Fact Sheet Date: March 12, 1998

NEW YORK STATE
- HUMAN HEALTH FACT SHEET -

Ambient Water Quality Value for
Protection of Sources of Potable Water

SUBSTANCE: 1,2-Dichloroethane **CAS REGISTRY NUMBER:** 107-06-2

AMBIENT WATER QUALITY VALUE: 0.6 ug/L

BASIS: Oncogenic

I INTRODUCTION

The Ambient Water Quality Value applies to the water column and is designed to protect humans from the effects of contaminants in sources of drinking water; it is referred to as a Health (Water Source) or H(WS) value. Regulations (6 NYCRR 702.2) require that the water quality value be based on the procedures in sections 702.3 through 702.7. A previous fact sheet supported a value of 0.8 ug/L for 1,2-dichloroethane based on oncogenic effects (NYS, 1985). Available information on 1,2-dichloroethane published after 1985 was examined as described in "Scope of Review," below. Potential water quality values are derived below, and the value of 0.6 ug/L selected as described under "Selection of Value."

II PRINCIPAL ORGANIC CONTAMINANT CLASSES AND SPECIFIC MCL (702.3)

A. Discussion

1,2-Dichloroethane does not have a Specific MCL as defined in 700.1. However, 1,2-dichloroethane is in principal organic contaminant class (i) as defined in 700.1.

Under the State Sanitary Code (10 NYCRR Part 5, Public Water Supplies), the New York State Department of Health has established a general maximum contaminant level of 5 ug/L for principal organic contaminants such as 1,2-dichloroethane in drinking water.

The U.S. Environmental Protection Agency has established a maximum contaminant level goal (MCLG) of zero ug/L and a MCL of 5 ug/L for drinking water for 1,2-dichloroethane.

B. Derivation of Water Quality Value

Because 1,2-dichloroethane is in a principal organic contaminant class and has no Specific MCL, a water quality value of 5 ug/L can be derived based on 702.3(b).

III ONCOGENIC EFFECTS (702.4)

A. Data

U.S. EPA (1995) classifies 1,2-dichloroethane as Group B2 (probable human carcinogen). IARC (1987) classifies 1,2-dichloroethane in Group 2B ("possibly carcinogenic to humans"). Both groups agree that 1,2-dichloro-ethane caused oncogenic effects in both rats and mice.

In an NCI (1978) bioassay, statistically significant associations were found between 1,2-dichloroethane administration and the incidences of several neoplasms in male and female rats and mice. Male and female rats were exposed to 0, 47 or 95 mg/kg/day of 1,2-dichloroethane by gavage 5 days/week for 78 weeks and observed for an additional 32 weeks. Male rats had significant incidences of hemangiosarcomas at both doses relative to controls in a variety of sites. Female rats had significant increases in mammary adenocarcinomas and mammary adenocarcinomas plus fibro-adenomas at the highest dose relative to controls.

Male mice were exposed to 0, 97, or 195 mg/kg/day of 1,2-dichloroethane 5 days/week for 78 weeks and observed for an additional 12-13 weeks. The incidences of hepatocellular carcinomas and alveolar bronchiolar adenomas were significantly increased compared to controls. Female mice were exposed to 0, 149 or 299 mg/kg/day 1,2-dichloroethane 5 days/week for 78 weeks and exhibited increased incidences of mammary adenocarcinomas, compared to controls.

The NCI (1978) study has a number of limitations including dosage adjustments throughout the course of the bioassay (because of the toxicity of 1,2-dichloroethane), small numbers of concurrent controls, poor survival of treated animals, imprecise reporting of 1,2-dichloroethane purity and use of a corn oil vehicle which can alter the disposition of lipophilic compounds and incidence of some spontaneous tumors. These limitations, however, do not disqualify the use of the study for quantitative risk assessment.

Supportive evidence of tumorigenic responses by other exposure routes to 1,2-dichloroethane have been reported (Van Duren et al., 1979; Theiss et al.,

1977; Stoner, 1991). Maltoni et al. (1980) reported negative results by inhalation exposure in a flawed study (ATSDR, 1994).

