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: Hexachloroethane **CAS REGISTRY NUMBER:** 67-72-1

AMBIENT WATER QUALITY VALUE: 5 ug/L

BASIS: Principal Organic Contaminant Classes and 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. Potential water quality values are derived below, and the value of 5 ug/L is selected for hexachloroethane as described under "Selection of Value."

II PRINCIPAL ORGANIC CONTAMINANT CLASSES AND SPECIFIC MCL (702.3)

A. Discussion

Hexachloroethane does not have a Specific MCL as defined in 700.1. However, hexachloroethane is in principal organic contaminant class i as defined in 700.1.

The U.S. Environmental Protection Agency has not established a maximum contaminant level goal (MCLG) or a MCL for drinking water for

hexachloroethane.

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 hexachloroethane in drinking water.

B. Derivation of Water Quality Value

Because hexachloroethane is in a principal organic contaminant class and has no Specific MCL, regulations require that the water quality value not exceed 5 ug/L.

III ONCOGENIC EFFECTS (702.4)

U.S. EPA (1995) conducted a comprehensive evaluation of the oncogenic effects of hexachloroethane as part of its criteria development for the Great Lakes Water Quality Initiative (GLI). The GLI was a joint undertaking by U.S. EPA and the Great Lakes States and included representatives of interest groups. Its final regulations and the criteria document for this substance received extensive public review in a formal rule making process. U.S. EPA's documentation for their oncogenic criteria has been reviewed. The Department concludes that hexachloroethane is an oncogen under New York's definition in 6 NYCRR 700.1 and that U.S. EPA's toxicological basis is appropriate for derivation of a statewide value.

Exhibit I, excerpted from U.S. EPA (1995), provides U.S. EPA's scientific basis for their criteria. These data will be used to calculate a water quality value for protection from oncogenic effects using New York State procedures as described below.

U.S. EPA (1995) selected the results of the NCI (1978) bioassay as the most appropriate dose-response data for deriving a water quality value. A summary of the data sets showing statistically and biologically significant increases in tumor response is presented in Exhibit I. U.S. EPA derived an oral cancer slope factor of 1.4×10^{-2} $[mg/(kg \cdot day)]^{-1}$ from data on male mice in the above key study.

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 mouse data (body weight of 0.030 kg) is a multiplication factor of 0.52, which results in a slope of 7.28×10^{-3} $[mg/kg \cdot day)]^{-1}$.

This slope factor is converted to a human dose, at a lifetime risk level of one-in-one million as shown below.

$$\text{Human dose} = \frac{\text{risk}}{\text{slope}} = \frac{10^{-6}}{7.28 \times 10^{-3}\ [\text{mg/(kg} \cdot \text{day)}]^{-1}}$$

$$= 1.37 \times 10^{-4}\ \text{mg/(kg} \cdot \text{day)} \equiv 0.137\ \text{ug/(kg} \cdot \text{day)}$$

The human dose above is converted to a potential water quality value based on a 70 kg adult consuming 2 liters of water per day as follows:

$$\text{Water Quality Value} = \frac{[0.137\ \text{ug/(kg} \cdot \text{day)}]\ [70\ \text{kg}]}{[2\ \text{L/day}]} = 4.80\ \text{ug/L},$$ rounded to 5 ug/L

IV NON-ONCOGENIC EFFECTS (702.5)

U.S. EPA (1995) also conducted a comprehensive review of toxicological data on non-oncogenic effects for hexachloroethane as part of criteria development under GLI. The Department reviewed the toxicological basis for EPA's non-oncogenic criteria and concludes it is appropriate for the derivation of a statewide value. Exhibit II, excerpted from U.S. EPA (1995), provides the scientific basis for their non-oncogenic criteria. These data will be used to develop a water quality value for protection from non-oncogenic effects using New York State procedures as described below.

U.S. EPA (1995) selected the results of the study by Gorzinski et al. (1985) as the most appropriate for deriving a water quality value based on non-oncogenic effects. From these, they calculated an acceptable daily exposure (ADE) of 1.0×10^{-3} mg/(kg · day), equivalent to an acceptable daily intake (ADI) developed under NYS procedures (702.5).

A potential 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 drinking water, as follows:

$$\text{Water Quality Value} = \frac{[1.0 \times 10^{-3}\ \text{mg/(kg} \cdot \text{day)}]\ [1000\ \text{ug/mg}]\ [70\ \text{kg}]\ [0.2]}{[2\ \text{L/day}]} = 7\ \text{ug/L}$$

V CHEMICAL CORRELATION (702.7)

A value based on chemical correlation for oncogenic or non-oncogenic effects is not applicable because data are sufficient to evaluate these effects.

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 for 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 value of 5 ug/L, based on both principal organic contaminant classes (702.3(b)) and oncogenic effects (702.4) is the most stringent value derived by these procedures and is the ambient water quality value for hexachloroethane.

