/[bw(kg)]

where:

[PCE(mg/L] = [PCE(ppm)] x (6.78 mg/$m^3$ - ppm) x (1 L/1000 $m^3$)

[min. vol.(L/hr)] = [min. vol.(L/min)] x (60 min/hr)

# TOLUENE

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

## I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for One-day, Ten-day, Longer-term (approximately 7 years, or 10% of an individual's lifetime) and Lifetime exposures based on data describing noncarcinogenic end points of toxicity. Health Advisories do not quantitatively incorporate any potential carcinogenic risk from such exposure. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

This Health Advisory is based on information presented in the Office of Drinking Water's Health Effects Criteria Document (CD) for Toluene (U.S. EPA, 1985a). The HA and CD formats are similar for easy reference. Individuals desiring further information on the toxicological data base or rationale for risk characterization should consult the CD. The CD is available for review at each EPA Regional Office of Drinking Water counterpart (e.g., Water Supply Branch or Drinking Water Branch), or for a fee from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Rd., Springfield, VA 22161, PB # 86-117975/REB. The toll-free number is (800) 336-4700; in the Washington, D.C. area: (703) 487-4650.

## II. GENERAL INFORMATION AND PROPERTIES

CAS No. 108-88-3

Structural Formula



Synonyms

- Methylbenzene, phenylmethane, toluol, methylbenzol, methacide

Uses

- Raw material in the production of benzene and other organic solvents
  Solvent (especially for paints, coatings, gums, oils and resins)
  Gasoline additive to elevate octane ratings

Properties (Amoore and Hautala, 1983; Cier, 1969; Sutton and Calder, 1975; Tute, 1971; Weast, 1977; Zoeteman et al., 1971)

| | |
|---|---|
| Chemical Formula | $C_7H_8$ |
| Molecular Weight | 92.15 |
| Physical State (room temp.) | Clear, colorless liquid |
| Melting Point | -94.9°C |
| Boiling Point | 110.6°C |
| Vapor Pressure | 28.7 mm Hg at 25°C |
| Specific Gravity | 0.8623 at 15.6°C |
| Water Solubility | |
| Fresh Water | 535 mg/L |
| Sea Water | 379 mg/L |
| Log Octanol/Water Partition Coefficient | 2.69 |
| Taste Threshold (water) | 0.04 mg/L; 1 mg/L |
| Odor Threshold (water) | 0.04 mg/L; 1 mg/L |
| Odor Threshold (air) | 0.6-140 $mg/m^3$ |
| Conversion Factor | 1 ppm = 3.77 $mg/m^3$ |

Occurrence

- Toluene occurs naturally as a component of petroleum oil.

- Toluene is produced in large amounts (5.1 billion lbs in 1981). Toluene also is produced indirectly in large volumes during gasoline refining and other operations. Toluene content of gasoline can be as high as several percent.

- Releases of toluene to the environment are mainly to air due to toluene's volatile nature, with smaller amounts to water and soil. Releases of toluene to water are due to spills and leaks of gasoline and other petroleum products and from the disposal of waste from paints, inks and other products containing toluene. Because of the widespread use of petroleum products, releases of toluene occur nationwide.

- Toluene degrades rapidly in air with a half life of a few days (Mabey et al., 1981). Toluene released to surface water rapidly volatilizes to air. Toluene released to the ground binds somewhat to soil and slowly migrates with ground water. Toluene is biodegraded readily in soils and surface waters. In the absence of biodegradation, toluene is expected to be stable in ground water (Marion and Malaney, 1963; Lutin et al., 1965; Price et al., 1974; Bridie et al., 1979; Patterson and Kodukala, 1981; Tabak et al., 1981).

- Toluene occurs at low levels in drinking water, food and air. Toluene occurs in both ground and surface public water supplies, with higher levels occurring in surface water supplies. Based upon EPA's Ground Water Supply Survey (U.S. EPA, 1983), approximately 1% of all ground water-derived public drinking water systems have levels greater than 0.5 ug/L. The highest level reported in ground water was 1.4 ug/L. Based upon EPA's National Screening Program Survey, approximately 3% of all surface water-derived drinking water systems are contaminated at levels higher than 0.1 ug/L. None of the systems were reported to contain levels higher than 1.4 ug/L. Toluene is found in foods as a naturally occurring compound at ppb levels and in the air of urban and suburban areas at levels of approximately 10 ppb. Toluene has been reported to occur in indoor air at levels higher than outside. Based upon the available data, the major source of toluene exposure is from air.

## III. PHARMACOKINETICS

Absorption

- Studies in humans showed that toluene is absorbed quickly through the respiratory tract (Astrand et al., 1972; Astrand, 1975). Toluene was detected in arterial blood within the first 10 seconds after exposure to 100 or 200 ppm toluene (Astrand et al., 1972).

- In humans, inhalation exposure at 115 ppm (430 mg/m$^3$) resulted in a pulmonary absorption of 57% after 1 hour which decreased to a stable 37% of inspired dose after 2-4 hours of exposure (Nomiyama and Nomiyama, 1974).

- Absorption from the GI tract in male rats was relatively rapid, with maximal blood-toluene levels being reached within 2 hours after gastric intubation with 100 uL toluene in 400 uL peanut oil. The oil may have slowed absorption (Pyykko et al., 1977).

- Dermal absorption of aqueous toluene (180 to 600 mg/L) across human hand skin was 160 to 600 ug/cm$^2$/hour. Absorption was related directly to concentration (Dutkiewicz and Tyras, 1968a,b).

Distribution

- Little is known about the tissue distribution of toluene in humans. Due to its lipophilic nature and low water solubility, toluene would be expected to distribute to and accumulate in lipid tissue (U.S. EPA, 1985a).

- In male rats, tissue distribution of toluene and its metabolites is similar following inhalation of high concentrations of toluene (17,340 mg/m$^3$) or oral administration of a single dose of labelled toluene (100 uL in 400 uL peanut oil) (Pyykko et al., 1977; Bergman, 1979). Toluene is distributed throughout the body with greatest accumulation in lipid tissues (adipose, bone marrow). Toluene and its metabolites also were found in relatively high concentration in tissues active in its metabolism and excretion (i.e., liver and kidney).

Metabolism

- Toluene is metabolized in humans, rats and rabbits by side-chain hydroxylation to benzyl alcohol, which is conjugated with glycine to form hippuric acid (70% of the dose) and then excreted in the urine (Daley et al., 1968; Ogata et al., 1970).

- In rats dosed orally with toluene, minor amounts of toluene undergo ring hydroxylation, probably via arene oxide intermediates, to form o-cresol and p-cresol (0.04-1.0% of the dose) which are excreted in the urine as sulphate or glucuronide conjugates (Bakke and Scheline, 1970; Angerer, 1979).

Excretion

- Following oral or inhalational exposure in both humans and animals, toluene is excreted rapidly as the unchanged compound in expired air and mainly as the metabolite, hippuric acid, in the urine (Smith et al., 1954; El Masri et al., 1956; Ogata et al., 1970).

- Most of the urinary excretion of toluene occurs within 12 hours of the termination of exposure. The concentration of toluene in exhaled air of human subjects declined rapidly as soon as inhalation exposure was terminated (Astrand et al., 1972).

- The supply of glycine needed to conjugate with toluene in hippuric acid formation may be a limiting factor in the rate of toluene excretion. Riihimaki (1979) suggested that toluene at 780 ppm (2,940

mg/m$^3$) during light work or 270 ppm (1,010 mg/m$^3$) during heavy work would saturate the capacity for glycine conjugation in humans.

## IV. HEALTH EFFECTS

### Humans

- Exposures of humans to toluene are usually the result of inhalation of toluene vapors in experimental or occupational settings or during episodes of intentional abuse.

- Acute exposure to toluene at approximately 200 ppm (754 mg/m$^3$) for 8 hours caused symptoms indicating CNS toxicity (fatigue, headache, nausea, muscular weakness, confusion and incoordination (von Oettingen et al., 1942a,b; Carpenter et al., 1944). These effects generally increased in severity with increases in toluene concentration (von Oettingen et al., 1942a,b). Toluene vapor at 100 ppm for 8-hour exposures appeared to be the NOAEL for these effects (von Oettingen et al., 1942a,b).

- Subacute occupational exposure to toluene (for 1 to 3 weeks) at levels of 50 to 1500 ppm (189 to 5660 mg/m$^3$) resulted in symptoms similar to those seen in acute exposure studies and which were related to level of exposure (Wilson, 1943).

- Chronic exposure to toluene vapors at levels of approximately 200 to 800 ppm have been associated primarily with CNS (von Oettingen et al., 1942a,b) and, possibly, peripheral nervous system effects (Matsushita et al., 1975; Seppalainen et al., 1978). Disturbances in memory, thinking, psychomotor skills, visual accuracy and sensorimotor speed were reported in a significant number of workers exposed to 200 to 800 ppm for "many years" (Munchinger, 1964). Hanninen et al. (1976) reported many differences in performance test results between non-exposed workers and painters exposed to approximately 30.6 ppm toluene for an average of 14.8 years. Effects indicative of cerebral and cerebellar dysfunction, such as ataxia, tremors, equilibrium disorders, impaired speech, vision and hearing, and impaired memory and coordination have been reported in chronic abusers of toluene (Knox and Nelson, 1966; Boor and Hurtig, 1977; Sasa et al., 1978).

- Chronic abuse of and occupational exposures to toluene (approximately 200 to 800 ppm) for periods ranging from 2 weeks to 6 years have been associated with hepatomegaly and hepatic function changes (Greenburg et al., 1942; Grabski, 1961). Renal function also appears to be affected in chronic abusers of toluene (Kroeger et al., 1980; Moss et al., 1980).

### Animals

#### Short-term Exposure

- The oral toxicity of toluene is relatively low, with an $LD_{50}$ between 6.4 and 7.53 g/kg in adult rats (Wolf et al., 1956; Smyth et al.,

1969; Kimura et al., 1971). The earliest observable sign of acute oral toluene toxicity in adult rats is inhibition of the functions of the CNS, which become evident at approximately 2.0 g/kg (Kimura et al., 1971).

- The $LC_{50}$ for inhaled toluene is 4,618 ppm (17,400 mg/m$^3$) after a 6-hour exposure in rats (Bonnet et al., 1982). No effects were reported after acute exposures to 620 or 1,100 ppm (2,340 or 4,150 mg/m$^3$) toluene, but 1250 ppm (4710 mg/m$^3$) affected coordination and irritated the mucous membranes in rats.

- The dermal $LD_{50}$ in rabbits is 12.2 g/kg (Smyth et al., 1969).

Long-term Exposure

- Subchronic oral administration of toluene to female rats at 118, 354 or 590 mg/kg/day for 193 days (5 days/week for 138 total doses) resulted in no effects at any level (hematological, clinical, gross or histopathological) and a NOAEL $\geq$590 mg/kg/day (Wolf et al., 1956).

- Subchronic inhalation of toluene for 6 weeks resulted in slight pulmonary irritation in rats exposed at 200 ppm (754 mg/m$^3$) for 7 hours/day, 5 days/week (von Oettingen et al., 1942a). Renal effects were evident in rats treated at 600 ppm (2260 mg/m$^3$) for 7 hours/day, 5 days/week for 6 weeks.

- Chronic inhalation of toluene was studied in F344 rats exposed to 30, 100 or 300 ppm (113, 377 or 1,130 mg/m$^3$) toluene 6 hr/day, 5 days/week for 24 months (CIIT, 1980). Reduced hematocrit values were reported in females exposed to 100 and 300 ppm. Increased corpuscular hemoglobin concentration was reported in females exposed to 300 ppm.

Reproductive Effects

- Data regarding the reproductive effects of toluene have not been located.

Developmental Effects

- Based on data reported in an abstract, oral administration of 1.0 mL/kg toluene in cottonseed oil to pregnant CD-1 mice, 3 times daily on days 6 through 15 of gestation, resulted in a statistically significant increase in the incidence of cleft palate (Nawrot and Staples, 1979). Maternal toxicity was not seen after exposure to toluene but a significant increase in embryonic lethality occurred at doses of 0.3 ml/kg and up.

- Inhalation exposures to 1,000 mg/m$^3$ by pregnant rats for 8 hours per day on gestational days 1 through 21 resulted in a significant increase in signs of skeletal retardation but did not cause internal or external malformations (Hudak and Ungvary, 1978).

Mutagenicity

- Toluene has been tested for mutagenicity by many investigators using various assay methods (reverse mutation, mitotic gene conversion and mitotic crossing-over) and has not been demonstrated to be genotoxic or mutagenic.

Carcinogenicity

- CIIT (1980) concluded that exposures to 0, 30, 100 or 300 ppm toluene for 24 months did not produce an increased incidence of neoplastic, proliferative, inflammatory or degenerative lesions in F344 rats. However, the highest dose used did not approach the Maximum Tolerated Dose (MTD) and, therefore, it has been suggested that toluene may not have been adequately tested for carcinogenicity (Powers, 1979).

- Other studies suggest that toluene is not carcinogenic when applied topically (twice weekly applications of 0.1 ml toluene for 20 weeks) to the shaved skin of mice (Frei and Stephens, 1968).

- No evidence of a promotion effect was noted when toluene (0.1 ml) was painted on the skin of mice twice weekly for 20 weeks following initiation with 7,12-dimethyl-benz(a)anthracene (Frei and Kingsley, 1968; Frei and Stephens, 1968).

- Toluene is used extensively as a solvent for lipophilic chemicals being tested for carcinogenic potential. Negative control studies employing 100% toluene were negative.

## V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for One-day, Ten-day, Longer-term (approximately 7 years) and Lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(NOAEL \text{ or } LOAEL) \times (BW)}{(UF) \times (\_\_ L/day)} = \_\_\_ mg/L (\_\_\_ ug/L)$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect-Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100 or 1,000), in accordance with NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

The effects of single inhalation exposures of humans to toluene for periods up to 8 hours have been reported by several investigators (von Oettingen et al., 1942a,b; Carpenter et al., 1944; Ogata et al., 1970; Gamberale and Hultengren, 1972). Based on the consistent dose-response data from a combination of these studies, it is evident that toluene at approximately 100 ppm for up to 8 hours/day causes no apparent adverse effects in humans. Complaints of headache and drowsiness were reported by one volunteer exposed to 50 and 100 ppm, while consistent toluene-induced effects (fatigue, muscular weakness, incoordination) were evident in persons exposed to 200 ppm for 8 hours. Gamberale and Hultengren (1972) reported that a 20-minute exposure to 100 ppm toluene was a no-effect level when determined by perceptual speed and reaction time tests. At 200 ppm, toluene was noted as clearly causing toxic effects such as incoordination, exhilaration and prolonged reaction time (von Oettingen et al., 1942a,b; Carpenter et al., 1944; Ogata et al., 1970). These data substantiate the selection of 100 ppm (377 $mg/m^3$) toluene as the NOAEL in humans exposed for up to 8 hours.

Using a NOAEL of 100 ppm (377 $mg/m^3$), a One-day HA is calculated as follows:

Step 1: Determination of the Total Absorbed Dose (TAD)

$$TAD = \frac{(377\ mg/m^3)(20\ m^3/day)(0.6)(8\ hr/24\ hr)}{70\ kg} = 21.5\ mg/kg/day$$

where:

377 $mg/m^3$ = NOAEL (converted from 100 ppm) for absence of toxic effects in humans (von Oettingen et al., 1942a,b).

8 hours/24 hours = duration of exposure in one day.

20 $m^3$/day = assumed daily ventilation volume for 70 kg adult

0.6 = estimated ratio of dose absorbed (Nomiyama and Nomiyama, 1974).

70 kg = assumed body weight of an adult.

Step 2:

The One-day HA for a 10-kg child is derived from the TAD as follows:

$$\text{One-day HA} = \frac{(21.5\ mg/kg/day)(10\ kg)}{(10)\ (1\ L/day)} = 21.5\ mg/L\ (21{,}500\ ug/L)$$

where:

21.5 mg/kg/day = TAD

10 kg = assumed body weight of a child.

10 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from a human study.

1 L/day = assumed daily water consumption of a child.

Ten-day Health Advisory

No information was found in the available literature that was suitable for determination of a Ten-day HA value. It is therefore recommended that the DWEL, adjusted for a 10 kg child (3.46 mg/L), be used at this time as a conservative estimate of the Ten-day HA value.

Longer-term Health Advisory

No information was found in the available literature that was suitable for determination of the Longer-term HA values. It is therefore recommended that the DWEL, adjusted for a 10 kg child (3.46 mg/L), be used at this time as a conservative estimate of the Longer-term HA values.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed for synthetic organic chemicals and a value of 10% is assumed for inorganic chemicals. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

The study by CIIT (1980) is the most appropriate from which to derive the Lifetime Health Advisory. Rats were exposed to toluene via inhalation at 0, 113, 337 or 1130 mg/m$^3$ for 6 hrs/day 5 days/wk for two years. All parameters measured at the end of the study, to include clinical chemistry, hematology and urinalysis, were normal with the exception of a decreased hematocrit in females exposed at 100 and 300 ppm (377 and 1130 mg/m$^3$, respectively) and an increased corpuscular hemoglobin concentration in the high-dosed females.

Similar changes did not occur in the males nor were they related to any pathological findings. From these results, a NOAEL of 300 ppm (1130 mg/kg) was identified.

Using this NOAEL, the Lifetime Health Advisory is derived as follows:

Step 1: Determination of the Total Absorbed Dose (TAD)

$$TAD = \frac{(1130\ mg/m^3)\ (6\ hours/24\ hours)\ (20\ m^3/day)\ (5/7)\ (0.6)}{70\ kg} = 34.6\ mg/kg/day$$

where:

1130 $mg/m^3$ = NOAEL from animal data.

6 hours/24 hours = exposure duration in one day.

20 $m^3$/day = assumed daily respiratory volume of an adult.

5/7 = conversion of 5 day/week dosing regimen to 7 day/week continuous exposure.

0.6 = estimated ratio of dose absorbed (Nomiyama and Nomiyama, 1974).

70 kg = assumed body weight of an adult.

Step 2: Determination of the Reference Dose (RfD)

$$RfD = \frac{(34.6\ mg/kg/day)}{100} = 0.346\ mg/kg/day$$

Where:

28.8 mg/kg/day = TAD.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

Step 3: Determination of the Drinking Water Equivalent Level (DWEL)

$$DWEL = \frac{(0.346\ mg/kg/day)\ (70\ kg)}{(2\ L/day)} = 12.1\ mg/L\ (12{,}100\ ug/L)$$

where:

0.346 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 4: Determination of the Lifetime Health Advisory

Lifetime HA = (12.1 mg/L) (20%) = 2.42 mg/L (2,420 ug/L)

where:

12.1 mg/L = DWEL.

20% = assumed relative source contribution from water.