Genotoxicity

There is sufficient evidence to conclude that 1,2-dichloroethane is mutagenic (ATSDR, 1994). The evidence from in-vitro studies overwhelmingly indicate that 1,2-dichloroethane is capable of interacting with DNA to produce genotoxic effects. In bacterial mutagenicity assays, results suggest that 1,2-dichloroethane is a very weak direct-acting mutagen that can be activated to a more effective species by glutathione and glutathione-S-transferase (DeMarini and Brooks, 1992). S-(2-chloroethyl)glutathione, a proposed intermediate product, was found to be a potent mutagen in S. typhimurium (Humphreys et al. 1990).

Results were positive in assays for point mutations in human cells (Crespi et al., 1985; Ferreri et al., 1983), animal cells (Tan and Hsie, 1981) and bacteria (ATSDR, 1994). 1,2-dichloroethane has been shown to bind covalently to DNA of rat liver and kidney cells (Inskeep et al. 1986). The results of in-vivo genotoxicity studies by all routes of exposure demonstrate the ability of 1,2-dichloroethane to bind DNA in rodent liver, kidney and lung (ATSDR, 1994).

B. Derivation of Water Quality Value

1. Oncogenic Definition

The evidence of multiple tumor types in two mammalian species after 1,2-DCE exposure in the NCI (1978) bioassay fulfills the definition of an oncogenic effect in 700.1 for 1,2-dichloroethane.

2. Selection of Data

The NCI (1978) bioassay is selected as the appropriate dose-response data for deriving a water quality value. The male rat hemangiosarcoma incidence data are the most appropriate as it is the most sensitive site (USEPA, 1985). A summary of the data sets showing statistically and biologically significant increases in tumor response is presented in Table I. U.S. EPA (1994) also used the male rat data from the assay to calculate a slope factor of

Table I. Tumor Incidence in Mice and Rats after Exposure to 1,2-dichloroethane (NCI, 1978) for 78 weeks

Species	Administered Dose (mg/kg/day)	Tumor Site/Type	Tumor Incidence	Post-administration Weeks Observed
male rat	0	--	0/40	32 weeks obs. died 23 wks.
	47	hemangiosarcomas	9/48*	
	95	hemangiosarcomas	7/27*	
female rat	0	--	0/20	32 weeks obs. died by 15 wk.
	47	mammary adenocarcinoma	1/50	
	95	mammary adenocarcinoma	18/50*	
female rat	0	--	0/20	32 week obs.
	47	mammary adenocarcinoma and fibroadenoma	15/50	
	95	mammary adenocarcinoma and fibroadenoma	24/50*	
male mice	0	--	0/19	12-13 wk. obs.
	97	alveolar, bronchiolar adenomas	1/47	
	195	aleveolar, bronchiolar adenomas	15/48*	
female mice	0	--	0/20	12-13 wk. obs.
	149	mammary adenocarcinoma, endometrial polyps and sarcoma	9/50*	
	299	mammary adenocarcinoma, endometrial polyps and sarcoma	7/48*	
male mice	0	hepatocellular carcinoma	1/19	12-13 wk. obs.
	97	hepatocellular carcinomas	6/47*	
	195	hepatocellular carcinomas	12/48*	

* Statistical difference by Fischer exact test.

9.1×10^{-2} per (mg/kg)/day and drinking water value of 0.4 ug/L. NYS (1985) previously calculated a water quality value of 0.8 ug/L on the basis of the hepatocellular carcinoma incidence in male mice in NCI (1978) and the use of a linearized multistage (LMS) model without time-to-death analysis.

3. Calculation of Human Doses from Animal Doses

U.S. EPA converted the administered animal doses to lifetime doses by factors accounting for 5 day a week dosing, less-than-lifetime dosing and the differing percentages of dose metabolized at each administered dose. U.S. EPA (1985) used a length of experiment (Le)/length of lifespan (L) factor of 0.75 to account for less-than-lifetime dosing. U.S. EPA (1985) calculated that 92% of the lower dose and 84% of the higher dose was metabolized. (Spreafico et al. 1979; Reitz et al. 1980). The administered doses were adjusted by multiplying them by (78 weeks/104 weeks), (5 days/7days) and the appropriate percentage of dose metabolized.