VII REFERENCES

6 NYCRR (New York State Codes, Rules and Regulations). Water Quality Regulations, Surface Water and Groundwater Classifications and Standards: Title 6 NYCRR, Chapter X, Parts 700-705. Albany, NY: New York State Department of Environmental Conservation.

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: New York State Department of Health, Bureau of Public Water Supply Protection.

U.S. EPA (Environmental Protection Agency). 1995. Great Lakes Water Quality Initiative Criteria Documents for the Protection of Human Health. Washington, D.C.: Office of Water. EPA-820-B-95-006.

New York State Department of Environmental Conservation
Division of Water

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EXHIBIT I
(From U.S. EPA, 1995)

GREAT LAKES WATER QUALITY INITIATIVE
TIER 1 HUMAN HEALTH CRITERIA FOR HEXACHLOROETHANE
CAS NO. 67-72-1

Tier 1 Human Cancer Criterion

A review of the available literature for HCE carcinogenicity reveals a lack of adequate epidemiological data and two chronic oral rodent bioassays (NCI, 1978; NTP, 1989). EPA (1986) has classified HCE as a class C carcinogen (possible human carcinogen), based on the observation of carcinomas in one mouse strain after oral exposure (NCI, 1978). The data are judged to be sufficient for Tier 1 HCC derivation.

In a NCI study (NCI, 1978), Osborne-Mendel rats and B6C3F1 mice were orally intubated with HCE in corn oil. Groups of 50 rats per sex per dose were administered HCE over a 78-week period with an exposure protocol involving intermittent treatment-free intervals. The time-weighted-average doses were 212 or 423 mg/kg/day. The rats were then observed for an additional 33-34 weeks. Groups of 50 mice per sex per dose were administered HCE 5 days per week for 78 weeks at time-weighted-average doses of 590 or 1179 mg/kg/day, and were then observed for an additional 12-13 weeks. Due to an unusually high mortality rate among the male control mice, the results in treated groups were compared against both the vehicle control group from this study as well as a pooled vehicle control group from several concurrent studies. A statistically significant increase in the incidence of hepatocellular carcinoma was reported in both sexes of the mice (only males exhibited a dose-related trend) while tumorigenicity was not observed in rats of either sex. The increased incidence was significant by the Cochran-Armitage test for both sexes of mice against both control groups and by the Fisher exact tests for both sexes as compared to the pooled controls. Survival of low- and high-dose male and female rats in this study was reduced compared with that of the vehicle controls.

Because findings from NCI (1978) in rats were inconclusive, additional studies on toxicity and carcinogenesis were conducted in F344/N rats by administering HCE in corn oil by gavage to groups of males and females for 2 years (NTP, 1989). HCE was administered 5 days/week in corn oil by gavage at 0, 10 or 20 mg/kg bw to groups of 50 male rats, and at 0, 80 or 160 mg HCE/kg bw to groups of 50 female rats. The incidence of renal adenomas and carcinomas alone and in combination increased in the high dose male group. One of the carcinomas in the high dose group metastasized to the lung. No compound-related neoplasms were observed in females. The incidence of pheochromocytomas of the adrenal gland in low dose male rats was significantly greater than that in vehicle controls, and the incidence for both dosed groups were greater than the mean historical control incidence rates.

The renal lesions were considered by NTP to be indicative of HCE carcinogenicity while the pheochromocytomas were judged to be supportive evidence for carcinogenic effects. On the basis of these data, NTP concluded that there was clear evidence of carcinogenicity for HCE in the male rat and no evidence of carcinogenicity in female rats. Renal tubule hyperplasia was observed at an increased incidence in high dose male rats. These lesions have been described as characteristic of the hyaline droplet nephropathy that is associated with an accumulation of liver-generated $\alpha_{2\mu}$-globulin in the cytoplasm of tubular epithelial cells (NTP, 1989). Using this assumption, it can be hypothesized that the male rat renal tumors were a secondary effect to hyaline droplet formation and that they may not be relevant to human risk assessment.

The Tier 1 Human Cancer Criteria for HCE are derived from the slope factor of 1.4 E-2 $(mg/kg/d)^{-1}$ based on a dose-response data-set for hepatocellular carcinoma induction in male mice from the NCI study (NCI, 1978; EPA, 1986).

References:

National Cancer Institute (NCI). 1978. Bioassay of Hexachloroethane for Possible Carcinogenicity. NCI Carcinogenesis Technical Report Series No. 68, NCI-CG-TR-68, DHEW Publication No. (NIH) 78-1318.

National Toxicology Program (NTP). 1989. Toxicology and Carcinogenesis Studies of Hexachloroethane (CAS No. 67-72-1) in F344/N Rats (Gavage Studies). NTP Technical Report. NTP-TR-361, NIH/PUB-89-2816, Order No. PB90-170895, 117 pp.