Evaluation of Carcinogenic Potential

- IARC (1982) has not classified toluene into various categories of carcinogenic risk to humans.
- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986), toluene may be classified in Group D: Not classified. This category is for agents with inadequate animal evidence of carcinogenicity.
- The chronic (106-week) bioassay of toluene in F-344 rats of both sexes resulted in no carcinogenic effects (CIIT, 1980). Gross and microscopic examination of tissues and organs revealed no increase in neoplastic tissue or tumor masses among rats treated at 30, 100 or 300 ppm when compared with controls. This bioassay, however, could have been performed at higher exposure levels, since the highest dose administered (300 ppm) was not a Maximum Tolerated Dose (MTD).
- Prechronic carcinogenicity testing of commercial toluene administered by gavage to F344 rats and B6C3F$_1$ mice has been conducted, but a technical report on the data has not been issued (NCI, 1983). The NTP (NCI, 1983) also has started a chronic bioassay of commercial toluene in rats and mice exposed by inhalation. Testing is in progress, but neither preliminary nor final data are available. The assessment of the carcinogenic potential of toluene must await the completion of these tests.

## VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- TLV = 100 ppm ( 375 mg/m$^3$); STEL = 150 ppm ( 560 mg/m)$^3$ for skin (ACGIH, 1981).
- EPA's ambient water quality criterion for toluene is 14.3 mg/L (U.S. EPA, 1980).
- The EPA has proposed a Recommended Maximum Contaminant Level (RMCL) of 2.0 mg/L based upon the Adjusted Acceptable Daily Intake (AADI) of 10.1 mg/L for noncarcinogenic effects assuming 20% contribution from drinking water (U.S. EPA, 1985d).

## VII. ANALYTICAL METHODS

- Analysis of toluene is by a purge-and-trap gas chromatographic procedure used for the determination of volatile aromatic and unsaturated organic compounds in water (U.S. EPA, 1985b). This method calls for the bubbling of an inert gas through the sample and trapping toluene on an adsorbant material. The adsorbant material is heated to drive off toluene onto a gas chromatographic column. The gas chromatograph is temperature programmed to separate the method analytes which are then detected by the photoionization detector. This method is applicable to the measurement of toluene over a concentration range of 0.02 to 1500 ug/L. Confirmatory analysis for toluene is by mass spectrometry (U.S. EPA, 1985c). The detection limit for confirmation by mass spectrometry is 0.2 ug/L.

## VIII. TREATMENT TECHNOLOGIES

- Treatment options for removing toluene from drinking water sources include aeration and adsorption onto granular activated carbon (GAC). Conventional treatment methods have been found to be ineffective for the removal of toluene from drinking water (ESE, 1982).

- The Henry's Law Constant for toluene (288 atm at 20°C) indicates it is amenable to removal by aeration. In a pilot-scale study, a packed column aerator, operated at 50 to 90% of its flooded condition, removed toluene from contaminated water (ESE, 1982). A field study by Cummins (1985) also demonstrated the efficacy of aeration treatment.

  Water containing 62 ug/L toluene from a gasoline spill was decontaminated successfully by air stripping (air to water ration was 30:1 or greater). The process was less effective at lower air to water ratios (i.e., 8:1) but even at this ratio about 70% of the toluene was removed.

- Air stripping is an effective, simple and relatively inexpensive process for removing toluene and other volatile organics from water. However, use of this process then transfers the contaminant directly to the air stream. When considering use of air stripping as a treatment process, it is suggested that careful consideration be given to the overall environmental occurrence, fate, route of exposure and various hazards associated with the chemical.

- Carbon adsorption isotherms developed by Dobbs and Cohen (1980) showed that GAC can remove toluene from water effectively. However, with Freundlich constants of 26 for K and 0.44 for 1/n, carbon usage rates would be relatively high (U.S. EPA, 1985b). Toluene was also successfully removed from a light hydrocarbon cracking quench using GAC. The solution treated contained 8.3 mg/L toluene. Breakthrough on a 6 ft x 4 inch GAC column (Filtrasorb® 300) occurred after the processing of about 1,200 gallons. Suffet et al., as cited by ESE (1982) found that GAC (Filtrasorb® 400) adsorbed toluene from water containing a mixture of contaminants. However, in this pilot study, breakthrough occurred after 10 weeks, whereas levels of the other contaminants remained below detection for 18 weeks.

## IX. REFERENCES

ACGIH. 1984. American Conference of Governmental Industrial Hygienists. Toluene. Documentation of threshold limit values for substances in workroom air. 3rd ed. Cincinnati, OH. p. 400.

Amoore, J.E., and E. Hautala. 1983. Odor as an aid to chemical safety: Odor threshold compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. J. Appl. Tox. 3:272-290.

Angerer, J. 1979. Occupational chronic exposure to organic solvents. VII. Metabolism of toluene in man. Int. Arch. Occup. Environ. Health. 43(1): 63-67.

Astrand, I. 1975. Uptake of solvents in the blood and tissues of man. A review. Scand. J. Work Environ. Health. 1(4):199-218.

Astrand, I., H. Ehrner-Samuel, A. Kilbom and P. Ovrum. 1972. Toluene exposure. I. Concentration in alveolar air and blood at rest and during exercise. Work Environ. Health. 72(3):119-130.

Bakke, O.H., and R.R. Scheline. 1970. Hydroxylation of aromatic hydrocarbons in the rat. Toxicol. Appl. Pharmacol. 16:691-700.

Bergman, K. 1979. Whole-body autoradiography and applied tracer techniques in distribution and elimination studies of some organic solvents. Benzene, toluene, xylene, styrene, methylene chloride, chloroform, carbon tetrachloride and trichloroethylene. Scand. J. Work Environ. Health. 5: Suppl. 1. (263 pp.).

Bonnet, P., Y. Morele, G. Raoult, D. Zissu and D. Gradiski. 1982. Determination of the median lethal concentration of the main aromatic hydrocarbons in the rats. Arch. Mal. Prof. Med. Trav. Secur. Soc. 43(4):261-265.

Boor, J.W., and H.I. Hurtig. 1977. Persistent cerebellar ataxia after exposure to toluene. Ann. Neurol. 2(5):440-442.

Bridie, A.L., et al. 1979. BOD and COD of some photochemicals. Water Research. 13:627-630.

Carpenter, C.P., C.B. Shaffer, C.S. Weil and H.F. Smyth, Jr. 1944. Studies on the inhalation of 2,3-butadiene; with a comparison of its narcotic effect with benzol, toluol and styrene, and a note on the elimination of styrene by the human. J. Ind. Hyg. Toxicol. 26:69-78.

CIIT. 1980. Chemical Industry Institute of Toxicology. A twenty-four month inhalation toxicology study in Fischer-344 rats exposed to atmospheric toluene. Executive Summary and Data Tables. October 15, 1980.

Cier, H.E. 1969. Toluene. In: Kirk-Othmer Encyclopedia of Chemical Technology, Vol. 20, 2nd ed., A. Standen, ed. John Wiley and Sons, Inc., N.Y., p. 528.

Cummins, M.D. 1985. Field evaluation of packed column air stripping. U.S. Environmental Protection Agency, Office of Drinking Water, Technical Support Division, Cincinnati, Ohio 45268.

Daley, J., D. Jerina and B. Witkop. 1968. Migration of deuterium drinking hydroxylation of aromatic substrates by liver microsomes. I. Influence of ring substituents. Arch. Biochem. Biophys. 128(2):517-527.

Dobbs, R.A., and J.M. Cohen. 1980. Carbon adsorption isotherms for toxic organics. EPA 600/8-80-023. MERL, U.S. EPA, Cincinnati, Ohio.

Dutkiewicz, T., and H. Tyras. 1968a. The quantitative estimation of toluene skin absorption in man. Arch. Gewerbepath Gewerbehyg. 24:253-257.

Dutkiewicz, T., and H. Tyras. 1968b. Skin adsorption of toluene, styrene and xylene by man. Br. J. Med. 25(3):243.

El Masri, A.M., J.N. Smith and R.T. Williams. 1956. Studies in detoxication. 69. The metabolism of alkylbenzenes: n-propylbenzene and n-butylbenzene with further observations on ethylbenzene. Biochem. J. 64:50-56.

ESE. 1982. Environmental Science and Engineering, Inc. ESE review of organic contaminants in ODW data base for summary of all available treatment techniques: Toluene. Office of Drinking Water, U.S. Environmental Protection Agency. EPA No. 68-01-6494.

Frei, J.V., and W.F. Kingsley. 1968. Observations on chemically induced regressing tumors of mouse epidermis. J. Natl. Cancer Inst. 41:1307-1313.

Frei, J.V., and P. Stephens. 1968. The correlation of promotion of tumor growth and of induction of hyperplasia in epidermal two-stage carcinogenesis. Br. J. Cancer. 22:83-92.

Gamberale, F., and M. Hultengren. 1972. Toluene exposure. II. Psychophysiological functions. Work Environ. Health. 9(3):131-139. (CA 79:950-1973).

Grabski, D.A. 1961. Toluene sniffing producing cerebellar degeneration. Am. J. Psychiatry. 118:461-462.

Greenburg, L., M.R. Mayers, H. Heimann and S. Moskowitz. 1942. The effects of exposure to toluene in industry. J. Am. Med. Assoc. 118:573-578.

Hanninen, H., L. Eskelinen, K. Husman and M. Nurmineen. 1976. Behavioral effects of long-term exposure to a mixture of organic solvents. Scand. J. Work Environ. Health. 2(4):240-255.

Hudak, A., and G. Ungvary. 1978. Embryotoxic effects of benzene and its methyl derivatives: toluene, xylene. Toxicology. 11:55-63.

IARC. 1982. International Agency for Research on Cancer. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Supplement 4. Lyon, France.

Kimura, E.T., D.M. Ebert and P.W. Dodge. 1971. Acute toxicity and limits of solvent residue for sixteen organic solvents. Toxicol. Appl. Pharmacol. 19(4):699-704.

Knox, J.W., and J.R. Nelson. 1966. Permanent encephalopathy from toluene inhalation. N. Engl. J. Med. 275:1494-1496.

Kroeger, R.M., R.J. Moore, T.H. Lehman, J.D. Giesy and E.D. Skeeters. 1980. Recurrent urinary calculi associated with toluene sniffing. J. Urol. 123(1):89-91.

Lutin, P.A., J.J. Cibulka and G.W. Malaney. 1965. Oxidation of selected carcinogenic compounds by activated sludge. Purdue Univ., Eng. Bull. Ext. Ser. 118:131-145.

Mabey, W.R., J.H. Smith, R.T. Podoll et al. 1981. Aquatic fate process data for organic priority pollutants: Final draft report. U.S. EPA, Washington, D.C. EPA 440/4-81-014.

Marion, C.V., and G.W. Malaney. 1963. Ability of activated sludge microorganisms to oxidize aromatic organic compounds. Proc. Indus. Waste Conf. 18:297-308. (CA 62:1437a, 1965)

Matsushita, T., Y. Arimatsu, A. Ueda, K. Satoh and S. Nomura. 1975. Hematological and neuro-muscular response of workers exposed to low concentration of toluene vapor. Ind. Health. 13:115-121.

Moss, A.H., P.A. Gabow, W.D. Kaehny, S.I. Goodman and L.L. Haut. 1980. Fanconi's syndrome and distal renal tubular acidosis after glue sniffing. Ann. Intern. Med. 92:69-70.

Munchinger, R. 1964. Der nachweis central nervoser storungen bei losungsmitt el-exponierten arbeitern. Excerpta Medica Series, Madrid; 16-21. 2(62):687-689. (Ger.)

Nawrot, P.S., and R.E. Staples. 1979. Embryo-fetal toxicity and teratogenicity of benzene and toluene in the mouse. Teratology. 19:41A. (Abst.)

NCI. 1983. National Cancer Institute. National Toxicology Program/Carcinogenesis Testing Program. Chemicals on Standard Protocol: Management Status, June 15. Tech. Info. Sec. CTP/NTP. Bethesda, Md.

Nomiyama, K., and H. Nomiyama. 1974. Respiratory retention, uptake and excretion of organic solvents in man. Benzene, toluene, n-hexane, trichloroethylene, acetone, ethyl acetate and ethyl alcohol. Int. Arch. Arbeitsmed. 32(1-2):75-83.

Ogata, M., K. Tomokuni and Y. Takatsuka. 1970. Urinary excretion of hippuric acid and m- or p-methylhippuric acid in the urine of persons exposed to vapours of toluene and m- or p-xylene as a test of exposure. Br. J. Ind. Med. 27(1):43-50.

Patterson, J.W., and P.S. Kodukala. 1981. Biodegradation of hazardous organic pollutants. Chem. Eng. Prog. 77(4):48-55.

Powers, M.B. 1979. Chemical selection meetings on toluene. Memorandum for the record from the NTP Chemical Selection Group, Toxicology Branch, CGT, DCCP, National Institute, Washington, D.C., May 25.

Price, K.S., G.T. Waggy and R.A. Conway. 1974. Brine shrimp bioassay and seawater BOD of petrochemicals. J. Water Pollut. Control Fed. 46(1):63-77.

Pyykko, K., H. Tahti and H. Vapaatalo. 1977. Toluene concentrations in various tissues of rats after inhalation and oral administration. Arch. Toxicol. 38:169-176.

Riihimaki, V. 1979. Conjugation and urinary excretion of toluene and m-xylene matabolites in a man. Scand. J. Work Environ. Health. 4(1):135-142.

Sasa, M., S. Igarashi, T. Miyazaki, K. Miyazaki, S. Nakano and I. Matsuoka. 1978. Equilibrium disorders with diffuse brain atrophy in long-term toluene sniffing. Arch. Oto-Rhino-Laryngol. 221(3):163-169.

Seppalainen, A.M., K. Husman and C. Martenson. 1978. Neurophysiological effects of long-term exposure to a mixture of organic solvents. Scand. J. Work Environ. Health. 4(4):304-314.

Smith, J.N., R.H. Smithies and R.T. Williams. 1954. Studies in detoxication. 55. The metabolism of alkylbenzenes: (a) Glucuronic acid excretion following the administration of alkylbenzenes: (b) Elimination of toluene in the expired air of rabbits. Biochem. J. 56:317-320.

Smyth, H.F., Jr., C.P. Carpenter, C.S. Weil, U.C. Pozzani, J.A. Striegel, and J.S. Nycum. 1969. Range-finding toxicity data. List. VII. Am. Ind. Hyg. Assoc. J. 30(5):470-476.

Sutton, C., and J.A. Calder. 1975. Solubility of alkylbenzenes in distilled water and seawater at 25°C. J. Chem. Eng. Data. 2(3):320-322. (CA 83:104181q, 1975)

Tabak, H.H., S.A. Quave, C.I. Mashni and E.F. Barth. 1981. Biodegradability studies with organic priority pollutants compounds. J. Water Pollut. Control Fed. 53:1503-1518.

Tute, M.S. 1971. Principles and practice of Hansch analysis: A guide to structure-activity correlation for the medicinal chemist. Adv. Drug. Res. 5:1-77.

U.S. EPA. 1980. United States Environmental Protection Agency. Water quality criteria documents; availability. Federal Register 45(231): 79318-79379.

U.S. EPA. 1983. U.S. Environmental Protection Agency. Ground Water Supply Survey. Computer data file provided by Office of Drinking Water, Technical Support Division, U.S. EPA, Cincinnati, OH.

U.S. EPA. 1985a. U.S. Environmental Protection Agency. Drinking water criteria document for toluene (Final Draft). March, 1985.

U.S. EPA. 1985b. United States Environmental Protection Agency. Method 503.1. Volatile aromatic and unsaturated organic compounds in water by purge and trap gas chromatography. Environmental Monitoring and Support Laboratory, Cincinnati, Ohio 45268.

U.S. EPA. 1985c. U.S. Environmental Protection Agency. Method 524.1. Volatile organic compounds in water by purge and trap gas chromatography/mass spectrometry. Environmental Monitoring and Support Laboratory, Cincinnati, Ohio 45268.

U.S. EPA. 1985d. U.S. Environmental Protection Agency. National primary drinking water regulations; Synthetic organic chemicals, inorganic chemicals and microorganisms; Proposed Rule. Federal Register. 50(219):46936-47022. November 13.

U.S. EPA. 1986. U.S. Environmental Protection Agency. Guidelines for carcinogen risk assessment. Federal Register 51(185):33992-34003. September 24.

von Oettingen, W.F., P.A. Neal, D.D. Donahue, et al. 1942a. The toxicity and potential dangers of toluene, with special reference to its maximal permissible concentration. U.S. Public Health Service Pub., Bull. No. 279. p. 50.

von Oettingen, W.F., P.A. Neal, and D.D. Donahue. 1942b. The toxicity and potential dangers of toluene -- Preliminary report. J. Am. Med. Assoc. 118:579-584.

Weast, R.C., ed. 1977. CRC handbook of chemistry and physics, 58th ed. Chemical Rubber Co., Cleveland, OH.

Wilson, R.H. 1943. Toluene poisoning. JAMA. 123:1106-1108.

Wolf, M.A., V.K. Rowe, D.D. McCollister, R.C. Hollingsworth and F. Oyen. 1956. Toxicological studies of certain alkylated benzenes and benzene. Arch. Ind. Health. 14:387-398.

Zoeteman, B.C.J., A.J.A. Kraayeveld and C.J. Piet. 1971. Oil pollution and drinking water odors. Water 4(16):367-371.

# 1,1,1-TRICHLOROETHANE

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

## I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

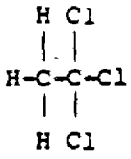
Health Advisories are developed for One-day, Ten-day, Longer-term (approximately 7 years, or 10% of an individual's lifetime) and Lifetime exposures based on data describing noncarcinogenic end points of toxicity. Health Advisories do not quantitatively incorporate any potential carcinogenic risk from such exposure. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

This Health Advisory is based on information presented in the Office of Drinking Water's Health Effects Criteria Document (CD) for 1,1,1-Trichloroethane (U.S. EPA, 1984a). The HA and CD formats are similar for easy reference. Individuals desiring further information on the toxicological data base or rationale for risk characterization should consult the CD. The CD is available for review at each EPA Regional Office of Drinking Water counterpart (e.g., Water Supply Branch or Drinking Water Branch), or for a fee from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Rd., Springfield, VA 22161, PB # 86-118130/AS. The toll free number is (800) 336-4700; in the Washington, D.C. area: (703) 487-4650.

## II. GENERAL INFORMATION AND PROPERTIES

CAS No. 71-55-6

Chemical Structure



Synonyms

- 1,1,1-TCA, methyl chloroform, ethane, 1,1,1-trichloro and methyltrichloromethane.

Uses

- In the cleaning and vapor degreasing of fabricated metal parts
- In the synthesis of other organic chemicals
- As a spot remover and film cleaner
- As an additive in metal cutting oils

Properties (U.S. EPA 1984)

| | |
|---|---|
| Chemical Formula | $C_2H_3Cl_3$ |
| Molecular Weight | 133.41 |
| Physical State | colorless, nonflammable liquid |
| Boiling Point | 74°C |
| Melting Point | -- |
| Density | 4.6 |
| Vapor Pressure | 100 mm Hg (25°C) |
| Water Solubility (25°C) | 44 mg/L |
| Log Octanol/Water Partition Coefficient | -- |
| Taste Threshold | -- |
| Odor Thresnold | -- |
| Conversion Factor | 5.4 $mg/m^3$ |

Occurrence

- 1,1,1-Trichloroethane is a synthetic chemical with no natural sources.

