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.

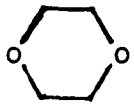
Health Advisories are developed for One-day, Ten-day, Longer-term (approximately 7 years, or 10% of an individual's lifetime) and Lifetime exposures based on data describing noncarcinogenic end points of toxicity. Health Advisories do not quantitatively incorporate any potential carcinogenic risk from 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).
- Applying the criteria described in EPA's guidelines for assessment of carcinogenic risk (U.S. EPA, 1986), p-dioxane 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.
- 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. ANALYTICAL METHODS

- 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 TECHNOLOGIES

- 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.

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