U.S. Environmental Protection Agency (EPA). 1986. Integrated Risk Information System (IRIS database). Chemical file for hexachloroethane (67-72-1). Verification Date 7/23/86. Last Reviewed 7/23/86.

EXHIBIT II
(From U.S. EPA, 1995)

GREAT LAKES WATER QUALITY INITIATIVE
TIER 1 HUMAN HEALTH CRITERIA FOR HEXACHLOROETHANE
CAS NO. 67-72-1

Tier 1 Human Noncancer Criteria

A review of the available literature indicates that the most appropriate basis for HNV derivation for hexachloroethane (HCE) is the NOAEL from a 16-week dietary study in rats (Gorzinski et al., 1985; Gorzinski et al., 1980, as cited in EPA, 1991). In this study male and female CDF Fischer 344 rats (10/sex/group) were administered a diet containing HCE at target levels of 0, 3, 30 and 100 mg/kg/day for 16 weeks. EPA (1991) reported that actual dose levels were analyzed to be approximately 0, 1.3, 20 and 82 mg/kg/day. From analysis of eating patterns and measurement of the time-related loss of HCE from the diets, a conservative estimate of exposure was determined by the investigators as 0, 1, 15 and 62 mg/kg/day (Gorzinski et al., 1985). The results indicate that male rats were slightly more sensitive than female rats to the nephrotoxic properties of HCE. Renal toxicity observed at 15 and 62 mg/kg/day in male rats included pale and mottled kidneys; significant increases in absolute and relative kidney weights; slight to moderate renal tubular atrophy and degeneration with or without peritubular fibrosis; a slight to moderate increase in renal tubular cytoplasmic clumping and droplet formation; and scattered or isolated renal tubules with slight hypertrophy and/or dilation of the proximal convoluted tubules. Liver weights were increased in male rats given 62 mg/kg/day. The liver exhibited a slight swelling of the hepatocytes in males given 15 or 62 mg/kg/day. Evidence of renal toxicity in female rats consisted of very slight renal tubular atrophy and degeneration observed histopathologically at the highest dose level. Female rats given 62 mg/kg/day also had an increase in relative liver weight ratios unaccompanied by microscopic alterations. Based on this study, a NOAEL of 1 mg/kg/day was derived for liver and kidney toxicity in male rats. While EPA (1991) indicates a NOAEL of 1.3 mg/kg/day based on the analyzed low dose, the estimated NOAEL of 1.0 mg/kg/day (Gorzinski et al., 1985; EPA, 1987) is used in the HNV derivation.

In a chronic (78-week) gavage study with rats and mice, the National Cancer Institute (NCI, 1978) administered HCE in a cyclic manner to 50 male and 50 female Osborne-Mendel rats and continuously to 50 male and 50 female B6C3F1 mice. The rats received HCE in corn oil at doses of 250 and 500 mg/kg/day, 5 days per week for a period of 22 consecutive weeks, followed by a 1-week, treatment-free interval. Thereafter, until the end of the 78 weeks, the rats were intubated for 4 consecutive weeks followed by 1 treatment-free week, in a cyclical pattern, for a total of 66 weeks of HCE treatment. The time-weighted-average doses for the rats for the 78-week period were 212 and 423 mg/kg/day. The mice were intubated orally with HCE in corn oil at initial levels of 500 and 1000 mg/kg/day for 8 weeks with these doses increased to 600 and 1200 mg/kg/day, respectively, for the

remaining 70 experimental weeks. A time-weighted-average dose of 590 and 1179 mg/kg/day for the low and high doses, respectively, was reported. The dosing regimes were followed by an observation period of 33 or 34 weeks for rats and 12 or 13 weeks for mice. Renal tubular nephropathy was observed during histopathological examination at the termination of the study in all groups of treated animals. In rats, significant pathology and mortality at both dose levels in the males precluded the development of a NOAEL or LOAEL for HCE. For the mice, due to the occurrence of hepatocellular carcinoma and non-neoplastic toxic nephropathy in both sexes at both dose levels, neither a NOAEL nor a LOAEL could be determined.