U.S. EPA (1985) has calculated human equivalent doses by conversion of animal doses by a transpecies scaling factor based on surface area from administered doses for the male rat data and presented them in U.S. EPA (1994):

Table II. Human Doses Converted from Administered Male Rat Doses (USEPA, 1994)

Administered Dose (mg/kg/day)	Human Equivalent Dose (mg/kg/day)	Tumor Incidence
0	0	0/40
47	4.46	9/48
95	8.23	7/27

4. Model Selection and Output

6 NYCRR Part 702 specifies that values shall be calculated using valid dose-response data and a linearized multistage (LMS) low-dose extrapolation model unless scientific evidence is sufficient to support the use of another model. U.S. EPA (1985) used a linearized multistage procedure with a time-to-death analysis because of the

high mortality rate in high-dose rats. The exact time of animal death is part of the input data.

The multistage model with time-to-death factor, which is considered appropriate for this study, provides the extrapolation from bioassay results to the risk level required by regulation. The model derives the 95% lower confidence limit (LCL) on the human dose and the maximum likelihood estimate (MLE) of the dose corresponding to an extra cancer risk of 1×10^{-6}. Part 702 specifies the 95% LCL as the basis of the value.

Using the above information (multi-stage model with time-to-dealth analysis) at the 95% LCL, USEPA (1994) calculated a cancer potency factor of 9.1×10^{-2} $(mg/kg/day)^{-1}$.

This slope factor was calculated by U.S. EPA using an interspecies scaling of doses based on the 2/3 power of relative body weights. Proposed New York State regulations call for such scaling to be done on the basis of the 3/4 power of relative body weights. An adjustment to U.S. EPA's slope is needed to account for the different scaling methods.

The adjustment factor for rat data (body weight of 0.50 kg) is a multiplication factor of 0.66, which results in a slope of 0.060 $(mg/kg/day)^{-1}$. This corresonds to a human dose of 0.0166 ug/kg/day at a risk level of 10^{-6}.

5. Selection of Human Dose and Discussion of Uncertainties

For the male rat, the critical site is the circulatory system. A human dose associated with 10^{-6} risk was calculated by USEPA from doses converted from the male rat data, using procedures consistent with 6 NYCRR 702.4.

With suitable data on more than one mammalian species, the data from the species that provides the best model for human response to a substance should be selected as the basis for the water quality value. Where, as for 1,2-dichloroethane, one cannot determine which test species is more appropriate, the one that yields the more stringent value is used to be most protective of public health. Thus, the human dose associated with 10^{-6} risk calculated from the male rat data is selected for calculation of the water quality value.

6. Calculation of Water Quality Value

The human dose associated with 10^{-6} risk calculated by the Department from USEPA's data was converted to a water quality

value based on a 70 kg adult consuming 2 liters of water per day as follows:

$$\text{Water Quality Value} = \left(\frac{0.0166 \text{ ug}}{\text{kg} \cdot \text{day}}\right) \left(\frac{70 \text{ kg}}{2 \text{ L/day}}\right) = 0.581 \text{ ug/L, rounded to } 0.6 \text{ ug/L}$$

IV NON-ONCOGENIC EFFECTS (702.5)

A. Data

NTP (1991) conducted 13-week gavage and drinking water studies in several strains of rats and $B_6C_3F_1$ mice with 1,2-dichloroethane. Gavage exposure resulted in significant dose-related increases in kidney weight and kidney-to-body-weight ratio at 30-120 mg/kg/day in male rats and 75-150 in female rats. Following 13-week drinking water exposure significant dose-related increases in kidney weight and kidney-to-body-weight ratio were evident in rats ($\geq$ 58 mg/kg/day) and mice ($\geq$ 244 mg/kg/day). Liver weight increases were noted at 60 mg/kg/day in rats (liver-to-bodyweight ratio significantly elevated at 60-518 mg/kg/day in Sprague-Dawley males) and at 249 mg/kg/day in male mice. NTP concluded the kidney was a target for 1,2-dichloroethane. A LOAEL of 58 mg/kg/day for drinking water exposure in rats is determined from this study (NTP, 1991).