- Production of 1,1,1-trichloroethane was 600 million lbs in 1982 (U.S. ITC, 1983). About 70% of all 1,1,1-trichloroethane is used in metal cleaning.

- The major source of 1,1,1-trichloroethane released to the environment is from its use as a metal degreaser. Since 1,1,1-trichloroethane is not consumed during degreasing operations, the majority of all 1,1,1-trichloroethane production is released to the environment. Most of the releases occur to the atmosphere by evaporation. However, 1,1,1-trichloroethane which is not lost to evaporation becomes heavily contaminated with grease and oil and is disposed of by burial in landfills or dumping on the ground or into sewers. Because metal working operations are performed nationwide, 1,1,1-trichloroethane releases occur in all industrialized areas. Releases of 1,1,1-trichloroethane from other uses also may be significant.

- 1,1,1-Trichloroethane released to the air degrades slowly with an estimated half life of from 1 [illegible] s. 1,1,1-Trichloroethane released to surface waters migrates to the atmosphere in a few days or weeks. 1,1,1-Trichloroethane which is released to the land does not sorb onto soil and migrates readily to ground water. 1,1,1-Trichloroethane slowly hydrolyzes in water with an estimated half-life of greater than 6 months. 1,1,1-Trichloroethane, unlike other chlorinated compounds, does not bioaccumulate in individual animals or food chains.

- Because of the large and dispersed releases, 1,1,1-trichloroethane occurs widely in the environment. 1,1,1-Trichloroethane is ubiquitous in the air with levels in the low ppb range, and is a common contaminant in ground and surface waters with higher levels found in ground water. Surveys of drinking water supplies have found that 3% of all public systems derived from well water contain 1,1,1-trichloroethane at levels of 0.5 ug/L or higher. A small number of systems (0.1%) have levels higher than 100 ug/L. Public systems derived from surface water also have been found to contain 1,1,1-trichloroethane but at lower levels. 1,1,1-Trichloroethane has been reported to occur in some foods in the ppb range.

- The major sources of exposure to 1,1,1-trichloroethane are from contaminated water and, to a lesser extent, air. Food is only a minor source.

## III. PHARMACOKINETICS

Absorption

- While inhalation of 1,1,1-TCA vapor through the lungs is the common route of entry into the body, 1,1,1-TCA also is absorbed rapidly and completely from the gastrointestinal tract (Stewart et al., 1969).

- Stewart and Andrews (1966) reported an observation of non-lethal acute intoxication after oral ingestion of a liquid ounce of 1,1,1-TCA (0.6 g/kg bw). The concentration of 1,1,1-TCA in the expired air was measured serially and found to be equivalent to an inhalation exposure of 500 ppm (2,700 mg/$m^3$) by experimental subjects.

- Monster et al. (1979) and Humbert and Fernandez (1977) reported 1,1,1-TCA retention in subjects exposed to 70 (378 mg/$m^3$) or 140 ppm (756 mg/$m^3$) respectively, to be 30 percent of the inspired air concentration at equilibrium after 4 hours of exposure.

Metabolism

- 1,1,1-TCA is metabolized to a very limited extent by animals and humans (Monster et al., 1979). The metabolites include trichloroethanol, TCA-glucuronide and trichloroacetic acid which are excreted primarily in urine; very small amounts of trichloroethanol (1 percent), however, are excreted unchanged by the lungs.

- Hake and his coworkers (1960), using $C^{14}$-labeled 1,1,1-TCA, determined that less than 3% of 1,1,1-TCA is metabolized by rats following a single intraperitoneal injection of 1,1,1-TCA.

- More recently, estimates of the extent of metabolism in the human have been made from controlled inhalation exposure with unlabeled 1,1,1-TCA (Seki et al., 1975; Humbert and Fernandez, 1977; Monster et al., 1979). From the experimentally determined retained dose and the amounts of 1,1,1-TCA metabolites excreted into the urine, no more than 6% of the dose is estimated to be metabolized.

- The metabolic fate of inhaled 1,1,1-TCA in rats and mice is not altered upon repeated exposures (Schumann et al., 1982).

Excretion

- Unchanged 1,1,1-TCA is primarily excreted via lungs.

## IV. HEALTH EFFECTS

Humans

- Acute pulmonary congestion and edema typically are found in fatalities resulting from inhalation of 1,1,1-TCA (Capalan et al., 1976; Bonventre et al., 1977). Fatty vacuolation in the livers of the exposed subjects also has been observed (Capalan et al., 1976).

Animals

Short-term Exposure

- The acute oral $LD_{50}$ for 1,1,1-TCA, as determined in several species of animals, ranges from 5.7 to 14.3 g/kg (Torkelson et al., 1958).

- Vainio et al. (1976) found that a single oral dose of approximately 1.4 g/kg depressed some hepatic microsomal metabolic indices in rats (including cytochrome P-450 and epoxide hydratase).

- Bruckner et al. (1985) observed that there was relatively little evidence of toxicity in a short-term study by gavage in rats receiving 1,1,1-TCA at 0.5 g/kg for 9 days. Higher doses of 5 and 10 g/kg caused transient hyperexcitability and protracted narcosis, as well as fatalities.

Long-term Exposure

- Bruckner et al. (1985) administered 1,1,1-TCA to rats by gavage 5 times weekly for up to 12 weeks at 0, 0.5, 2.5 or 5.0 g/kg. Rats given 2.5 or 5.0 g/kg exhibited reduced body weight gain and CNS effects. Approximately 35% of these rats died during the first 50 days of the experiment, but only the 5.0 g/kg group showed an increase in serum enzyme levels indicating an alteration in index of toxicity. Ingestion of 0.5 g/kg for 12 weeks did not result in alterations in indices of toxicity.

- McNutt et al. (1975) exposed mice continuously by inhalation to 1,1,1-TCA at 250 (1,365 mg/m$^3$) or 1,000 ppm (5,400 mg/m$^3$) for 14 weeks. Serial sacrifice of exposed and control mice from 1 to 14 weeks demonstrated significant changes in the centrilobular hepatocytes as well as evidence of triglyceride accumulation in the livers of the 1,000 ppm exposure group.

- In the NCI (1977) study, diminished body weight gain and decreased survival time were observed in both rats and mice. Male and female rats were given 750 or 1,500 mg/kg 1,1,1-TCA in corn oil by gavage 5 times weekly for 78 weeks. Similarly, male and female mice received approximately 2,800 or 5,600 mg/kg for 78 weeks.

- In the NTP bioassay (1983), rats and mice were gavaged 5 times weekly with 1,1,1-TCA in corn oil at doses of 375 or 750 mg/kg body weight (rats) and 1,500 or 3,000 mg/kg body weight (mice), respectively, for 103 weeks.

Reproductive Effects

- There appeared to be no dose-dependent effects on fertility, gestation, viability indices in mice exposed to 1,1,1-TCA at dose levels of 100, 300 or 1,000 mg/kg for 35 days (Lane et al., 1982).

Developmental Effects

- There appeared to be no dose-dependent effects on viability indices in mice exposed to 1,1,1-TCA at dose levels of 100, 300 or 1,000 mg/kg for 35 days (Lane et al., 1982).

Mutagenicity

- Simmon et al. (1977) reported that 1,1,1-TCA was mutagenic in various strains of S. typhimurium, with metabolic activation.

- Loprieno et al. (1979) stated that 1,1,1-TCA was not mutagenic in Saccharomyces cerevisiae or Schizosaccharomyes bombe.

Carcinogenicity

- NTP (1983) has reported a significant ($P < 0.05$) dose response trend and increased incidences of hepatocellular carcinomas in the low- and high-dose male and in the high-dose female mice exposed to 1,1,1-TCA for 103 weeks. However, it should be noted that these findings are based on the draft report and may change pending the outcome of the ongoing NTP audit of the study.

## V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for One-day, Ten-day, Longer-term (approximately 7 years) and Lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(NOAEL \text{ or } LOAEL) \times (BW)}{(UF) \times (\_\_\_ \text{ L/day})} = \_\_\_ \text{ mg/L } (\_\_\_ \text{ ug/L})$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect-Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100 or 1,000), in accordance with NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

The study by Vainio et al. (1976) in rats is used in calculating a One-day HA. In this study, 1,1,1-TCA at a single oral dose of approximately 1.4 g/kg depressed hepatic microsomal metabolic indices (cytochrome P-450, epoxide hydratase) in rats. Using this dose as a NOAEL (although its significance is not well established), a One-day HA for the 10 kg child is calculated as follows:

$$\text{One-day HA} = \frac{(1.4 \text{ g/kg/day})\ (10 \text{ kg})}{(100)\ (1 \text{ L/day})} = 140 \text{ mg/L} \quad \text{or} \quad 140000 \text{ ug/L}$$

where:

1.4 g/kg/day = NOAEL based on absence of changes in hepatic microsomal metabolic indices in rats.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

Ten-day Health Advisory

Insufficient toxicological data are available to derive a Ten-day HA for 1,1,1-TCA. However, in order to provide a health guidance level for 1,1,1-TCA for this duration of exposure, it is recommended that the Longer-term HA for the 10 kg child be used (35 mg/L or 35,000 ug/L).

Longer-term Health Advisory

A subchronic oral toxicity study in rats by Bruckner et al. (1985) is used for the Longer-term HA. In this study, rats (200 to 250 g) were given 1,1,1-TCA 5 times weekly by gavage for 12 weeks at 0, 0.5, 2.5 or 5 g/kg. Rats given 2.5 or 5.0 g/kg exhibited reduced body weight gain and CNS effects including transient hyperexcitability and protracted narcosis. Approximately 35% of these rats died during the first 50 days of the experiment, but only the 5.0 g/kg group showed an increase in serum enzyme levels. Ingestion of 0.5 g/kg for 12 weeks did not result in alteration in indices of toxicity (serum enzyme levels, organ weights or histopathological changes in the liver and kidney).

Using 0.5 g/kg/day as a NOAEL, a Longer-term HA for the 10 kg child is calculated as follows:

$$\text{Longer-term HA} = \frac{(500 \text{ mg/kg/day})\ (10 \text{ kg})\ (5/7)}{(100)\ (1 \text{ L/day})} = 35 \text{ mg/L } (35{,}000 \text{ ug/L})$$

where:

0.5 g/kg/day = NOAEL in a 12-week study based on absence of various parameters of toxicity in rats.

10 kg = assumed body weight of a child.

5/7 = conversion of 5 day/week exposure to daily exposure.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

Longer-term HA for 70 kg adult:

$$\text{Longer-term HA} = \frac{(500 \text{ mg/kg/day})\ (70 \text{ kg})\ (5/7)}{(100)\ (2 \text{ L/day})} = 125 \text{ mg/L } (125{,}000 \text{ ug/L})$$

where:

0.5 g/kg/day = NOAEL in a 12-week study based on absence of various parameters of toxicity in rats.

70 kg = assumed body weight of an adult.

5/7 = conversion of 5 day/week exposure to daily exposure.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

2 L/day = assumed daily water consumption of an adult.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed for synthetic organic chemicals and a value of 10% is assumed for inorganic chemicals. If the contaminant is classifed as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

In the absence of suitable ingestion toxicological data to derive a Lifetime HA, an inhalation study in mice is considered for a Lifetime HA.

McNutt et al. (1975) exposed male mice continuously via inhalation to 1,1,1-TCA at 250 (1,365 mg/$m^3$) or 1,000 ppm (5,460 mg/$m^3$) for 14 weeks. Control mice were exposed to room air. Serial sacrifice of exposed and control mice from 1 to 14 weeks demonstrated significant changes in the centrilobular hepatocytes of animals in the 1,000 ppm (5,460 mg/$m^3$) group. These changes consisted of vesiculation of the rough endoplasmic reticulum with loss of

attached polyribosomes, increased smooth endoplasmic reticulum, microbodies and triglyceride droplets. A NOAEL could not be identified but a LOAEL of 250 ppm (1,365 mg/$m^3$) from this study can be used with appropriate uncertainty factors. A Lifetime HA based upon these data is derived as follows:

Step 1: Determination of the Total Absorbed Dose (TAD)

$$TAD = \frac{(1{,}365\ mg/m^3)\ (1\ m^3/hr)\ (6\ hrs)\ (0.3)}{(70\ kg)} = 35\ mg/kg/day$$

where:

1,365 mg/$m^3$ (250 ppm) = LOAEL based on histological changes in liver of animals.

1 $m^3$/hr = ventilation volume for a 70 kg adult.

6 hrs = Exposure assumed to be saturable; thus, 6 hrs is considered equivalent to exposure for a 24-hour period.

0.30 = ratio of administered dose absorbed.

70 kg = assumed body weight of an adult.

Step 2: Determination of the Reference Dose (RfD)

$$RfD = \frac{(35\ mg/kg/day)}{(1{,}000)} = 0.035\ mg/kg/day$$

where:

35 mg/kg/day = TAD and LOAEL based on histological change in liver of animals

1,000 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a LOAEL from an animal study.

Step 3: Determination of the Drinking Water Equivalent Level (DWEL)

$$DWEL = \frac{(0.035\ mg/kg/day)\ (70\ kg)}{(2\ L/day)} = 1.0\ mg/L\ (1{,}000\ ug/L)$$

where:

0.035 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 4: Determination of the Lifetime Health Advisory

Lifetime HA = 1 mg/L x 0.20 = 200 ug/L

where:

1 mg/L = DWEL.

0.20 = assumed relative source contribution from water.

Evaluation of Carcinogenic Potential

- IARC (1982) has classified 1,1,1-trichloroethane in Group 3: Inadequate data to evaluate.
- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986), 1,1,1-trichloroethane is classified in Group D: Not classified (inadequate aniaml evidence of carcinogenicity).

## VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- NAS (1980) has calculated a chronic SNARL of 3.8 mg/L for an adult consuming 2 liters of water and contribution from water being 20%.
- An ambient water quality criterion of 18.7 mg/L was calculated for an adult consuming 2 liters of water daily (U.S. EPA, 1980).

## VII. ANALYTICAL METHODS

- Analysis of 1,1,1-trichloroethane is by a purge-and-trap gas chromatographic procedure used for the determination of volatile organohalides in drinking water (U.S. EPA, 1985a). This method calls for the bubbling of an inert gas through the sample and trapping 1,1,1-trichloroethane on an adsorbant material. The adsorbant material is heated to drive off the 1,1,1-trichloroethane onto a gas chromatographic column. This method is applicable to the measurement of 1,1,1-trichloroethane over a concentration range of 0.03 to 1500 ug/L. Confirmatory analysis for 1,1,1-trichloroethane is by mass spectrometry (U.S. EPA 1985b). The detection limit for confirmation by mass spectrometry is 0.3 ug/L.

## VIII. TREATMENT TECHNOLOGIES

- Treatment technologies which will remove 1,1,1-trichloroethane from water include granular activated carbon (GAC) adsorption, aeration and boiling.
- Dobbs and Cohen (1980) developed adsorption isotherms for several organic chemicals including 1,1,1-TCA. It was reported that

Filtrasorb® 300 carbon exhibited adsorption capacities of 1.1 mg and 0.5 mg 1,1,1-TCA/gm carbon at equilibrium concentrations of 100 and 10 ug/L, respectively. U.S. EPA installed pilot-scale adsorption columns in Connecticut and New Jersey. In Connecticut, contaminated well water with 1,1,1-TCA concentrations ranging from 10 to 50 ug/L was passed through a Filtrasorb® 400 GAC column. Breakthrough occurred after 11,360 bed volumes (BV) or approximately 12 weeks of continuous operation. In New Jersey, contaminated groundwater with an average of 300 ug/L of 1,1,1-TCA was passed over a Witcarb® 950 GAC column. Breakthrough occurred after 16,800 bed volumes (BV) or approximately 30 weeks of continuous operation. A similar study assessed the effects of differing contact time and carbon adsorption of 1,1,1-TCA (Love and Eilers, 1982). It was reported that 1,1,1-TCE concentrations of 100 ug/L were reduced to 0.5 ug/L when loadings of 0.26 mg, 0.51 mg and 0.74 mg 1,1,1-TCA/gm of Filtrasorb® 400 carbon for contact times of 7.5, 15 and 22.5 minutes, respectively, were used.

- 1,1,1-TCA is amenable to aeration on the basis of its Henry's Law Constant of 400 atm (Kavanaugh and Trusell, 1980). In a pilot-scale diffused aeration column, removal efficiency of 90% of 1,1,1-TCA was achieved from an initial concentration of 237 ug/L at an air-to-water ratio of 4:1 (Love and Eilers, 1982). In a pilot-scale packed tower aeration study, removal efficiencies of 74-97% were achieved for 42-110 ug/L 1,1,1-TCA for a broad spectrum of operating parameters (Love and Eilers, 1982).

- Boiling also is effective for removing 1,1,1-TCA from water on a short-term, emergency basis. Studies have shown that 5 minutes of vigorous boiling will remove 96% of 1,1,1-TCA originally present (Love and Eilers, 1982).

- Air stripping is an effective, simple and relatively inexpensive process for removing 1,1,1-TCA and other volatile organics from water. However, use of this process then transfers the contaminant directly to the air stream. When considering use of air stripping as a treatment process, it is suggested that careful consideration be given to the overall environmental occurrence, fate, route of exposure and various other hazards associated with the chemical.

## IX. REFERENCES

Bonventre, J., O. Brennan, D. Jason, A. Henderson and M.L. Bastos. 1977. Two deaths following accidental inhalation of dichloromethane and 1,1,1-trichloroethane. J. Analyt. Toxicol. 4:158-160.

Bruckner, J.V., S. Muralidhara, W.F. Mackenzie, G.M. Kyle and R. Luthra. 1985. Acute and subacute oral toxicity studies of 1,1,1-trichloroethane (TRI) in rats. The Toxicologist. 5(1):100.

Caplan, Y.J., R.C. Backer and J.Q. Whitaker. 1976. 1,1,1-Trichloroethane: report of a fatal intoxication. Clin. Toxicol. 9:69-74.

Dobbs, R.A., and J.M. Cohen. 1980. Carbon adsorption isotherms for toxic organics, EPA 600/8-80-023, Office of Research and Development, MERL, Wastewater Treatment Division, Cincinnati, Ohio.

ESE. 1984. Environmental Science and Engineering. Technologies and costs for the removal of volatile organic chemicals from potable water supplies. ESE No. 84-912-0300 prepared for U.S. EPA Science and Technology Branch, CSD, ODW, Washington, DC.

Hake, C.L., D. Waggoner, N. Robertson and V.K. Rowe, 1960. The metabolism of 1,1,1-trichloroethane by rat. Arch. Environ. Health. 1:101-105.

Humbert, B.E., and J.G. Fernandez. 1977. Exposure to 1,1,1-trichloroethane: contribution to the study of absorption, excretion and metabolism in human subjects. Arch. Mal. Prof. 38:415-425.

IARC. 1982. International Agency for Research on Cancer. IARC Monographs on the evaluation of carcinogenic risk to men. Suppl. 4.

Kavanaugh, M.C., and R.R. Trussell. 1980. Design of aeration towers to strip volatile contaminants from drinking water. Journal AWWA. December.

Lane, R.W., B.L. Riddle and J.F. Borzelleca. 1982. Effects of 1,2-dichloroethane and 1,1,1-trichloroethane in drinking water on reproduction and development in mice. Toxicol. Appl. Pharmacol. 63:409-421.