Because of the inconclusive nature of results from the NCI (1978) study, additional toxicological and carcinogenesis studies were conducted by administering HCE in corn oil by gavage to groups of male and female F344/N rats (50/sex/group) 5 days per week for 2 years (NTP, 1989). The male rats received doses of 0, 10 or 20 mg/kg/day while the females received doses of 0, 80 or 160 mg/kg/day. The foremost toxic effect was kidney toxicity, demonstrated by increased incidence of mineralization and hyperplasia of the pelvic transitional epithelium in dosed male rats, increased severity of renal tubule hyperplasia in high dosed male rats, and increased incidence and severity of renal tubule hyperplasia in female rats. The LOAEL was 10 mg/kg bw/day for male rats. In this study, it was hypothesized that the increased sensitivity of male rats to the renal toxicity of HCE was a result of the accumulation of α_{2u}-globulin in hyaline droplets synthesized by the liver and secreted into the blood (EPA, 1991). It is then apparently filtered through the glomeruli and partially reabsorbed through the proximal tubules. In the presence of HCE, as well as several nonpolar hydrocarbons such as decalin and gasoline, α_{2u}-globulin accumulates in hyaline droplets in the renal tubular cells. α_{2u}-Globulin is an excretory protein in male but not female rats. This may explain the male's greater sensitivity to kidney damage from HCE.

In a 13-week rat study, also by NTP (1989), groups of 10 F344/N rats of each sex were administered 0, 47, 94, 188, 375 or 750 mg/kg HCE in corn oil by gavage, 5 days/week for 13 weeks. Five/10 male rats and 2/10 female rats at 750 mg/kg/day died before the end of the study. The final mean body weight of male rats that received 750 mg/kg/day was 19% lower than that of vehicle controls. Compound-related clinical signs for both sexes included hyperactivity at doses of $\geq$ 94 mg/kg/day and convulsions at $\geq$ 375 mg/kg/day. The relative weights of liver, heart and kidney were increased for exposed males and females. Kidney lesions were seen in all dosed male groups, and the severity increased with dose. Papillary necrosis and tubular cell necrosis and degeneration in the kidney and hemorrhagic necrosis in the urinary bladder were observed in the five male rats at 750 mg/kg/day which died before the end of the study. At all lower doses in males, hyaline droplets, tubular regeneration, and granular casts were present in the kidney. No chemical-related kidney lesions were observed in females. Foci of hepatocellular necrosis were observed in several male and female rats at $\geq$ 188 mg/kg/day.

Weeks et al. (1979) studied the effects of repeated exposure to HCE vapor in 25 male and 25 female rats, 4 male dogs, 10 male guinea pigs, 20 male or female quail and 22

pregnant rats per exposure group. The animals were exposed for 6 hours/day, 5 days/week for 6 weeks and doses were analyzed at 0, 15, 48 or 260 ppm of the HCE vapor (equivalent to 0, 145, 465 or 2515 mg/m^3; EPA, 1991). Toxic effects at the highest concentrations included tremors and other neurotoxic signs. No effects were observed at $\leq$ 465 mg/m^3.

Weeks et al. (1979) performed an oral study, in which HCE doses of 100, 320 and 1000 mg/kg/day were administered by gavage to rabbits for 12 days. The two highest doses resulted in liver degeneration and necrosis, toxic tubular nephrosis of the convoluted tubules of the corticomedullary region of the kidney, minimal tubular nephrocalcinosis, and decreased body weights. The NOAEL for this study was 100 mg/kg/day based on the effects of HCE on the kidneys of male rabbits.

The database is judged to be sufficient for Tier 1 HNC derivation. The key study (Gorzinski et al., 1985) provides a subchronic NOAEL which is supported and supplemented by chronic toxicity data (EPA 1989; EPA, 1991; NCI, 1978; NTP, 1989; Weeks et al., 1979). The HNC is based on the subchronic rat NOAEL of 1 mg/kg/day, with a total uncertainty factor of 1000. The LOAEL of 15 mg/kg/day resulted in male rat renal toxicity. It may be argued that the high sensitivity of this endpoint is peculiar to male rats, secondary to hyaline droplet formation and α_{2u}-globulin accumulation. However, liver affects also occurred at a LOEL of 15 mg/kg/day. The use of the NOAEL of 1 mg/kg/day for risk assessment is consistent with the oral RfD development by EPA (1987) and the Lifetime Health Advisory (EPA, 1991).

$$ADE = \frac{NOAEL}{UF} = \frac{1.00\ mg/kg/d}{1000} = 1.0 \times 10^{-3}\ mg/kg/day$$

Where: Uncertainty Factor = 1,000, composed of:

10x for interspecies variability
10x for intraspecies differences
10x for subchronic exposure duration

References:

Gorzinski, S.J., R.J. Nolan, S.B. McCollister, D.C. Morden, E.A. Hermann, D.A. Dittenbar, R.V. Kainis, J.E. Battjes and R.J. Kociba. 1980. Hexachloroethane: Results of a 16-Week Toxicity Study in the Diet of CDF Fischer 344 Rats. Toxicology Research Laboratory, Dow Chemical U.S.A., Midland, MI. As cited in EPA (1991).

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U.S. Environmental Protection Agency (EPA). 1989. Health and Environmental Effects Document for Hexachloroethane. Environmental Criteria and Assessment Office, Cincinnati, OH. EPA/600/8-88/043. PB88-178736/GAR. ECAO-CIN-G041.

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