No adverse renal effects were noted in mice after exposure to 189 mg/kg/day in drinking water for 90 days (Munson et al. 1982).

B. Derivation of Water Quality Value

1. Selection of Data

The study by NTP (1991) was judged appropriate for deriving a water quality value based on non-oncogenic effects. It was selected because it contains data on exposure to 1,2-dichloroethane for two species in drinking water. Gavage exposure results in temporary high-level doses absorbed at one time resulting in spikes in blood levels, unlike continuous lower-level exposures via drinking water. Drinking water data are preferable, if available. A weakness in the study is the less-than-lifetime exposure.

2. Calculation of Acceptable Daily Intake (ADI)

An ADI is calculated from the study of NTP (1991) by multiplying the LOAEL of 58 mg/kg/day by a total uncertainty factor of 10,000 as follows:

$$ADI = \left(\frac{58}{10{,}000} \right) \text{ mg/kg/day} = 0.0058 \text{ mg/kg/day}$$

This uncertainty factor was selected to account for intra- and interspecies differences (10 x 10) and the use of a LOAEL rather than a NOAEL (10) and the use of a less than lifetime study(10).

3. Calculation of Water Quality Value

A water quality value is calculated from the ADI, above, based on a 70 kg adult consuming 2 liters of water per day and allocating 20% of the ADI to come from drinking water, as follows:

$$\text{Water Quality Value} = \frac{(0.0058 \text{ mg/kg/day})(1000 \text{ ug/mg})(70 \text{ kg})(0.2)}{(2 \text{ L/day})}$$

Water Quality Value = 40.6 ug/L, rounded to 40 ug/L

V CHEMICAL CORRELATION (702.7)

A value based on chemical correlation is not applicable because data are sufficient to evaluate 1,2-dichloroethane based on each of sections 702.4 and 702.5.

VI SELECTION OF VALUE

The H(WS) value is designed to protect humans from oncogenic and non-oncogenic effects from contaminants in sources of drinking water. To protect from these effects, regulations (6 NYCRR 702.2(b)) require that the value be the most stringent of the values derived using the procedures found in sections 702.3 through 702.7. The oncogenic (6 NYCRR 702.4) value of 0.6 ug/L is the most stringent value derived by these procedures and is the ambient water quality value for 1,2-dichloroethane.

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NTP (National Toxicology Program). 1991. Toxicity studies of 1,2-dichloroethane (ethylene dichloride) (CAS No. 107-06-2) in F344/N rats, Sprague Dawley rats, Osborne-Mendel rats and B6C3F1 mice (drinking water and gavage studies).

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10 NYCRR (New York State Codes, Rules and Regulations). Public Water Systems: Title 10 NYCRR, Chapter 1, State Sanitary Code, Subpart 5-1. Albany, NY: Department of Health, Bureau of Public Water Supply Protection.

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VIII SCOPE OF REVIEW

Several of the widely-recognized sources listed below can provide a comprehensive review and often a quantitative assessment of the toxicity of a substance. These sources were searched for information on 1,2-DCE; where none was found it is so noted.

- IRIS (U.S. EPA's Integrated Risk Information System). On-line database.
- RTECS (Registry of Toxic Effects of Chemical Substances). On-line database.
- CCRIS (Chemical Carcinogenesis Research Information System). On-line database.
- ATSDR (Agency for Toxic Substances and Disease Registry) toxicological profile.
- IARC (International Agency for Research on Cancer) Monographs Supplement 7.
- U.S. EPA ambient water quality criteria document (document not found).
- U.S. EPA health advisory.
- U.S. EPA drinking water criteria document (document not found).

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The sources above are deemed adequate to assess the literature through 1991. Coverage of recent literature (through 1994) was provided by a New York State Library on-line search of the databases listed below.

- NTIS (National Technical Information Service)

- TOXLINE

- BIOSIS

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