Loprieno, N., R.A.M. Rossi, S. Fumero, G. Meriggi, A. Mondino and S. Silvest. 1979. *In vivo* mutagenicity studies with trichloroethylene and other solvents. Preliminary results. Institute di ricerche biomediche. Ivrea, Italy.

Love, O.T., Jr., and R.G. Eilers. 1982. Treatment of drinking water containing trichloroethylene and related industrial solvents. Journal AWWA. August.

McNutt, N., R. Amster, E. McConnell and F. Morris. 1975. Hepatic lesions in mice after continuous inhalation exposure to 1,1,1-trichloroethane. Lab. Invest. 32:642-654.

Monster, A.C., G. Boersma and M. Steenweg. 1979. Kinetics of 1,1,1-trichloroethane in volunteers; influence of exposure concentration and workload. Int. Arch. Occup. Environ. Health. 42:293-301.

NAS. 1980. National Academy of Sciences. Drinking Water and Health. Volume 3. National Academy Press. Washington, DC

NAS. 1983. National Academy of Sciences. Drinking Water and Health. Vol. 5. National Academy Press. Washington, DC.

NCI. 1977. National Cancer Institute. Bioassay of 1,1,1-trichloroethane for possible carcinogenicity. CAS No. 71-55-6. Technical Report Series No. 3. January 1977.

NTP. 1983. National Toxicology Program. Carcinogenesis bioassay of 1,1,1-trichlorethane in F344/N rats and B6C3F1 mice.

Perry, R.H., and C.H. Chilton. 1973. Chemical Engineers Handbook. 5th Edition. McGraw Hill Book Company.

Schumann, A.M., T.R. Fox and P.G. Watanabe. 1982. A comparison of the fate of inhaled methyl chloroform (1,1,1-trichloroethane) following single or repeated exposure in rats and mice. Fund. Appl. Toxicol. 2:27-32.

Seki, Y., Y. Urashima, H. Aikawa, H. Matsumura, Y. Ichikawa, F. Kiratsuka, Y. Hoshioka, S. Shimbo and M. Ikeda. 1975. Trichloro-compounds in the urine of humans exposed to methyl chloroform at sub-threshold levels. Int. Arch. Arbeitsmed. 34:39-49.

Simmon, V.F., A. Kauhanen and R.G. Tardiff. 1977. Mutagenic activity of chemicals identified in drinking water. In: Scott, Bridges and Sobels, eds. Progress in Genetic Toxicology. Developments in Toxicology and Environmental Toxicology. Developments in Toxicology and Environmental Science, Vol. 2, Elsevier, North Holland, Amsterdam. pp. 249-258.

Stewart, R.D., H.H. Gay, A.W. Schaffer, D.S. Erley and V.K. Rowe. 1969. Experimental human exposure to methyl chloroform vapor. Arch. Environ. Health. 19:467-474.

Stewart, R.D., and J.T. Andrews. 1966. Acute intoxication with methyl chloroform vapor. JAMA. 195:705-706.

Torkelson, T.R., F. Oyen, D. McCollister and V. Rowe. 1958. Toxicity of 1,1,1-trichloroethane as determined on laboratory animals and human subjects. Am. Ind. Hyg. Assn. J. 19:353-362.

U.S. EPA. 1980. U.S. Environmental Protection Agency. Ambient water quality criteria for chlorinated ethanes. NTIS PB81-117400.

U.S. EPA. 1984. U.S. Environmental Protection Agency. Draft health effects criteria document for 1,1,1-trichloroethane. Office of Drinking Water.

U.S. EPA. 1985a. U.S. Environmental Protection Agency. Method 502.1. Volatile halogenated organic compounds in water by purge and trap gas chromatography. Environmental Monitoring and Support Laboratory, Cincinnati, Ohio 45268, June 1985.

U.S. EPA. 1985b. U.S. Environmental Protection Agency. Method 524.1. Volatile organic compounds in water by purge and trap gas chromatography/mass spectrometry. Environmental Monitoring and Support Laboratory, Cincinnati, Ohio 45268, June 1985.

U.S. EPA. 1986. U.S. Environmental Protection Agency. Guidelines for carcinogenic risk assessment. Federal Register. 51(185) 33992-34003. September 24.

U.S. ITC. 1983. U.S. International Trade Commission. Synthetic organic chemicals, United States production, 1983.

Vainio, H., M.A. Parkki and J.A. Marniemi. 1976. Effects of aliphatic chlorohydrocarbons on drug-metabolizing enzymes in rat liver in vivo. Xenobiotica. 6:599.

March 31,.1987

# TRICHLOROETHYLENE

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

## I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

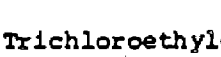
Health Advisories are developed for One-day, Ten-day, Longer-term (approximately 7 years, or 10% of an individual's lifetime) and Lifetime exposures based on data describing noncarcinogenic end points of toxicity. Health Advisories do not quantitatively incorporate any potential carcinogenic risk from such exposure. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

This Health Advisory is based upon information presented in the Office of Drinking Water's Health Effects Criteria Document (CD) for Trichloroethylene (U.S. EPA, 1985a). The HA and CD formats are similar for easy reference. Individuals desiring further information on the toxicological data base or rationale for risk characterization should consult the CD. The CD is available for review at each EPA Regional Office of Drinking Water counterpart (e.g., Water Supply Branch or Drinking Water Branch), or for a fee from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Rd., Springfield, VA 22161, PB # 86-118106/AS. The toll free number is (800) 336-4700; in Washington, D.C. area: (703) 487-4650.

## II. GENERAL INFORMATION AND PROPERTIES

CAS No. 79-01-6

Structural Formula



Trichloroethylene

Synonyms

TCE, trichloroethene, acetylene trichloride, Tri, Trilene

Uses

Industrial solvent and degreaser for metal components

Properties (Torkelson and Rowe, 1981; Windholtz, 1983)

| | |
|---|---|
| Chemical Formula | $C_2HCl_3$ |
| Molecular Weight | 131.40 |
| Physical State | Colorless liquid |
| Boiling Point | 86.7°C |
| Vapor Pressure | 77 mm (25°C) |
| Density at 25°C | 1.4 g/mL |
| Water Solubility | 0.1 g/100 mL (20°C) |
| Odor Threshold (water) | 0.5 mg/L |
| Odor Threshold (air) | 2.5-900 $mg/m^3$ |
| Organoleptic Threshold (water) | 0.31 mg/L (Amoore and Hautala, 1983) |
| Conversion Factor | 1 ppm = 5.46 $mg/m^3$ |

Occurrence

- Trichloroethylene (TCE) is a synthetic chemical with no natural sources.
- Production of TCE was 200 million lbs in 1982 (U.S. ITC, 1983).
- The major source of TCE released to the environment is from its use as a metal degreaser. Since TCE is not consumed during this use, the majority of all TCE production is released to the environment. Most

of the releases occur to the atmosphere by evaporation. However, TCE which is not lost to evaporation becomes heavily contaminated with grease and oil and has been disposed of by burial in landfills, dumping on the ground or into sewers. Because metal working operations are performed nationwide, TCE releases occur in all industrialized areas. Releases of TCE during production and other uses are relatively minor.

- Trichloroethylene released to the air is degraded in a matter of a few days. Trichloroethylene released to surface waters migrates to the atmosphere in a few days or weeks where it also degrades. Photo-oxidation appears to be the predominant fate of this compound (U.S. EPA, 1979). Trichloroethylene which is released to the land does not degrade rapidly, migrates readily to ground water and remains in ground water for months to years. Under certain conditions, TCE in groundwater appears to degrade to dichloroethylene and vinyl chloride. Trichloroethylene also may be formed in ground water by the degradation of tetrachloroethylene (Parsons et al., 1984; Vogel and McCarty, 1985). Trichloroethylene, unlike other chlorinated compounds, does not bioaccumulate in individual animals or food chains.

- Because of the large and dispersed releases, TCE occurs widely in the environment. Trichloroethylene is ubiquitous in the air with levels in the ppt to ppb range. Trichloroethylene is a common contaminant in ground and surface waters with higher levels found in ground water. Surveys of drinking water supplies have found that 3% of all public systems derived from well water contain TCE at levels of 0.5 ug/L or higher. A small number of systems (0.04%) have levels higher than 100 ug/L. Public systems derived from surface water also have been found to contain TCE but at lower levels. Trichloroethylene has been reported to occur in some foods in the ppm range.

- The major sources of exposure to TCE are from contaminated water and to a lesser extent air; food is only a minor source of TCE exposure (U.S. EPA, 1983).

## III. PHARMACOKINETICS

### Absorption

- Data on absorption of ingested TCE are limited. When a dose of 200 mg/kg of $^{14}C$-TCE in corn oil was administered to rats, 97% of the dose was recovered during 72 hours after dosing (DeKant et al., 1984).

### Distribution

- Doses of 0, 10, 100 or 1,000 mg TCE/kg/day were administered by gavage to rats five days/week for six weeks (Zenick et al., 1984). Marginal increases in TCE tissue levels were detected in the 10 mg/kg/day and 100 mg/kg/day dose groups. Compared to controls, a marked increase in TCE levels in most tissues was observed in the highest dose group. Trichloroethylene was distributed in all tissues examined with the highest concentrations in the fat, kidney, lung, adrenals, vas deferens, epididymis, brain and liver.

Metabolism

- Studies indicate that TCE is metabolized to trichloroethylene oxide, trichloracetaldehyde, trichloroacetic acid, monochloroacetic acid, trichloroethanol and trichloroethanol glucuronide (U.S. EPA, 1985a).

Excretion

- Trichloroethylene and its metabolites are excreted in urine, by exhalation and, to a lesser degree, in sweat, feces and saliva (Soucek and Vlachova, 1959).

## IV. HEALTH EFFECTS

### Humans

#### Short-term Exposure

- Oral exposure of humans to 15 to 25 ml (21 to 35 g) quantities of TCE resulted in vomiting and abdominal pain, followed by transient unconsciousness (Stephans, 1945).

#### Long-term Exposure

- Studies of humans exposed occupationally have shown an increase in serum transaminases, which indicates damage to the liver parenchyma (Lachnit, 1971). Quantitative exposure levels were not available.

### Animals

#### Short-term Exposure

- The acute oral $LD_{50}$ of TCE in rats is 4.92 g/kg (NIOSH, 1980).

#### Long-term Exposure

- Rats exposed to 300 mg/m$^3$ (55 ppm) TCE five days/week for 14 weeks had elevated liver weights (Kimmerle and Eben, 1973).

#### Reproductive Effects

- No data were available on the reproductive effects of TCE.

#### Developmental Effects

- No data were available on the developmental effects of TCE.

#### Mutagenicity

- Trichloroethylene was mutagenic in *Salmonella typhimurium* and in the *B. coli* K-12 strain, utilizing liver microsomes for activation (Greim et al., 1975, 1977).

Carcinogenicity

- Technical TCE (containing epichlorohydrin and other compounds) was found to induce a hepatocellular carcinogenic response in B6C3F$_1$ mice (NCI, 1976). Under the conditions of this experiment, a carcinogenic response was not observed in Osborne-Mendel rats. The "time-weighted" average doses were 549 and 1,097 mg/kg for both male and female rats. The time-weighted average daily doses were 1,169 and 2,339 mg/kg for male mice and 869 and 1,739 mg/kg for female mice.

- Epichlorohydrin-free TCE was reported to be carcinogenic in B6C3F$_1$ mice when administered in corn oil at 1,000 mg/kg/day, 5 days/wk, for 103 weeks (NTP, 1982). It was not found to be carcinogenic in female Fischer 344 rats when administered in corn oil at 500 or 1,000 mg/kg/day, 5 days/wk, for 103 weeks. The experiment with male rats was considered to be inadequate since these rats received doses of TCE that exceeded the maximum tolerated dose.

- TCE has been shown to be carcinogenic in mice utilizing the inhalation as well as the oral route of exposure. The National Cancer Institute (1976) and the National Toxicology Program (1982) each conducted an oral gavage study with TCE, one contaminated with epichlorohydrin and the other free of epichlorohydrin, respectively. In these studies, as described above, B6C3F$_1$ mice were used, and the results were unequivocally positive, showing liver neoplasms.

- In an inhalation study, Henschler et al. (1980) reported dose-related malignant lymphomas in female mice exposed to 100 or 500 ppm TCE vapor 6 hrs/day, 5 days/wk, for 18 months (HAN:NMRI strain). However, the authors downplayed the significance of this observation, indicating that this strain of mice has a high incidence of spontaneous lymphomas.

- Fukuda et al. (1983) found pulmonary adenocarcinomas in female ICR mice on exposure to TCE vapor.

- Henschler et al. (1984) tested Swiss (ICR/HA) mice and reported that when the animals were treated by gavage with TCE in corn oil, no statistical differences were observed in the incidence of cancers. The results of this study can be questioned because the dose schedule was often interrupted even with half of the original dose. Therefore, it is very difficult to assess the exposure. A slight increase in tumors was found in all groups treated with TCE but did not approach statistical significance.

- The Van Duuren study (1979) with skin applications of TCE in ICR/HA mice does not negate the positive findings with other strains of mice and other routes of exposure.

## V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for One-day, Ten-day, Longer-term (approximately 7 years) and Lifetime exposures if adequate data

are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(NOAEL \text{ or } LOAEL) \times (BW)}{(UF) \times (\_\_\_ L/day)} = \_\_\_ mg/L \ (\_\_\_ ug/L)$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect-Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100 or 1,000), in accordance with NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day and Ten-day Health Advisory

Suitable data were not available to estimate One-day and Ten-day Health Advisories.

Longer-term Health Advisory

No suitable data are available from which to calculate a Longer-term Health Advisory.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed for synthetic organic chemicals and a value of 10% is assumed for inorganic chemicals. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

Trichloroethylene may be classified in Group B: Probable Human Carcinogen, according to EPA's weight-of-evidence scheme for the classification of carcinogenic potential (U.S. EPA, 1986). Because of this, caution must be exercised in making a decision on how to deal with possible lifetime exposure to this substance. The risk manager must balance this assessment of carcinogenic potential against the likelihood of occurrence of health effects related to non-carcinogenic end-points of toxicity. In order to assist the risk manager in this process, drinking water concentrations associated with estimated excess lifetime cancer risks over the range of one in ten thousand to one in a million for the 70 kg adult, drinking 2 liters of water per day, are provided in the following section. In addition, in this section, a Drinking Water Equivalent Level (DWEL) is derived. A DWEL is defined as the medium-specific (in this case, drinking water) exposure which is interpreted to be protective for non-carcinogenic end-points of toxicity over a lifetime of exposure. The DWEL is determined for the 70 kg adult, ingesting 2 liters of water per day. Also provided is an estimate of the excess cancer risk that would result if exposure were to occur at the DWEL over a lifetime.

Neither the risk estimates nor the DWEL take relative source contribution into account. The risk manager should do this on a case-by-case basis, considering the circumstances of the specific contamination incident that has occurred.

The study by Kimmerle and Eben (1973)is the most appropriate from which to derive the DWEL. This study evaluated the subacute exposure to trichloroethylene via inhalation by adult rats for some 14 weeks following exposure to 55 ppm (300 mg/$m^3$), five days a week. Indices 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 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 since only a single concentration was administered. From these results, a LOAEL of 55 ppm (300 mg/$m^3$) was identified. Using the LOAEL, the DWEL is derived as follows:

Step 1: Determination of the Total Absorbed Dose (TAD)

$$TAD = \frac{(300\ mg/m^3)\ (8\ m^3/day)\ (5/7)\ (0.3)}{(70\ kg\ )} = 7.35\ mg/kg/day$$

where:

300 mg/$m^3$ = LOAEL for liver effects in rats

8 $m^3$/day = Volume of air inhaled during the exposure period

5/7 = Conversion factor for adjusting from 5 days/week exposure to a daily dose

0.3 = Ratio of the dose absorbed.

70 kg = Assumed weight of adult.

Step 2: Determination of the Reference Dose (RfD)

$$RfD = \frac{7.35 \text{ mg/kg/day}}{(100)\ (10)} = 0.00735 \text{ mg/kg/day}$$

where:

7.35 mg/kg/day = TAD.

1,000 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a LOAEL from an animal study.

Step 3: Determination of the Drinking Water Equivalent Level (DWEL)

$$DWEL = \frac{(0.00735 \text{ mg/kg/day})(70 \text{ kg})}{2 \text{ L/day}} = 0.26 \text{ mg/L } (260 \text{ ug/L})$$

where:

0.00735 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumptiion of an adult.

The estimated excess cancer risk associated with lifetime exposure to drinking water containing TCE at 260 ug/L is approximately $1 \times 10^{-4}$. This estimate represents the upper 95% confidence limit from extrapolations prepared by EPA's Carcinogen Assessment Group using the linearized, multistage model. The actual risk is unlikely to exceed this value, but there is considerable uncertainty as to the accuracy of risks calculated by this methodology.

Evaluation of Carcinogenic Potential

- IARC (1982) has classified TCE in Group 3.
- Trichlcroethylene has been classified in Group B2: Probable Human Carcinogen. This classification for carcinogenicity was determined by a technical panel of EPA's Risk Assessment Forum using the EPA risk assessment guidelines for carcinogens (U.S. EPA, 1986). This category is used for agents for which there is "sufficient evidence" for human carcinogenicity from animal studies and for which there is "inadequate evidence" or "no data" from human studies.
- Using the improved multistage linearized model, it can be estimated that water with TCE concentrations of 280 ug/L, 28 ug/L or 2.8 ug/L may increase the risk of one excess cancer per $10^4$, $10^5$ or $10^6$ people exposed, respectively. These estimates were calculated from the 1976 NCI bioassay data, which utilized TCE contaminated with epichlorohydrin. Since then, an NTP (1982) bioassay utilizing epichlorohydrin-free TCE has become available; the data from this bioassay have been reviewed and evaluated for carcinogenicity, and epichlorohydrin-free TCE has been reported to be carcinogenic in mice.

## VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- ACGIH (1984) has recommended a threshold limit value (TLV) of 50 ppm ( ~270 mg/m$^3$) and a short-term exposure limit (STEL) of 150 ppm ( ~805 mg/m$^3$.

- The NAS (1980) recommended One- and Seven-day SNARLS of 105 and 15 mg/L, respectively.

- The WHO (1981) recommended a drinking water guidance level of 30 ug/L based on a carcinogenic end point.

- The EPA (U.S. EPA, 1980) recommended a water quality criterion of 6.77 mg/L for effects other than cancer.

- The EPA (U.S. EPA, 1985d) has promulgated a Recommended Maximum Contaminant Level (RMCL) of zero based upon its classification as a known or probable human carcinogen and has proposed a Maximum Contaminant Level (MCL) of 0.005 mg/L based on its RMCL and appropriate feasibility studies.

## VII. ANALYTICAL METHODS

- Analysis of TCE is by a purge-and-trap gas chromatographic procedure used for the determination of volatile organohalides in drinking water (U.S. EPA, 1985b). This method calls for the bubbling of an inert gas through the sample and trapping TCE on an adsorbant material. The adsorbant material is heated to drive off the TCE onto a gas chromatographic column. This method is applicable to the measurement of TCE over a concentration range of 0.01 to 1500 ug/L. Confirmatory analysis for TCE is by mass spectrometry (U.S. EPA, 1985c). The detection limit for confirmation by mass spectrometry is 0.2 ug/L.

## VIII. TREATMENT TECHNOLOGIES

- Treatment technologies which will remove TCE from water include granular activated carbon (GAC) adsorption, aeration and boiling.

- Dobbs and Cohen (1980) developed adsorption isotherms for several organic chemicals including TCE. It was reported that Fibrasorb® 300 carbon exhibited adsorptive capacities of 7 mg, 1.6 mg and 0.4 mg TCE/gm carbon at equilibrium concentrations of 100, 10 and 1 mg/L, respectively. USEPA-DWRD installed pilot-scale adsorption columns at different sites in New England and Pennsylvania. In New England, contaminated well water with TCE concentrations ranging from 0.4 to 177 mg/L was passed through GAC columns until a breakthrough concentration of 0.1 mg/L was achieved with empty bed contact time (EBCT) of 18 and 9 minutes, respectively (Love and Eilers, 1982). In Pennsylvania, TCE concentrations ranging from 20 to 130 mg/L were reduced to 4.5 mg/L by GAC after 2 months of continuous operation (ESE, 1985).

- TCE is amenable to aeration on the basis of its Henry's Law Constant of 550 atm (Kavanaugh and Trussell, 1980). In a full plant-scale (3.78 MGD) redwood slat tray aeration column, a removal efficiency of 50-60% was achieved from TCE initial concentrations of 8.3-39.5 mg/L at an air-to-water ratio of 30:1 (Hess et al., 1981). In another full plant-scale (6.0 MGD) multiple tray aeration column study, TCE removal of 52% was achieved from 150 mg/L (Hess et al., 1981). A full plant-scale packed tower aeration column removed 97-99% of TCE from 1,500-2,000 mg/L contaminated groundwater at air-to-water ratio of 25:1 (ESE, 1985).

- Boiling also is effective in eliminating TCE from water on a short-term, emergency basis. Studies have shown 5 minutes of vigorous boiling will remove 95% of TCE originally present (Love and Eilers, 1982).

- Air stripping is an effective, simple and relatively inexpensive process for removing TCE and other volatile organics from water. However, use of this process then transfers the contaminant directly to the air stream. When considering use of air stripping as a treatment process, it is suggested that careful consideration be given to the overall environmental occurrence, fate, route of exposure and various other hazards associated with the chemical.

## IX. REFERENCES

ACGIH. 1984. American Conference of Governmental Industrial Hygienists. Documentation of the threshold limit values. 4th ed. 1980-1984 Supplement. pp. 406-408.

Amoore, J.E., and E. Hautala. 1983. Odor as an aid to chemical safety: Odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. J. Appl. Tox. 3:272-290.

deKant, W. Metzderm and D. Henschler. 1984. Novel metabolites of trichloroethylene through dechlorination reactions in rats, mice and humans. Biochem. Pharmacol. 33:2021-2027.

Dobbs, R.A., and J.M. Cohen. 1980. Carbon adsorption isotherms for toxic organics. EPA 600/8-80-023, Office of Research and Development, MERL, Wastewater Treatment Division, Cincinnati, Ohio.

ESE. 1985. Environmental Science and Engineering. Draft technologies and costs for the removal of volatile organic chemicals from potable water supplies. ESE No. 84-912-0300 prepared for U.S. EPA, Science and Technology Branch, CSD, ODW, Washington, D.C.

Fukuda, K., K. Takemoto and H. Tsuruta. 1983. Inhalation carcinogenicity of trichloroethylene in mice and rats. Ind. Health. 21:243-254.

Greim, H., D. Bimboes, G. Egert, W. Giggelmann and M. Kramer. 1977. Mutagenicity and chromosomal aberrations as an analytical tool for *in vitro* detection of mammalian enzyme-mediated formation of reactive metabolites. Arch. Toxicol. 39:159.

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

Henschler, D., W. Romen, H.M. Elsasser, D. Reichert, E.Eder and Z. Radwan. 1980. Carcinogenicity study of trichloroethylene by long-term inhalation in the animal species. Arch. Toxicol. 43:237-248.

Henschler, D., H. Elsasser, W. Romen and E. Eder. 1984. Carcinogenicity study of trichloroethylene, with and without epoxide stabilizers, in mice. J. Cancer Res. Clin. Oncol. 104:149-156.

Hess, A.F., J.E. Dyksen and G.C. Cline. 1981. Case study involving removal of organic chemical compounds from ground water. Presented at Annual American Water Works Association Conference, St. Louis, Missouri.

IARC. 1982. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Supplement 4, Lyon, France.

Kavanaugh, M.C., and R.R. Trussell. 1980. Design of aeration towers to strip volatile contaminants from drinking water. JAWWA. December.

Kimmerle, G., and A. Eben. 1973. Metabolism, excretion and toxicology of trichloroethylene after inhalation. 1. Experimental exposure on rats. Arch. Toxicol. 30:115.

Lachnit, V. 1971. Halogenated hydrocarbons and the liver. Wien. Klin. Wochenschr. 83(41):734.

Love, O.T., Jr., and R.G. Eilers. 1982. Treatment of drinking water containing trichloroethylene and related industrial solvents. JAWWA. August.

NAS. 1980. National Academy of Sciences. Drinking Water and Health. Volume 3. National Academy Press. Washington, DC.

NCI. 1976. National Cancer Institute. Carcinogenesis bioassay of trichloroethylene. U.S. Department of Health, Education and Welfare, Public Health Service, CAS No. 79-01-6, February.

NIOSH. 1980. Registry of Toxic Effects of Chemical Substances. U.S. Department of Health and Human Services. DHHS (NIOSH) 81-116.

NTP. 1982. National Toxicology Program. Carcinogenesis bioassay for trichloroethylene. CAS # 79-01-6. No. 82-1799. (Draft).

Parsons, F., P.R. Wood and J. DeMarco. 1984. Transformation of tetrachloroethene and trichloroethene in microcosms and groundwater. JAWWA, 26(2):56f.

Soucek, B., and D. Vlachova. 1959. Metabolites of trichloroethylene excreted in the urine by man. Pracoc. Lek. 11:457.

Stephens, C.A. 1945. Poisoning by accidental drinking of trichloroethylene. Brit. Med. J. 2:218.

Torkelson, T.R., and V.K. Rowe. 1981. Halogenated aliphatic hydrocarbons. In: Industrial Hygiene and Toxicology. 3rd ed. Vol. 2B. John Wiley and Sons, New York. p. 3553.

U.S. EPA. 1979. U.S. Environmental Protection Agency. Water Related Environmental Fate of 129 Priority Pollutants, Office of Water Planning and Standards, EPA-440/4-79-029.

U.S. EPA. 1980. U.S. Environmental Protection Agency. Ambient water quality criteria document for trichloroethylene. Office of Water Research and Standards. Cincinnati, Ohio.

U.S. EPA. 1983. U.S. Environmental Protection Agency. Trichloroethylene occurrence in drinking water, food, and air. Office of Drinking Water.

U.S. EPA. 1985a. U.S. Environmental Protection Agency. The drinking water criteria document on trichloroethylene. Office of Drinking Water.

U.S. EPA. 1985b. Method 502.1. Volatile Halogenated Organic Compounds in Water by Purge and Trap Gas Chromatography, Environmental Monitoring and Support Laboratory, Cincinnati, Ohio 45268.

U.S. EPA. 1985c. Method 524.1. Volatile Organic Compounds in Water by Purge and Trap Gas Chromatography/Mass Spectrometry, Environmental Monitoring and Support Laboratory, Cincinnati, Ohio 45268.

U.S. EPA. 1985d. U.S. Environmental Protection Agency. National primary drinking water regulations; Volatile synthetic organic chemicals; final rule and proposed rule. Federal Register 50(219):46880-46933.

U.S. EPA. 1986. U.S. Environmental Protection Agency. Guidelines for carcinogenic risk assessment. Federal Register 51(185):33992-34003. September 24.

U.S. ITC. 1983. United States International Trade Commission. Synthetic organic chemicals. United States production, USITC Publication 1422. Washington, D.C. 20436.

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

Vogel, T., and P. McCarty. 1985. Biotransformation of tetrachloroethylene to trichloroethylene, dichloroethylene, vinyl chloride, and carbon dioxide under methanogenic conditions. Appl. Environm. Microbiol. 49(5).

WHO. 1981. World Health Organization. Guidelines for drinking water quality. Vol. I. Recommendations. Geneva, Switzerland. pp. 63, 66.

Windholz, M. 1983. The Merck Index. 10th edition. Merck and Co., Inc. Rahway, NJ. p. 1378.

Zenick, H., K. Blackburn, E. Hope, N. Richards and M.K. Smith. 1984. Effects of trichloroethylene exposure on male reproductive function in rats. Toxicology. 31:237.

# VINYL CHLORIDE

Health Advisory Draft
Office of Drinking Water
U.S. Environmental Protection Agency

## I. INTRODUCTION

The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

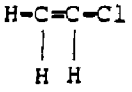
Health Advisories are developed for One-day, Ten-day, Longer-term (approximately 7 years, or 10% of an individual's lifetime) and Lifetime exposures based on data describing noncarcinogenic end points of toxicity. Health Advisories do not quantitatively incorporate any potential carcinogenic risk from such exposure. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

This Health Advisory (HA) is based on information presented in the Office of Drinking Water's Health Effects Criteria Document (CD) for vinyl chloride (U.S. EPA, 1985a). The HA and CD formats are similar for easy reference. Individuals desiring further information on the toxicological data base or rationale for risk characterization should consult the CD. The CD is available for review at each EPA Regional Office of Drinking Water counterpart (e.g., Water Supply Branch or Drinking Water Branch), or for a fee from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Rd., Springfield, VA 22161, PB # 86-118320/AS. The toll-free number is (800) 336-4700; in the Washington, D.C. area: (703) 487-4650.

## II. GENERAL INFORMATION AND PROPERTIES

CAS No. 75-01-4

Structural Formula



Synonyms

- Monochloroethylene, chloroethene

Uses

- Vinyl chloride and polyvinyl chloride (PVC) are used as raw materials in the plastics, rubber, paper, glass and automotive industries. In addition, vinyl chloride and PVC are used in the manufacture of electrical wire insulation and cables, piping, industrial and household equipment, medical supplies, food packaging materials and building and construction products. Vinyl chloride copolymers and PVC are distributed and processed in a variety of forms, including dry resins, plastisol (dispersions in plasticizers), organosol (dispersions in plasticizers plus volatile solvent), and latex (a colloidal dispersion in water used to coat paper, fabric or leather) (U.S. EPA, 1985a).

Properties (U.S. EPA (1985a)

| | |
|---|---|
| Chemical Formula | $H_2C=CHCl$ |
| Molecular Weight | 62.5 |
| Physical State | Gas |
| Boiling Point | -13.3°C |
| Melting Point | -- |
| Density | -- |
| Vapor Pressure | 2,530 mmHg at 20°C |
| Specific Gravity | 0.91 |
| Water Solubility | 1.1 g/L water at 28°C |
| Taste Threshold (water) | not available |
| Odor Threshold (water) | 3.4 mg/L* |
| Conversion Factor (air) | 1 ppm = 2.6 $mg/m^3$ |

*Amoore and Hautala (1983)

Occurrence

° Vinyl chloride is a synthetic chemical with no natural sources.

° Since 1979, yearly production of vinyl chloride has been approximately 7 billion lbs (U.S. ITC, 1983). Vinyl chloride is polymerized, and little is released to the environment. Environmental releases will be limited to the areas where vinyl chloride is produced and used.

° Vinyl chloride released to the air is degraded in a matter of a few hours (U.S.EPA, 1980a). Vinyl chloride released to surface waters migrates to the atmosphere in a few hours or days where it undergoes photochemical oxidation. Vinyl chloride which is released to the ground does not adsorb onto soil and migrates readily to ground water. Evidence from laboratory studies suggests that vinyl chloride in ground water may degrade to $CO_2$ and $Cl^-$ (Vogel and McCarty, 1985). Vinyl chloride is expected to remain in ground water for months to years. Vinyl chloride has been reported to be a degradation product of trichloroethylene and tetrachloroethylene in ground water (Parsons, 1984). Vinyl chloride does not bioaccumulate in individual animals or food chains.

° Vinyl chloride does not occur widely in the environment because of its rapid degradation and limited release. Vinyl chloride is a relatively rare contaminant in ground and surface waters with higher levels found in ground water. The Ground Water Supply Survey of drinking water supplies have found that less than 2% of all ground water derived public water systems contain vinyl chloride at levels of 1 ug/L or higher. Vinyl chloride almost always co-occurs with trichloroethylene. Public systems derived from surface water also have been found to contain vinyl chloride but at lower levels. No information on the levels of vinyl chloride in food have been identified. Based upon the limited uses of vinyl chloride and its physical chemical properties, little or no exposure is expected from food. Vinyl chloride occurs in air in urban areas and near the sites of its production and use. Atmospheric concentrations are in the ppt range (U.S. EPA, 1979).

° The major source of exposure to vinyl chloride is from contaminated water.

## III. PHARMACOKINETICS

Absorption

° Vinyl chloride is absorbed rapidly in rats following ingestion and inhalation (Withey, 1976; Duprat et al., 1977).

° Using statistical modeling, Withey and Collins (1976) concluded that, for rats, a total liquid intake containing 20 ppm (wt/wt) vinyl chloride would be equivalent to an inhalation exposure of about 2 ppm (vol/vol) for 24 hours.

Distribution

- Upon either inhalation or ingestion of $^{14}C$-vinyl chloride in rats, the greatest amount of $^{14}C$ activity was found 72 hours after treatment in liver followed by kidney, muscle, lung and fat (Watanabe et al., 1976a,b). Another study of inhalation exposure of rats to $^{14}C$-vinyl chloride showed the highest $^{14}C$ activity immediately after treatment in liver and kidney, followed by spleen and brain (Bolt et al., 1976).

**Metabolism**

- Bartsch and Montesano (1975) reported two possible metabolic pathways for vinyl chloride, one involving alcohol dehydrogenase, the other involving mixed function oxidase. Hefner et al. (1975) concluded that the dominant pathway at lower exposure levels probably involves alcohol dehydrogenase.

- Vinyl chloride metabolism is saturable (Hefner et al., 1975; Watanabe et al., 1976a; Bolt et al., 1977).

- Chloroethylene oxide, presumably through mixed-function oxidase, may be the main metabolite capable of alkylating intracellular macromolecules (Laib and Bolt, 1977).

Excretion

- Rats administered vinyl chloride by ingestion or inhalation exhale greater amounts of unmetabolized vinyl chloride as the dose is increased (Watanabe et al., 1976a, b).

- Vinyl chloride metabolites are excreted mainly in the urine. In rats, urinary metabolites include N-acetyl-S-(2-hydroxyethylcysteine) and thiodiglycolic acid (Watanabe et al., 1976a).

HEALTH EFFECTS

Humans

- Cancer findings in humans are described under Carcinogenicity.

- Mutagenic effects in humans are described under Mutagenicity.

- Developmental studies in humans are described under Developmental Effects.

- At high inhalation exposure levels, e.g., 40-900 ppm (104-2,344 mg/m$^3$), workers have experienced dizziness, headaches, euphoria and narcosis (U.S. EPA, 1985a).

- Symptoms of chronic inhalation exposure of workers to the vinyl chloride-polyvinyl chloride industry include hepatotoxicity (Marstellar et al. 1975), acro-osteolysis (Lilis et al., 1975), central nervous

system disturbances, pulmonary insufficiency, cardiovascular toxicity, and gastrointestinal toxicity (Miller et al., 1975; Selikoff and Hammond, 1975; Suciu et al., 1975). Data on dose-responses in humans are scarce because few measurements of ambient vinyl chloride levels in the workplace were made before 1975 (Mancuso, 1975).

Animals

Short-term Exposure

- Inhalation exposure to high levels (ca. 100,000 ppm or 260,417 mg/m$^3$) of vinyl chloride can induce narcosis and death, and, to lower doses, ataxia, narcosis, congestion and edema in lungs and hyperemia in liver in several species (U.S. EPA, 1985a).

Long-term Exposure

- Administration of vinyl chloride monomer to rats by gavage for 13 weeks resulted in hematologic, biochemical and organ weight effects at doses above 30 mg/kg (Feron et al., 1975).

- Inhalation exposure of rats, guinea pigs, rabbits and dogs to 50 ppm (130 mg/m$^3$) vinyl chloride, 7 hours/day, 130 exposures in 189 days, did not induce toxicity as judged by appearance, mortality, growth, hematology, liver weight and pathology. Rats exposed to 100 ppm (260 mg/m$^3$) 2 hours/day for six months, had increased liver weights (Torkelson et al., 1961).

Reproductive Effects

- Potential effects on reproductive capacity have not been studied.

Developmental Effects

- Infante et al. (1976a,b) reported an association between human exposure to vinyl chloride and birth defects and fetal loss, but this association was contradicted by Edmonds et al. (1975) and Hatch et al. (1981).

- Inhalation exposure of rats and rabbits to vinyl chloride concentrations as high as 2,500 ppm (6,500 mg/m$^3$) on days 6 to 15 (rats) and 6 to 18 (rabbits) of gestation and mice to vinyl chloride levels as high as 500 ppm (1,300 mg/m$^3$) on days 6 to 15 of gestation did not induce teratogenic effects but did increase skeletal variants in high dose mice (John et al., 1977).

- A developmental effects study with vinyl chloride in rats exposed by inhalation to 600 or 6,000 ppm (2,160 or 21,160 mg/m$^3$) 4 hours daily on gestation days 9 through 21 was negative for teratogenicity and inconclusive for fetotoxicity (Radike et al., 1977).

Mutagenicity

- Chromosomal effects of vinyl chloride exposure in workers is conflicting in that positive (Ducatmann et al., 1975; Purchase et al., 1975) and negative (Killian et al., 1975; Picciano et al., 1977) results have been reported. Picciano et al. (1977) reported exposures of 0.13 to 15.2 ppm (0.34 to 40 mg/$m^3$, time-weighted averages) for 1 to 332 months.

- Vinyl chloride is mutagenic, presumably through active metabolites in various systems including metabolically activated systems with S. typhimurium (Bartsch et al., 1975); E. coli (Greim et al., 1975); yeast (Loprieno et al., 1977); germ cells of Drosophila (Verburgt and Vogel, 1977); and Chinese hamster V79 cells (Hubermann et al., 1975).

- Dominant lethal studies with vinyl chloride in CD-1 mice were negative (Anderson et al., 1976).

Carcinogenicity

- Increases in the occurrence of liver angiosarcomas as well as in tumors of the brain, lung, and hematopoietic and lymphopoietic tissues have been associated with occupational exposure to the vinyl chloride-polyvinyl chloride industry in humans (IARC, 1979). The initial report of a link between vinyl chloride exposure and cancer in humans by Creech and Johnson (1974), as well as subsequent reports by others, indicates the nigh risk and specificity of association with liver angiosarcoma, a very rare tumor in humans.

- Ingestion of vinyl chloride monomer in the diet by rats at feeding levels as low as 1.7 and 5 mg/kg/day over their lifespan induced hepatocellular carcinomas and liver angiosarcomas, respectively, as well as other adverse hepatic effects (Feron et al., 1981). Til et al. (1983) extended the Feron et al. (1981) work to include lower doses and did not find a significant ($P<0.05$) increase in carcinogenic effects at feeding levels as high as 0.13 mg/kg/day. Administration of vinyl chloride monomer by gastric intubation for at least 52 weeks resulted in carcinogenic effects in liver and other tissue sites in rats (Feron et al., 1981; Maltoni et al., 1981).

- Chronic inhalation of vinyl chloride has induced cancer in liver and other tissue sites in rats and mice (Lee et al., 1977, 1978; Maltoni et al., 1981).

## V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for One-day, Ten-day, Longer-term (approximately 7 years) and Lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(NOAEL \text{ or } LOAEL) \times (BW)}{(UF) \times (\_\_\_ L/day)} = \_\_\_ mg/L \ (\_\_\_ ug/L)$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect-Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100 or 1,000), in accordance with NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

There are insufficient data for calculation of a One-day Health Advisory. The Ten-day HA of 2.6 mg/L is proposed as a conservative estimate for a One-day HA.

Ten-day Health Advisory

Inhalation data by Torkelson et al. (1961) were not selected for the Ten-day HA calculation because of preference for studies with oral exposure. Feron et al. (1975) reported a subchronic toxicity study in which vinyl chloride monomer (VCM) dissolved in soybean oil was administered by gavage to male and female Wistar rats, initially weighing 44 g, at doses of 30, 100 or 300 mg/kg once daily, 6 days per week for 13 weeks. Several hematological, biochemical and organ weight values were significantly ($P<0.05$ or less) different in both mid- and high-dose animals compared to controls. The NOAEL in this study was identified as 30 mg/kg.

The Ten-day HA, as well as the One-day HA, for a 10-kg child is calculated as follows:

$$\text{Ten-day HA} = \frac{(30 \text{ mg/kg/day}) (6/7) (10 \text{ kg})}{(100) (1 \text{ L/day})} = 2.6 \text{ mg/L } (2{,}600 \text{ ug/L})$$

where:

30 mg/kg/day = NOAEL based on absence of biochemical and organ weight effects in rats exposed orally to vinyl chloride.

6/7 = expansion of 6 days/week treatment in the Feron et al. (1975) study to 7 days/week to represent daily exposure.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

Longer-term Health Advisory

The Longer-term HA can be calculated from the lifetime feeding study in rats by Til et al. (1983). Til et al. (1983) have extended the earlier work by Feron et al. (1981) to include lower doses with basically the same protocol used in the latter study. Carcinogenic and noncarcinogenic effects were evident with a vinyl chloride dietary level of 1.3 mg/kg/day. At dietary levels of 0.014 and 0.13 mg/kg/day, increased incidences of basophilic foci of cellular alteration in the liver of female rats were evident. However, basophilic foci by themselves are concluded not to represent an adverse effect on the liver in the absence of additional effects indicative of liver lesions such as those found in the 1.3 mg/kg/day group; and a dose-related increase in basophilic foci was not evident. Therefore, the dose of 0.13 mg/kg/day is identified as the NOAEL for noncarcinogenic effects for the Longer-term HA calculation.

Using the 0.13 mg/kg/day NOAEL from the Til et al. (1983) study, the Longer-term HA for a 10-kg child is calculated as follows:

$$\text{Longer-term HA} = \frac{(0.13 \text{ mg/kg/day})\ (10 \text{ kg})}{(100)\ (1 \text{ L/day})} = 0.013 \text{ mg/L } (13 \text{ ug/L})$$

where:

0.13 mg/kg/day = NOAEL based on absence of adverse liver effects in rats.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

The Longer-term HA for a 70-kg adult is calculated as follows:

$$\text{Longer-term HA} = \frac{(0.13 \text{ mg/kg/day})\ (70 \text{ kg})}{(100)\ (2 \text{ L/day})} = 0.046 \text{ mg/L } (46 \text{ ug/L})$$

where:

0.13 mg/kg/day = NOAEL based on absence of adverse liver effects in rats.

70 kg = assumed body weight of an adult.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

2 L/day = assumed daily water consumption of an adult.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed for synthetic organic chemicals and a value of 10% is assumed for inorganic chemicals. If the contaminant is classified as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

Because vinyl chloride is classified as a human carcinogen (IARC Group 1 and EPA Group A), a Lifetime Health Advisory is not recommended.

Evaluation of Carcinogenic Potential

- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986), vinyl chloride may be classified in Group A: Human carcinogen. This category is for agents for which there is sufficient evidence to support the causal association between exposure to the agents and cancer.

- The IARC (1979) has concluded that there is sufficient evidence to classify vinyl chloride as a human carcinogen in its Category 1.

- EPA's Carcinogen Assessment Group (CAG) recently has recalculated its excess carcinogenic risk estimates resulting from lifetime exposure to vinyl chloride through the drinking water (U.S. EPA, 1985a). CAG based its preliminary revised estimates on the Feron et al. (1981) study. The total number of tumors, considering tumors of the lung and liver, in rats exposed through the diet was used to calculate the excess cancer risk. Using the 95% upper limit [$q_1^* = 2.3$ (mg/kg/day)$^{-1}$] with the linearized multistage model, they calculated that consuming 2 liters of water per day with vinyl chloride concentration of 1.5 ug/L, 0.15 ug/L and 0.015 ug/L would increase the risk of one excess cancer per 10,000 ($10^{-4}$), 100,000 ($10^{-5}$) or 1,000,000 ($10^{-6}$) people exposed, respectively, per lifetime. The CAG is presently reassessing the cancer risk estimate based on the Feron et al. (1981) study by taking into account the more recent data by Til et al. (1983) which, as

described previously, is an extension of the earlier Feron et al. (1981) work to include lower doses.

- Maximum likelihood estimates as well as 95% upper limits of cancer risks by the multistage model are presented. Expressing risk as cases/lifetime/person, examples would be 0.01 mg/kg/day or 0.35 mg/L exposure associated with risks of $1.6 \times 10^{-2}$ (MLE) and $1.9 \times 10^{-2}$ (UL) and 0.001 mg/kg/day exposure associated with risks of $1.6 \times 10^{-3}$ (MLE) and $1.9 \times 10^{-3}$ (UL).

- Cancer risk estimates (95% upper limit) with other models are presented for comparison with that derived with the multistage. For example, one excess cancer per 1,000,000 ($10^{-6}$) is associated with exposure to vinyl chloride in drinking water at levels of 50 ug/L (probit), 0.5 ug/L (logit), and 0.02 ug/L (Weibull). While recognized as statistically alternative approaches, the range of risks described by using any of these modeling approaches has little biological significance unless data can be used to support the selection of one model over another. In the interest of consistency of approach and in providing an upper bound on the potential cancer risk, the EPA has recommended use of the linearized multistage approach.

## VI. OTHER CRITERIA, GUIDANCE, AND STANDARDS

- The National Academy of Sciences (NAS, 1977) estimated a $10^{-6}$ risk (95% upper bound estimate) from lifetime exposure to 1 ug vinyl chloride/L drinking water with the multistage model and the lifetime ingestion study in rats by Maltoni et al. (1981).

- The final RMCL by the U.S. EPA Office of Drinking Water is zero, the proposed MCL is 1 ug/L, and the practical quantitation level is 1 ug/L (U.S. EPA, 1985b).

- Ambient water quality criteria (U.S. EPA, 1980b) are 20, 2 and 0.2 ug/L for risks of $10^{-5}$, $10^{-6}$, and $10^{-7}$, respectively, assuming consumption of 2 liters of water and 6.5 grams of contaminated fish per day by a 70 kg adult.

- A workplace standard of 1 ppm (time-weighted average) was set by OSHA in 1974 based on the demonstration of angiosarcoma of the liver in vinyl chloride workers (Federal Register. 39:35890).

- The ACGIH (1982) has recommended a TLV of 5 ppm (10 $mg/m^3$).

## VII. ANALYTICAL METHODS

- Analysis of vinyl chloride is by a purge and trap gas chromatographic procedure used for the determination of volatile organohalides in drinking water (U.S. EPA, 1985c). This method calls for the bubbling of an inert gas through a sample of water and trapping the purged vinyl chloride on an adsorbent material. The adsorbent material is

heated to drive off the vinyl chloride onto a gas chromatographic column. This method is applicable to the measurement of vinyl chloride over a concentration range of 0.06 to 1500 ug/L. Confirmatory analysis for vinyl chloride is by mass spectrometry (U.S. EPA, 1985d). The detection limit for confirmation by mass spectrometry is 0.3 ug/L.

## VIII. TREATMENT TECHNOLOGIES

- The value of the Henry's Law Constant for vinyl chloride (6.4 atm-$m^3$/mole) suggests aeration as a potential removal technique for vinyl chloride in water (ESE,1984). Removals of up to 99.27% were achieved at 9°C using a pilot packed tower aerator. In similar studies, vinyl chloride was removed from ground water using a spray aeration system with total VOC concentration was 100 to 200 ug/L (ESE, 1984). Greater than 99.9% VOC removal was obtained using a four-stage aeration system; each stage employed 20 shower heads with a pressure drop of approximately 10 pounds per square inch. In-well aeration has also demonstrated up to 97% removal of vinyl chloride using an air-lift pump. However, practical considerations are likely to limit the application of this (Miltner, 1984).

- The concentration of vinyl chloride in southern Florida ground water declined by 25% to 52% following passage through lime softening basins and filters (Wood and DeMarco, 1980). Since vinyl chloride is a highly volatile compound, it is probably volatilized during treatment (ESE, 1984).

- Adsorption techniques have been less successful than aeration in removing vinyl chloride from water. In a pilot study, water from a ground water treatment plant was passed through a series of four 30-inch granular activated carbon (Filtrasorb 400) columns (Wood and DeMarco, 1980; Symons, 1978); the empty bed contact time was approximately six minutes per column. Influent vinyl chloride concentrations ranged from below detection to 19 ug/l; erratic removal was reported. To maintain effluent concentrations below 0.5 ug/l, the estimated column capacity to breakthrough was 810, 1,250, 2,760 and 2,050 bed volumes for empty bed contact times of 6, 12, 19 and 25 minutes, respectively. In addition, the estimated service life of the activated carbon was low. Similarly, poor removal of vinyl chloride was achieved using an experimental synthetic resin, Ambersorb XE-340, (Symons, 1978).

- Treatment technologies for the removal of vinyl chloride from water have not been extensively evaluated except on an experimental level. Available information suggests aeration merits further investigation. Selection of individual or combinations of technologies to achieve vinyl chloride removal must be based on a case-by-case technical evaluation, and an assessment of the economics involved.

## IX. REFERENCES

ACGIH. 1982. American Conference of Governmental Industrial Hygienists. Threshold limit values for chemical substances and physical agents in the workroom environment. Cincinnati, OH.

Amoore, J.E., and E. Hautala. 1983. Odor as an aid to chemical safety: Odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. J. Appl. Toxicol. 3:272-290.

Anderson, D., M.C.E. Hodge and I.F.H. Purchase. 1976. Vinyl chloride: Dominant lethal studies in male CD-1 mice. Mutat. Res. 40:359-370.

Bartsch, H., C. Malaveille and R. Montesano. 1975. Human, rat and mouse liver-mediated mutagencity of vinyl chloride in S. typhimurium strains. Int. J. Cancer. 15:429-437.

Bartsch, H., and R. Montesano. 1975. Mutagenic and carcinogenic effects of vinyl chloride. Mutat. Res. 32:93-114.

Bolt, H.M., H. Kappus, A. Buchter and W. Bolt. 1976. Disposition of (1,2-$^{14}$C) vinyl chloride in the rat. Arch. Toxicol. 35:153-162.

Bolt, H.M., R.J. Laib, H. Kappus and A. Buchter. 1977. Pharmacokinetics of vinyl chloride in the rat. Toxicol. 7:179-188.

Creech, J.L., and M.N. Johnson. 1974. Angiosarcoma of the liver in the manufacture of polyvinyl chloride. J. Occup. Med. 20:338-340.

Ducatman, A., K. Hirschhorn and I.J. Selikoff. 1975. Vinyl chloride exposure and human chromosome aberrations. Mutat. Res. 31:163-168.

Duprat, P., J.P. Fabry, D. Gradiski and J.L. Magadur. 1977. Metabolic approach to industrial poisoning: blood kinetics and distribution of $^{14}$C-vinyl chloride monomer (V.C.M.). Acta. Pharmacol. Toxicol. Suppl. (Kbh) 41(1):142-143.

Edmonds, L.D., H. Falk and J.E. Nissim. 1975. Congenital malformations and vinyl chloride. Lancet. 2:1098.

ESE. 1984. Environmental Science and Engineering. Technologies and costs for the removal of volatile organic chemicals from potable water supplies. (Draft) ESE No. 84-912-0300. Prepared for U.S. EPA, Science and Technology Branch, CSD, ODW, Washington, DC.

Federal Register. 39:35890.

Feron, V.J., A.J. Speek, M.I. Williams, D. van Battum and A.F. de Groot. 1975. Observations on the oral administration and toxicity of vinyl chloride in rats. Fd. Cosmet. Toxicol. 13:633-638.

Feron, V.J., C.F.M. Hendrikson, A.J. Speek, H.P. Til and B.J. Spit. 1981. Lifespan oral toxicity study of vinyl chloride in rats. Fd. Cosmet. Toxicol. 19:317-331.

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

Hatch, M., J. Kline and Z. Stain. 1981. Power considerations in studies of reproductive effects of vinyl chloride and some structural analogs. Environ. Health Perspec. 41:195-201.

Hefner, R.E., Jr, P.G. Watanabe and P.J. Gehring. 1975. Preliminary studies on the fate of inhaled vinyl chloride monomer in rats. Ann. NY. Acad. Sci. 246:135-148.

Huberman, E., H. Bartsch and L. Sachs. 1975. Mutation induction in Chinese hamster V79 cells by two vinyl chloride metabolites, chloroethylene oxide and 2-chloro-acetaldehyde. Int. J. Cancer. 16:639-644.

IARC. 1979. International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risk of chemicals to man. Vol. 19. pp. 377-438. Lyon, France.

Infante, P.F., J.K. Wagoner and R.J. Waxweiler. 1976a. Carcinogenic, mutagenic and teratogenic risks associated with vinyl chloride. Mutat. Res. 41:131-142.

Infante, P.F., J.K. Wagoner, R.J. Waxweiler, A.J. McMichael and H. Falk. 1976b. Genetic risks of vinyl chloride. Lancet. 1:734-735.

John, J.A., F.A. Smith, B.K.J. Leong and B.A. Schwetz. 1977. The effects of maternally inhaled viny chloride on embryonal and fetal development in mice, rats and rabbits. Toxicol. Appl. Pharmacol. 39;497-513.

Killian, D.J., D.C. Picciano and C.B. Jacobson. 1975. Industrial monitoring: A cytogenetic approach. Ann. N.Y. Acad. Sci. 269:4-11.

Laib, R.J., and H.M. Bolt. 1977. Alkylation of RNA by vinyl chloride metabolites in vitro and in vivo: Formation of 1-N'-etheno-adenosine. Toxicology. 8:185-195.

Lee, C.C., J.C. Bhandari, J.M. Winston, W.B. House, R.L. Dixon and J.S. Woods. 1977. Inhalation toxicity of vinyl chloride and vinylidene chloride. Environ. Health Perspect. 21:25-32.

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

Lilis, R., H. Anderson, W.J. Nicolson, S. Daum, A.S. Fischbein and I.J. Selikoff. 1975. Prevalence of disease among vinyl chloride and polyvinyl chloride workers. Ann. N.Y. Acad. Sci. 246:22-41.

Loprieno, N., R. Barale, S. Baroncelli, H. Bartsch, G. Bronzetti, A. Cammellini, C. Corsi, D. Frezza, R. Nieri, C. Leporini, D. Rosellini and A.M. Rossi. 1977. Induction of gene mutations and gene conversions by vinyl chloride metabolites in yeast. Cancer Res. 253-257.

Maltoni, C., G. Lefemine, A. Ciliberti, G. Cotti and D. Carretti. 1981. Carcinogenicity bioassays of vinyl chloride monomer: a model of risk assessment on an experimental basis. Environ. Health Perspec. 41:3-31.

Mancuso, T.F. 1975. Comments for opening of discussion on "neoplastic effects." Ann. N.Y. Acad. Sci. 246:251-254.

Marsteller, H.J., W.K. Lelbach, R. Muller and P. Gedigk. 1975. Unusual splenomegalic liver disease as evidence by peritoneoscopy and guided liver biopsy among polyvinyl chloride production workers. Ann. N.Y. Acad. Sci. 246:95-134.

Miller, A., A.S. Tiersten, M. Chuang, I.J. Selikoff and R. Warshaw. 1975. Changes in pulmonary function in workers exposed to vinyl chloride and polyvinyl chloride. Ann. N.Y. Acad. Sci. 246:42-52.

Miltner, R., 1984. Personal communication, U.S. EPA Technical Support Division, ODW, Cincinnati, OH. Cited in Technologies and Costs for the Removal of Volatile Organic Chemicals from Potable Water Supplies by Environmental Science and Engineering.

NAS. 1977. National Academy of Sciences. Drinking Water and Health. Volume 1, National Academy Press. Washington, DC. pp. 783-787.

Parsons, F., P.R. Wood and J. DeMarco. 1984. Transformation of Tertrachloroethene and Trichloroethene in Microcosms and Groundwater, J.A.W.W.A., Vol. 26 No. 2, pg 56f.

Picciano, D.J., R.E. Flake, P.C. Gay and D.J. Killian. 1977. Vinyl chloride cytogenetics. J. Occup. Med. 19:527-530.

Purchase, I.F.H., C.R. Richardson and D. Anderson. 1975. Chromosomal and dominant lethal effects of vinyl chloride. Lancet. 2(7931):410-411.

Radike et al. 1977. Transplacental effects of vinyl chloride in rats. Annual Report, pp. 183-185. USPHS-ES-00159. Center for Study of the Human Environment, Dept. Environ. Health, University of Cincinnati Medical Center.

Selikoff, I.J., and E.C. Hammond, eds. 1975. Toxicity of vinyl chloride-polyvinyl chloride. Ann. N.Y. Acad. Sci., Vol. 246.

Suciu, I., L. Prodan, E. Ilea, A. Paduracu and L. Pascu. 1975. Clinical manifestations in vinyl chloride poisoning. Ann. N.Y. Acad. Sci. 246:53-69.

Symons, J.M. 1978. Interim Treatment Guide for Controlling Organic Contaminants in Drinking Water Using Granular Activated Carbon. U.S. EPA Office of Research and Development, MERL, DWRD, Cincinnati, OH. Cited in U.S. EPA SNARL Document for Vinyl Chloride (Draft) and in U.S. EPA May, 1983. Treatment of Volatile Organic Compounds in Drinking Water. Report No. EPA-600/8-83-019, Office of Research and Development, MERL, DWRD, Cincinnati, OH.

Til, H.P., H.R. Immel and V.J. Feron. 1983. Lifespan oral carcinogenicity study of vinyl chloride in rats. Final report. Civo Institutes TNO. Report No. V 83.285/291099.

Torkelson, R.R., F. Oyen and V.K. Rowe. 1961. The toxicity of vinyl chloride as determined by repeated exposure of laboratory animals. Amer. Ind. Hyg. Assoc. J. 22:354-361.

U.S. EPA. 1979. U.S. Environmental Protection Agency. Water related environmental fate of 129 priority pollutants. Office of Water Planning and Standards. EPA-440/4-79-029.

U.S. EPA. 1980a. U.S. Environmental Protection Agency. Vinyl chloride Occurrence in drinking Water, food and air. Office of Drinking Water.

U.S. EPA. 1980b. U.S. Environmental Protection Agency. Ambient water quality criteria for vinyl chloride. Office of Water Regulations and Standards. EPA 440/5-80-078.

U.S. EPA. 1985a. U.S. Environmental Protection Agency. Final draft for the drinking water criteria document on vinyl chloride (Office of Drinking Water). TR-540-162.

U.S. EPA. 1985b. U.S. Environmental Protection Agency. National primary drinking water regulations; Volatile synthetic organic chemicals; Final rule and proposed rule. Federal Register. 50(219):46880-46933, November 13.

U.S. EPA. 1985c. U.S. Environmental Protection Agency. Method 502.1. Volatile halogenated organic compounds in water by purge and trap gas chromatography. Environmental Monitoring and Support Laboratory, Cincinnati, Ohio 45268. June 1985.

U.S. EPA. 1985d. U.S. Environmental Protection Agency. Method 524.1. Volatile organic compounds in water by gas chromatography/mass spectrometry. Environmental Monitoring and Support Laboratory, Cincinnati, Ohio 45268. June 1985.

U.S. EPA. 1986. U.S. Environmental Protection Agency. Guidelines for carcinogenic risk assessment. Federal Register 51(185):33993-34003. September 24.

U.S. ITC. 1983. U.S. International Trade Commission. Synthetic organic chemicals United States production, 1982. USTIC Publication 1422. Washington, D.C. 20436. 1983.

Verburgt, F.G., and E. Vogel. 1977. Vinyl chloride mutagenesis in Drosophila melanogaster. Mutat. Res. 48:327-333.

Vogel, T., and P. McCarty. 1985. Biotransformation of Tetrachloroethylene to Trichloroethylene, Dichloroethylene, Vinyl Chloride, and Carbon Dioxide Under Methanogenic Conditions, Applied and Environmental Microbiology, Vol 49 No.5.

Watanabe, P.G., G.R. McGowan and P.J. Gehring. 1976a. Fate of ($^{14}C$) vinyl chloride after single oral administration in rats. Toxicol. Appl. Pharmacol. 36:339-352.

Watanabe, P.G., G.R. McGowan, E.O. Madrid and P.J. Gehring. 1976b. Fate of ($^{14}C$) vinyl chloride following inhalation exposure in rats. Toxicol. Appl. Pharmacol. 37:49-59.

Withey, J.R. 1976. Pharmacodynamics and uptake of vinyl chloride monomer administered by various routes to rats. J. Toxicol. Environ. Health. 1:381-394.

Withey, J.R., and B.T. Collins. 1976. A statistical assessment of the quantitative uptake of vinyl chloride monomer from aqueous solution. J. Toxicol. Environ. Health. 2:311-321.

Wood, P.R., and J. DeMarco. 1980. Effectiveness of various adsorbents in removing organic compounds from water. 1: Removing purgeable halogenated organics. In: Activated Carbon Adsorption of Organics from the Aqueous Phase. Volume 2. Ann Arbor Science. pp. 85-114.

March 31, 1987

# XYLENES

Health Advisory
Office of Drinking Water
U.S. Environmental Protection Agency

## I. INTRODUCTION

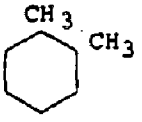
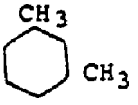
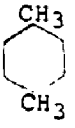
The Health Advisory (HA) Program, sponsored by the Office of Drinking Water (ODW), provides information on the health effects, analytical methodology and treatment technology that would be useful in dealing with the contamination of drinking water. Health Advisories describe nonregulatory concentrations of drinking water contaminants at which adverse health effects would not be anticipated to occur over specific exposure durations. Health Advisories contain a margin of safety to protect sensitive members of the population.

Health Advisories serve as informal technical guidance to assist Federal, State and local officials responsible for protecting public health when emergency spills or contamination situations occur. They are not to be construed as legally enforceable Federal standards. The HAs are subject to change as new information becomes available.

Health Advisories are developed for One-day, Ten-day, Longer-term (approximately 7 years, or 10% of an individual's lifetime) and Lifetime exposures based on data describing noncarcinogenic end points of toxicity. Health Advisories do not quantitatively incorporate any potential carcinogenic risk from such exposure. For those substances that are known or probable human carcinogens, according to the Agency classification scheme (Group A or B), Lifetime HAs are not recommended. The chemical concentration values for Group A or B carcinogens are correlated with carcinogenic risk estimates by employing a cancer potency (unit risk) value together with assumptions for lifetime exposure and the consumption of drinking water. The cancer unit risk is usually derived from the linear multistage model with 95% upper confidence limits. This provides a low-dose estimate of cancer risk to humans that is considered unlikely to pose a carcinogenic risk in excess of the stated values. Excess cancer risk estimates may also be calculated using the One-hit, Weibull, Logit or Probit models. There is no current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than another. Because each model is based on differing assumptions, the estimates that are derived can differ by several orders of magnitude.

This Health Advisory is based on information presented in the Office of Drinking Water's Health Effects Criteria Document (CD) for Xylenes (U.S. EPA, 1985a). The HA and CD formats are similar for easy reference. Individuals desiring further information on the toxicological data base or rationale for risk characterization should consult the CD. The CD is available for review at each EPA Regional Office of Drinking Water counterpart (e.g., Water Supply Branch or Drinking Water Branch), or for a fee from the National Technical Information Service, U.S. Department of Commerce, 5285 Port Royal Rd., Springfield, VA 22161, PB # 86-117942/AS. The toll-free number is (800) 336-4700; in the Washington, D.C. area: (703) 487-4650.

## II. GENERAL INFORMATION AND PROPERTIES

| | Xylene | Ortho- | Meta- | Para- |
|---|---|---|---|---|
| CAS No. | 1330-20-7 | 95-47-6 | 108-38-3 | 106-42-3 |
| Structural Formula | |  |  |  |

Synonyms

- Xylols: dimethylbenzene

Uses

- As solvents for paints, inks and adhesives, and as components of detergents and other industrial and household products.

Properties (Verschueren, 1983)

| | Xylene | Ortho- | Meta- | Para- |
|---|---|---|---|---|
| Chemical Formula | | $C_8H_{10}$ | $C_8H_{10}$ | $C_8H_{10}$ |
| Molecular Weight | | 106.16 | 106.16 | 106.16 |
| Boiling Point | | 144.4°C | 139.0°C | 138.4°C |
| Melting Point | | -25°C | -48°C | -13°C |
| Density | | -- | -- | -- |
| Vapor Pressure, mm Hg, 20° C | | 5 | 6 | 6.5 |
| Water Solubility, mg/l, 20° C | | 175 | 160 | -- |
| 25° C | | -- | -- | 198 |
| Log Octanol/Water Partition Coefficient[a] | | 3.12 | 3.20 | 3.15 |
| Taste Threshold[b] | 0.3-1.0 mg/L | -- | -- | -- |
| Odor Threshold | | -- | -- | -- |
| Conversion Factor | 1 ppm = 4.3 mg/m$^3$ | | | |

[a] Leo et al. (1971)
[b] National Inst. for Water Supply (1977)

Occurrence

- Xylene occurs naturally as a component of petroleum oil.

- Xylenes are produced in large amounts, 5 billion lbs in 1982 (U.S. ITC, 1984). Xylenes are also produced indirectly in large volumes during gasoline refining and other operations. Xylene content of gasoline can be as high as several percent.

- Releases of xylenes to the environment are largely to air due to their volatile nature, with smaller amounts to water and soil. Releases of xylenes to water are due to spills and leaks of gasoline and other petroleum products and, to a lesser extent, from the disposal of waste from paints, inks and other industrial products. Because of the widespread use of petroleum products, releases of xylene occur nationwide.

- Xylenes degrade rapidly in air with a half life of a few days. Xylenes released to surface water rapidly volatilize to the air. Xylenes released to the ground bind somewhat to soil and slowly migrate with ground water. Xylenes are biodegraded readily in soils and surface waters. In the absence of biodegradation, xylenes are expected to be stable in ground water.

- Xylenes occur at low levels in drinking water, food, and air. Xylene occurs in both ground and surface public water supplies, with higher levels occurring in surface water supplies. The EPA's Community Water Supply Survey, found 3% of all ground water derived public drinking water systems sampled had levels greater than 0.5 ug/L. The highest level reported in ground water was 2.5 ug/L. The survey reported that 6% of all surface water derived drinking water system are contaminated at levels higher than 0.5 ug/L. None of the systems were reported to contain levels higher than 5.2 ug/L. No information on the occurrence of xylene in foods has been identified. Xylenes are found in the air of urban and suburban areas at levels of approximately 2 ug/L. Because of the widely dispersed low levels of xylenes reported in water, air is likely to be the major source of exposure.

## III. PHARMACOKINETICS

Absorption

- Xylenes are absorbed readily after inhalation. Data on absorption after ingestion are not available. Sedivec and Flek (1976) exposed human volunteers to 0.2 mg/L (200 mg/$m^3$) o-, m- and p-xylene vapors and also to their mixture at a ratio of 1:1:1 for an 8-hour period. The amount absorbed or retained was 63.6% $\pm$ 4.2% for all-isomers.

Distribution

- Using whole-body autoradiography to detect radiolabeled xylene and metabolites, Bergman (1978) reported distribution of the compound in many tissues and organs of exposed mice. $^{14}$C-m-Xylene was administered

to mice by inhalation for 10 minutes. Whole mice were frozen and sectioned before exposure to X-ray film. In mice sacrificed immediately after xylene exposure, radiolabel was detected in the lungs, liver and kidneys. Rapid distribution to the brain and adipose tissue also was evident. Two hours after exposure, radiolabel in the lungs was restricted to the bronchi. In addition to the previously noted organs, radiolabel was detected in the intestine after two hours. The last traces of xylene were detected in the adipose tissue of mice sacrificed four hours after exposure.

- In rats exposed to $^{14}C$-p-xylene for 1-8 hours by inhalation at 208 mg/m$^3$ (48 ppm), radiolabel was detected (in decreasing concentration) in the kidneys, subcutaneous fat, sciatic nerve, blood, liver, lungs, spleen, muscles, cerebrum and cerebellum (Carlson, 1981). Distribution to all tissues was rapid, allowing near maximal levels in tissues (except in kidneys and subcutaneous fat) within one hour.

Metabolism

- Metabolism of xylenes varies somewhat according to the isomer but, in general, proceeds by oxidation of methyl groups and ring hydroxylation. The resulting metabolites include methyl hippuric acid (95%) and xylenols (1-2%) (Harper et al. 1975).

Excretion

- Elimination of xylenes is primarily through urinary excretion of metabolites, representing nearly 95% of the absorbed dose, and the remaining 5% by pulmonary exhalation of unchanged solvent (Sedivec and Flek, 1976; Astrand et al., 1978).

## IV. HEALTH EFFECTS

Humans

- The lowest oral lethal dose (LDLo) for humans has been reported as 50 mg/kg (NIOSH, 1978).

- Xylenes produce central nervous system disturbances as reflected in changes in numerative ability, short-term memory and electroencephalographic patterns.

- Gamberale et al. (1978) observed no adverse health effects in fifteen male subjects at rest following 70 minutes of inhalational exposure to xylene at 435 and 1300 mg/m$^3$. However, in another experiment, eight male subjects were exposed to xylene at 1300 mg/m$^3$ with 30 minutes of exercise on a bicycle ergometer which was continued during behavior tests. The authors concluded that there was evidence of reduction in the performance level on three of the four tests. The tests conducted were: simple addition and choice reaction time, short-term memory and critical Hicker fusion frequency.

- Savolainen et al. (1980) observed adverse effects on the psychophysiological functions in eight male students following inhalational exposure to m-xylene at 391 mg/m$^3$ for five consecutive days and one day after the weekend. Body balance, reach on time and manual coordination were impaired. However, tolerance against the observed effects developed during one working week.

Animals

Short-term exposure

- In rats, oral $LD_{50}$ values range from 4,300 to 5,000 mg/kg(NIOSH, 1978), whereas inhalation $LC_{50}$s (four hours) are 20,600 to 29,000 mg/m$^3$ (Carpenter et al., 1975; Harper et al., 1975).

Long-term Exposure

- Carpenter et al. (1975) exposed rats to mixed xylenes at 770, 2000 or 3500 mg/m$^3$ for six hours/day, five days/week for 13 weeks duration. No effects on body weight gain, hematology, blood chemistry, kidney, or liver weights or tissue histology were reported at two lower dose levels. At the highest dose level, one rat treated at 3500 mg/m$^3$ for seven weeks showed slight renal tubular regeneration and, at 13 weeks, the response was noted in rats in a non-dose-related manner.

- Jenkins et al. (1970) reported the results of repeated (30 exposures) or continuous inhalation exposure (90 days) to o-xylene by rats, guinea pigs, monkeys and dogs. The exposure levels were 337 or 3,358 mg/m$^3$ in rats and monkeys. One of the dogs exhibited tremors of varying severity throughout exposure. No significant effects were observed with respect to body weight, hematology, and histopathological examination at the lower dose of 337 mg/m$^3$ xylene.

- Ultrastructural hepatic effects have been reported in rats following subchronic oral exposure (200 mg/kg diet for up to 6 months) (Bowers et al., 1982). Two types of intracellular vesicles in rats treated with o-xylene were observed. One type appeared to be an extension of the endoplasmic reticulum and the second vesicle type was associated with the hepatocyte plasmalemma.

- Tatrai et al. (1981) reported hepatomegally and ultrastructurally evident proliferation of the smooth endoplasmic reticulum following chronic inhalation exposure of 4750 mg/m$^3$, eight hours/day, seven days/week for one year in rats.

Reproductive Effects

- No information was found in the available literature on the reproductive effects of xylene.

Developmental Effects

- Twenty CFY rats, 240 to 280 g, were exposed to 1,000 mg/m$^3$ of mixed xylenes 24 hours/day during days 9 to 14 of pregnancy, and although

there were increased incidences of fused sternebrae and extra ribs in the offspring, the authors interpreted these as signs of embryotoxicity rather than teratogenicity (Hudak and Ungvary, 1978). No signs of maternal toxicity were noted. In another study, Charles River rats aged 12 weeks were exposed to 0, 100 or 400 ppm of xylenes (0, 434 or 1,730 mg/m$^3$) during days 6 to 15 of pregnancy (25 rats per group); the authors reported no signs of teratogenicity whether on the per-fetus or the per-litter basis (Litton Bionetics, 1978).

Mutagenicity

- Xylene was not mutagenic in the Ames test with or without activation or in other short-term in vitro assays (Litton Bionetics, 1978).

Carcinogenicity

- A long-term carcinogenicity bioassay in rats and mice has been conducted by the NTP; however, the final report is not yet released by the NTP (1986).

## V. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Health Advisories (HAs) are generally determined for One-day, Ten-day, Longer-term (approximately 7 years) and Lifetime exposures if adequate data are available that identify a sensitive noncarcinogenic end point of toxicity. The HAs for noncarcinogenic toxicants are derived using the following formula:

$$HA = \frac{(NOAEL \text{ or } LOAEL) \times (BW)}{(UF) \times (\_\_\_ L/day)} = \_\_\_ mg/L \ (\_\_\_ ug/L)$$

where:

NOAEL or LOAEL = No- or Lowest-Observed-Adverse-Effect-Level in mg/kg bw/day.

BW = assumed body weight of a child (10 kg) or an adult (70 kg).

UF = uncertainty factor (10, 100 or 1,000), in accordance with NAS/ODW guidelines.

___ L/day = assumed daily water consumption of a child (1 L/day) or an adult (2 L/day).

One-day Health Advisory

A One-day HA for xylenes may be developed from the experiment conducted in human subjects by Gamberale et al. (1978). In this study, a NOAEL was identified at an inhalation concentration of 1300 mg/m$^3$ for approximately one hour. Other researchers also have observed CNS effects at or near similar concentrations following exercise in terms of performance tests. The calculations for a One-day HA for a 10 kg child are as follows:

Step 1: Determination of the Total Absorbed Dose (TAD)

$$\text{Total absorbed dose} = \frac{(1300\ mg/m^3)\ (1\ m^3)\ (0.64)}{(70\ kg)} = 11.9\ mg/kg/day$$

where:

1,300 $mg/m^3$ = NOAEL based on absence of reduction in the performance level on tests in humans.

1 $m^3$ = assumed amount of air inhaled during one hour by a human.

0.64 = 64% absorption factor in humans (Sedivek and Flek, 1976).

70 kg = assumed body weight of an adult.

Step 2: Determination of a One-day HA

$$\text{One-day HA} = \frac{(11.9\ mg/kg/day)\ (10\ kg)}{(10)\ (1\ L/day)} = 11.9\ mg/L \approx 12\ mg/L\ (12{,}000\ ug/L)$$

where:

11.9 mg/kg/day = TAD.

10 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from a human study.

10 kg = assumed body weight of a child.

1 L/day = assumed daily water consumption of a child.

Ten-day Health Advisory

Insufficient data using oral exposure to calculate a Ten-day Health Advisory are available currently. The Longer-term HA for the 10 kg child (7800 ug/L) is recommended for a ten-day exposure.

Longer-term Health Advisory

The study by Carpenter et al. (1975) is the most appropriate basis for calculating a Longer-term HA. A group of male rats were exposed by inhalation to mixed xylenes at 770, 2000, or 3500 $mg/m^3$ for six hours/day on five days/week for up to thirteen weeks. No effects on body weight, hematology, blood chemistry, kidney or liver weight, or tissue histology were observed at 770 or 2000 $mg/m^3$ exposure levels of xylene. Based on the 2000 $mg/m^3$ exposure level as a NOAEL, a Longer-term HA may be derived for a 10 kg child as follows:

Step 1: Determination of the Total Absorbed Dose (TAD)

$$\text{TAD} = \frac{(2{,}000\ mg/m^3)\ (6\ hours/day)\ (1\ m^3/hour)\ (5/7)\ (0.64)}{(70\ kg)} = 78\ mg/kg/day$$

where:

2,000 mg/m$^3$ = NOAEL based on the absence of various toxicological parameters in rats.

6 hr/day = duration of exposure.

1 m$^3$/hr = assumed respiratory volume for a rat.

5/7 = Conversion of 5 day/week dosing regimen to daily dosing regimen.

0.64 = absorption efficiency in humans.

70 kg = assumed body weight of an adult.

Step 2: Determination of the Longer-term HAs

For a 10 kg child:

$$\text{Longer-term HA} = \frac{(78 \text{ mg/kg/day})\ (10 \text{ kg})}{(100)\ (1 \text{ L/day})} = 7.8 \text{ mg/L } (7{,}800 \text{ ug/L})$$

where:

78 mg/kg/day = TAD.

10 kg = assumed body weight of a child.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

1 L/day = assumed daily water consumption of a child.

For a 70 kg adult:

$$\text{Longer-term HA} = \frac{(78 \text{ mg/kg/day})\ (70 \text{ kg})}{(100)\ (2 \text{ L/day})} = 27.3 \text{ mg/L } (27{,}300 \text{ ug/L})$$

where:

78 mg/kg/day = TAD.

70 kg = assumed body weight of an adult.

100 = uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study.

2 L/day = assumed daily water consumption of an adult.

Lifetime Health Advisory

The Lifetime HA represents that portion of an individual's total exposure that is attributed to drinking water and is considered protective of noncarcinogenic adverse health effects over a lifetime exposure. The Lifetime HA is derived in a three step process. Step 1 determines the Reference Dose (RfD), formerly called the Acceptable Daily Intake (ADI). The RfD is an estimate of a daily exposure to the human population that is likely to be without appreciable risk of deleterious effects over a lifetime, and is derived from the NOAEL (or LOAEL), identified from a chronic (or subchronic) study, divided by an uncertainty factor(s). From the RfD, a Drinking Water Equivalent Level (DWEL) can be determined (Step 2). A DWEL is a medium-specific (i.e., drinking water) lifetime exposure level, assuming 100% exposure from that medium, at which adverse, noncarcinogenic health effects would not be expected to occur. The DWEL is derived from the multiplication of the RfD by the assumed body weight of an adult and divided by the assumed daily water consumption of an adult. The Lifetime HA is determined in Step 3 by factoring in other sources of exposure, the relative source contribution (RSC). The RSC from drinking water is based on actual exposure data or, if data are not available, a value of 20% is assumed for synthetic organic chemicals and a value of 10% is assumed for inorganic chemicals. If the contaminant is classifed as a Group A or B carcinogen, according to the Agency's classification scheme of carcinogenic potential (U.S. EPA, 1986), then caution should be exercised in assessing the risks associated with lifetime exposure to this chemical.

Compound-specific, chronic ingestion data for xylenes do not exist at this time. In the absence of appropriate ingestion studies, the Lifetime Health Advisory for xylenes will be derived from the inhalation studies of Jenkins et al. (1970) instead of the Bowers et al. (1982) study, even though the route and duration of exposure used in the Jenkins study are not ideal for development of a Lifetime HA.

The study by Bowers et al. (1982) was designed primarily to investigate the first hepatocyte changes following long-term exposure to low levels of o-xylene or other methylbenzenes administered to aged male rats, weighing 800 to 900 g, in the diet at 200 mg/kg food for up to six months prior to electron microscopic examination of their livers, but not other tissues. Certain major weaknesses of this study rule out its consideration in the development of a Lifetime HA. These weaknesses are: (1) the use of aged animals weighing 800 to 900 g in the experiment; (2) the stability of o-xylene was not monitored (i.e., any loss due to evaporation not mentioned); (3) the use of a single exposure level; (4) the lack of histological examination of tissues other than liver of animals on test diet; and (5) ultrastructural changes in the hepatocytes of rats ingesting o-xylene was not stated specifically for o-xylene.

The inhalation study by Jenkins et al. (1970) was selected as the basis for the Lifetime HA. In sthis study, o-xylene was administered by inhalation to rats, guinea pigs, monkeys and dogs for 30 repeated exposures at 3,358 $mg/m^3$, eight hours/day, five days/week or 90 days continuous exposure at 337 $mg/m^3$. At 3,358 $mg/m^3$, two rats died on the third day of exposure and another rat and one monkey died on day seven; one of the dogs exhibited tremors of varying severity throughout the exposure. Besides the above mentioned observations, no significant effects were observed with respect to body weight, hematology, and histopathological examination at either dose.

Using 337 mg/m$^3$ as a NOAEL, the Lifetime HA for a 70 kg adult is calculated as follows:

Step 1: Determination of the Total Absorbed Dose (TAD):

$$TAD = \frac{(337\ mg/m^3)\ (20\ m^3/day)\ (0.64)}{70\ kg} = 61.62\ mg/kg/day$$

where:

337 mg/m$^3$ = NOAEL based on the absence of toxicological effects in rats.

20 m$^3$/day = assumed respiratory volume per day of a rat.

0.64 = assumed absorption factor for xylenes (64%).

70 kg = assumed body weight of an adult.

Step 2: Determination of the Reference Dose (RfD)

$$RfD = \frac{61.62\ mg/kg/day}{(1,000)} = 0.06162\ mg/kg/day$$

where:

61.62 mg/kg/day = TAD.

1,000 - uncertainty factor, chosen in accordance with NAS/ODW guidelines for use with a NOAEL from an animal study of less-than-lifetime duration.

Step 3: Determination of the Drinking Water Equivalent Level (DWEL)

$$DWEL = \frac{(0.06162\ mg/kg/day)\ (70\ kg)}{(2\ L/day)} = 2.16\ mg/L\ (2,200\ ug/L)$$

where:

0.06162 mg/kg/day = RfD.

70 kg = assumed body weight of an adult.

2 L/day = assumed daily water consumption of an adult.

Step 4: Determination of Lifetime HA:

$$Lifetime\ HA = 2\ mg/L \times 0.20 = 0.4\ mg/L\ (400\ ug/L)$$

where:

2 mg/L = DWEL.

0.20 = assumed relative source contribution of water.

It should be noted that an estimated concentration for detection by taste and odor in surface water was 0.3 to 1.0 mg/L (National Inst. for Water Supply, 1977) and that the HA may exceed these thresholds for some individuals.

Evaluation of Carcinogenic Potential

- The carcinogenic potential of xylene will be assessed when the report of the NTP animal bioassay for carcinogenicity (1986) is available for review.
- IARC has not evaluated the xylenes for their carcinogenic potential.
- Applying the criteria proposed in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986), the xylenes may be classified in Group D: Not classified. This category is for agents with inadequate animal evidence of carcinogenicity.

## VI. OTHER CRITERIA, GUIDANCE AND STANDARDS

- NAS (1980) calculated SNARLs (Suggested-no-adverse-response-levels) for xylenes in drinking water. The NAS-SNARL value was 21 mg/L xylene for a 1-day exposure and 11.2 mg/L for a 7-day exposure (for a 70 kg adult).
- U.S. EPA (1981) also provided draft HAs for a 1-day, 10-day, and longer-term exposure to xylenes in drinking water. These HAs for a 10 kg child were 12.0 mg/L, 1.2 mg/L, and 0.62 mg/L of xylene, respectively.
- ACGIH (1981) has recommended a TWA of 100 ppm.

## VII. ANALYTICAL METHODS

- Analysis of xylene(s) is by a purge-and-trap gas chromatographic procedure used for the determination of volatile aromatic and unsaturated organic compounds in water (U.S. EPA, 1985b). This method calls for the bubbling of an inert gas through the sample and trapping benzene on an adsorbent material. The adsorbant material is heated to drive off xylene(s) onto a gas chromatographic column. The gas chromatograph is temperature programmed to separate the method analytes which are then detected by the photoionization detector. This method is applicable to the measurement of xylene(s) over a concentration range of 0.02 to 1500 ug/L. Confirmatory analysis for xylene(s) is by mass spectrometry (U.S. EPA, 1985c). The detection limit for confirmation by mass spectrometry is 0.2 ug/L.

## VIII. TREATMENT TECHNOLOGIES

- Treatment technologies which will remove xylene from water include granulated activated carbon (GAC) and aeration. Limited data suggest that conventional treatment may be partially effective in xylene removal.

- Dobbs and Cohen (1980) developed adsorption isotherms for several organic compounds including p-xylene. It was reported that Filtrasorb® 300 carbon exhibited adsorptive capacities of 130 mg, 85 mg, 54 mg and 35 mg p-xylene/g carbon when the initial xylene concentrations were 10, 1.0, 0.1 and 0.01 mg/L, respectively. These values along with Freundlich constants of K = 85 and 1/n = 0.19 indicate that p-xylene and its closely related isomers, o-xylene and m-xylene, should be amenable to carbon adsorption. Powdered activated carbon (PAC) added at the well field to xylene-contaminated water containing 0.03 to 0.5 ug/L removed 60 to >99% of the xylene (U.S. EPA, 1985d). The higher the xylene load the less efficient the adsorption. GAC was slightly less effective when used on water containing 0.05 ug/L in xylene. In 16 samples tested the average removal efficiency was 50% (McCarty et al., 1979a). When the m-xylene (0.046 ug/L) and p-xylene (0.012 ug/L) were measured separately only 20% and 17% removals were experienced using adsorption on GAC. Each of these studies, however, were conducted on wastewater containing a number of organic contaminants and therefore are not completely representative of what might be expected with potable water treatment.

- Xylene is amenable to aeration on the basis of its Henry's Law Constant of 255 atoms at 20°C (U.S. EPA, 1985d). Although only 19% of the xylene in wastewater could be removed by aeration, the process was much more successful in the treatment of potable well water contaminated by a gasoline spill (McCarty et al., 1979b). At air-to-water ratios of 17 to 1 or greater, 80 to 100% removal of all three xylene isomers was accomplished. At low air to water ratios (8:1), poor removal performance was experienced. Average influent concentrations for the o, m and p isomers were 10, 2.9 and 6.9 ug/L, respectively.

- Air stripping is an effective, simple and relatively inexpensive process for removing xylene and other organics from water. However, use of this process then transfers the contaminant directly to the air stream. When considering use of air stripping as a treatment process, it is suggested that careful consideration be given to the overall environmental occurrence, fate, route of exposure, and various hazards associated with the chemical.

## IX. REFERENCES

ACGIH. 1981. American Conference of Governmental Industrial Hygienists. TLVs - Threshold limit values for chemical substances in workroom air adopted by ACGIH for 1981. Cincinnati, OH.

Astrand, I., J. Engstrom and P. Ovrum. 1978. Exposure to xylene and ethylbenzene. I. Uptake, distribution and elimination in man. Scand. J. Work Environ. Health. 4(3):185-194.

Bergman, K. 1978. Application of whole-body autoradiography to distribution studies of organic solvents. Int. Symp. Control Air Pollut. Work Environ. (Part 2):128-139.

Bowers, D.E., Jr., M.S. Cannon and D.H. Jones. 1982. Ultrastructural changes in livers of young and aging rats exposed to methylated benzenes. Am. J. Vet. Res. 43(4):679-683.

Carlson, A. 1981. Distribution and elimination of carbon $C^{14}$-labeled xylene in rats. Scand. J. Work Environ. Health. 7:51-55.

Carpenter, C.P., E.R. Kinkead, D.L. Geary, Jr., L.J. Sullivan and J.M. King. 1975. Petroleum hydrocarbon toxicity studies: V. Animal and human response to vapors of mixed xylenes. Toxicol. Appl. Pharmacol. 33:543-558.

Dobbs, R.A., and J.M. Cohen. 1980. Carbon adsorption isotherms for toxic organics. EPA 600/8-80-023. MERL, EPA. Cincinnati, Ohio.

Gamberale, F., G. Annwall and M. Hultegren. 1978. Exposure to xylene and ethylbenzene. III. Effects on central nervous functions. Scand. J. Work Environ. Health. 4:204-211.

Harper, C., R.T. Drew and J.R. Fouts. 1975. Benzene and p-xylene: A comparison of inhalation toxicities and in vitro hydroxylations. In: D.J. Jollow, J.J. Kocsis, R. Snyder and H. Vainio, eds. Biologically reactive intermediates. London, England: Plenum Press. pp. 302-311.

Hudak, A., and G. Ungvary. 1978. Embryotoxic effects of benzene and its methyl derivatives: toluene, xylene. Toxicology. 11:55-63.

Jenkins, L.J., R.A. Jones and J. Siegel. 1970. Long-term inhalation screening studies of benzene, toluene, o-xylene and cumene on experimental animals. Toxicol. Appl. Pharmacol. 16:818-823.

Leo, A., C. Hansch and D. Elkins. 1971. Partition coefficients and their uses. Chem. Rev. 71:583.

Litton Bionetics, Inc. 1978. Mutagenicity evaluation of xylene: Final report. LBI Project No. 20847. Submitted to American Petroleum Institute, Washington, D.C. 150 pp.

McCarty, P.L., D. Argo and M. Reinhard. 1979a. Operational experiences with activated carbon adsorbers at Water Factory 21. J. AWWA. 11:683-689.

McCarty, P.L., K.H. Sutherland, J. Graydon and M. Reinhard. 1979b. Volatile organic contaminants removal by air stripping. Presented at the Seminar on Controlling Organics in Drinking Water, American Water Works Annual Conference, San Francisco, CA.

Middleton, F.M., A.A. Rosen and R.H. Burttschell. 1958. Taste and odor research tools for water utilities. J. Am. Water Works Assoc. 50:21-28.

NAS. 1980. National Academy of Sciences. Drinking Water and Health, Volume 3. National Academy Press. Washington, D.C. p. 181.

National Institute for Water Supply. 1977. Compilation of odor threshold values in air and water.

NIOSH. 1978. Registry of toxic effects of chemical substances. U.S. Department of Health, Education and Welfare. Publication No. 79-100, p. 1303.

NTP. 1986. National Toxicology Program. National Toxicology Program/Toxicology Testing Program. Chemicals on Standard Protocol. Management Status Report. Nov. 1986.

Savolainen, K., V. Riihimaki, A.M. Seppalainen and M. Linnoila. 1980. Effects of short-term m-xylene exposure and physical exercise on the central nervous system. Int. Arch. Occup. Environ. Hlth. 45:105-121.

Sedivec, V., and J. Flek. 1976. The adsorption, metabolism and excretion of xylenes in man. Int. Arch. Occup. Environ. Hlth. 37:205-217.

Tatrai, E., G. Ungvary and I.R. Cseh. 1981. The effect of long-term inhalation of o-xylene on the liver. Ind. Environ. Xenobiotics. Proc. Int. Conf.. pp. 293-300.

U.S. EPA. 1979. U.S. Environmental Protection Agency. Water Related Environmental Fate of 129 Priority Pollutants, Office of Water Planning and Standards, EPA-440/4-79-029, December, Washington, D.C.

U.S. EPA. 1980a. U.S. Environmental Protection Agency. Ambient water quality criterion for xylenes. Office of Water Planning and Standards, Washington, D.C.

U.S. EPA. 1980b. U.S. Environmental Protection Agency. The analysis of aromatic chemical indicators of industrial contamination in water by purge and trap method. Cincinnati, Ohio: U.S. EPA Organic Analyses Section, Environmental Monitoring and Support Laboratory.

U.S. EPA. 1981. U.S. Environmental Protection Agency. Advisory opinion for xylenes (dimethylbenzenes). Office of Drinking Water.

U.S. EPA. 1983. U.S. Environmental Protection Agency. Xylene occurrence in drinking water, food, and air. Office of Drinking Water.

U.S. EPA. 1984a. U.S. Environmental Protection Agency. Intermedia priority pollutants guidance documents. Office of Toxic Substances.

U.S. EPA. 1985a. U.S. Environmental Protection Agency. Draft health effects criteria document. Office of Drinking Water.

U.S. EPA. 1985b. U.S. Environmental Protection Agency. Method 503.1. Volatile Aromatic and Unsaturated Organic Compounds in Water by Purge and Trap/Gas Chromatography. Environmental Monitoring and Support Laboratory, Cincinnati, Ohio 45268, June 1985.

U.S. EPA. 1985c. U.S. Environmental Protection Agency. Method 524.1. Volatile Organic Compounds in Water by Purge and Trap Gas Chromatography/ Mass Spectrometry. Environmental Monitoring and Support Laboratory, Cincinnati, Ohio 45268, June 1985.

U.S. EPA. 1985d. U.S. Environmental Protection Agency. Technologies and costs for the removal of synthetic organic chemicals from potable water supplies. Science and Technology Branch, CSD, ODW, Washington, D.C.

U.S. EPA. 1986. U.S. Environmental Protection Agency. Final guidelines for carcinogenic risk assessment. Federal Register. 51(185):33992-34003. September 24.

U.S. ITC. 1984. U.S. International Trade Commission. Synthetic organic chemicals United States production, 1983. USITC Publication 1422. Washington, D.C. 20436.

Verschueren, K. 1983. Handbook of environmental data on organic chemicals. New York: Van Nostrand Reinhold Company. pp. 638-642.

**TECHNICAL REPORT DATA**
*(Please read Instructions on the reverse before compl*

PB87-235578

| 1. REPORT NO. | 2. | 3. |
|---|---|---|

| 4. TITLE AND SUBTITLE | 5. REPORT Date |
|---|---|
| Health Advisories for 25 Organics | March, 1987 |
| | 6. PERFORMING ORGANIZATION CODE |
| 7. AUTHOR(S) U.S. Environmental Protection Agency Office of Drinking Water | 8. PERFORMING ORGANIZATION REPORT NO. |
| 9. PERFORMING ORGANIZATION NAME AND ADDRESS U.S. Environmental Protection Agency Office of Drinking Water (WH-550D) 401 M St., S.W. Washington, D.C. 20460 | 10. PROGRAM ELEMENT NO. |
| | 11. CONTRACT/GRANT NO. |
| 12. SPONSORING AGENCY NAME AND ADDRESS Same as box 9. | 13. TYPE OF REPORT AND PERIOD COVERED |
| | 14. SPONSORING AGENCY CODE |

15. SUPPLEMENTARY NOTES

16. ABSTRACT

These documents summarize the health effects of 25 organics including: acrylamide, benzene, carbon tetrachloride, chlorobenzene, dichlorobenzene(s), 1,2-dichloroethane, 1,1-dichloroethylene, cis-1,2-dichloroethylene, trans-1,2-dichloroethylene, dichloromethane, p-dioxane, dioxin, epichlorohydrin, ethylbenzene, ethylene glycol, hexachlorobenzene, hexane, methyl ethyl ketone, styrene, tetrachloroethylene, toluene, 1,1,1-trichloroethane, trichloroethylene, vinyl chloride, xylenes. Topics discussed include: General Information and Properties, Pharmacokinetics, Health Effects in Humans and Animals, Quantification of Toxicological Effects, Other Criteria Guidance and Standards, Analytical Methods and Treatment Technologies.

REPRODUCED BY
U.S. DEPARTMENT OF COMMERCE
NATIONAL TECHNICAL
INFORMATION SERVICE
SPRINGFIELD, VA. 22161

17. KEY WORDS AND DOCUMENT ANALYSIS

| a. DESCRIPTORS | b. IDENTIFIERS/OPEN ENDED TERMS | c. COSATI Field/Group |
|---|---|---|
| Organics<br>Drinking Water<br>Health Advisory<br>Toxicity | | |

| 18. DISTRIBUTION STATEMENT | 19. SECURITY CLASS (This Report) | 21. NO. OF PAGES |
|---|---|---|
| Open Distribution | non-sensitive | 399 |
| | 20. SECURITY CLASS (This page) | 22. PRICE |
| | non-sensitive | |

EPA Form 2220-1 (Rev. 4-77) PREVIOUS EDITION IS OBSOLETE

