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: Heptachlor epoxide **CAS REGISTRY NUMBER:** 1024-57-3

AMBIENT WATER QUALITY VALUE: 0.03 ug/L

BASIS: Oncogenic

I INTRODUCTION

This value applies to the water column and is designed to protect humans from the effects of contaminants in souces 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 0.009 ug/L for the sum of heptachlor and heptachlor epoxide (NYS, 1984). Available information on heptachlor epoxide was examined as described in "Scope of Review," below. Potential water quality values are derived below, and the value of 0.03 ug/L selected as described under "Selection of Value."

II PRINCIPAL ORGANIC CONTAMINANT CLASSES AND SPECIFIC MCL (702.3)

A. Discussion

Heptachlor epoxide has a Specific MCL of 0.2 ug/L as defined in 700.1. This maximum contaminant level for drinking water was adopted by the New York State Department of Health under the State Sanitary Code (10 NYCRR Part 5,

Public Water Supplies). Heptachlor epoxide is also in principal organic contaminant class vi as defined in 700.1.

The U.S. Environmental Protection Agency has established a maximum contaminant level goal (MCLG) of 0 and a MCL of 0.2 ug/L for heptachlor epoxide.

B. Derivation of Water Quality Value

Because heptachlor epoxide has a Specific MCL, the fact that it is also in a principal organic class does not bear upon the water quality value. Regulations require that the water quality value not exceed the Specific MCL of 0.2 ug/L.

III ONCOGENIC EFFECTS (702.4)

A. Data

U.S. EPA (1995) classifies heptachlor epoxide as B2, a probable human carcinogen, based on sufficient evidence from rodent studies. Specifically, liver carcinomas were induced in mice (two strains, both sexes) and rats (CFN, females). Also, U.S. EPA noted that several structurally related substances are liver carcinogens.

Heptachlor epoxide is an animal oncogen as defined in 6 NYCRR 700.1.

U.S. EPA (1995) provides data on hepatocellular carcinomas in mice from two dietary studies, as shown in Table 1.

B. Discussion and Selection of Data

U.S. EPA (1995) presents an oral slope factor of 9.1 $(mg/kg/day)^{-1}$ for heptachlor epoxide. This slope factor represents a geometric mean of four slope factors, from data on male and female C3H mice (Davis, 1965) and male and female CD-1 mice (Velsicol, 1973). The individual slope factors were 27.7, 36.2, 6.48 and 1.04 $(mg/kg/day)^{-1}$ for these groups, respectively. EPA further notes that this geometric mean is consistent with the slope factor of 5.8 $(mg/kg/day)^{-1}$ for female CFN rats.

U.S. EPA's rationale for presenting a geometric mean of four mouse slope factors is because they judged mice to be the more sensitive species tested and to avoid discarding relevant data.

We do not agree with U.S. EPA's approach of including the Davis study in their calculation of the geometric mean. It is of questionable quality and poorly documented. It is a single-dose study using heptachlor epoxide of unspecified purity. It was completed in 1965, prior to the existence of Good Laboratory Practice (GLP) guidelines, and was never published as a formal report. Both control and dosed groups showed excessive early mortality and data on tumor onset and cause of death were not provided. Although it does provide qualitative evidence that heptachlor epoxide causes liver tumors, it is of limited value for quantitative risk assessment. It will not be used as the basis of a value in this fact sheet.

Table 1

Mouse Oral Dose Response Data for Heptachlor Epoxide
(adapted from U.S. EPA, 1995)

Administered Dose (ppm)	Human Equivalent Dose (mg/kg/day)	Tumor Incidence	Strain	Reference
male				
0	0.0	22/73	C3H	Davis, 1965 as diagnosed by Reuber, 1977 (cited in Epstein, 1976)
10	0.108	73/79		
female				
0	0.000	2/53	C3H	
10	0.108	77/81		
female				
0	0.00	6/76	CD1	Velsicol, 1973 as evaluated by Reuber, 1977
1	0.01	1/70		
5	0.052	6/65		
10	0.10	30/57		
male				
0	0.00	0/62	CD1	
1	0.01	2/68*		
5	0.052	18/68		
10	0.10	52/80		

* Apparently should be 2/61 (Bogdan, 1995)

As noted above, U.S. EPA (1995) also presents an oral slope factor of 5.8 $(mg/kg/day)^{-1}$ for female CFN rats. Consideration was given to combining

this with the male CD-1 mouse slope, but this approach was rejected given uncertainties over dose and interpretation of treatment of data, as described by Epstein (1976).

What remains are the slope factors of 6.48 and 1.04 $(mg/kg/day)^{-1}$ for male and female CD-1 mice respectively. As it is unknown whether males or females best predict overall human response and even whether these similar slopes indicate differences other than random experimental variability, we will use a geometric mean as the basis of the water quality value for heptachlor epoxide. The geometric mean of 6.48 and 1.04 is 2.60 $(mg/kg/day)^{-1}$.

C. Derivation of Water Quality Value

The above mean slope factor is based on slope factors that were 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 the mean 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 1.35 $(mg/kg/day)^{-1}$.

The human dose at a one-in-one million lifetime risk level is calculated:

$$\text{human dose} = \frac{1 \times 10^{-6} \times 10^{3}\ ug/mg}{1.35\ (mg/kg/day)^{-1}} = 7.41 \times 10^{-4}\ ug/kg/day$$

A potential water quality value is then calculated, assuming a body weight of 70 kg and a daily water consumption of 2 L:

$$\text{Water Quality Value} = \frac{7.41 \times 10^{-4}\ ug/kg/day \times 70\ kg}{2\ L/day}$$

$$= 0.0259\ ug/L, \text{ rounded to } 0.03\ ug/L$$

IV NON-ONCOGENIC EFFECTS (702.5)

A. Data

U.S. EPA (1995) based its oral reference dose for heptachlor epoxide on a 1958 Dow Chemical Company study on dogs. In this 60-week feeding study, the lowest-effect level (LEL) was 0.5 ppm in the diet, or 0.0125 mg/kg/day (the

lowest dose tested). The critical effect was increased liver-to-body weight ratio in both sexes. ATSDR (1993) raised questions about this study, and described "minimal physiological changes in beagle dogs" resulting from chronic exposure to low concentrations of this substance. They do not list any NOAEL or LOAEL for chronic exposure to heptachlor epoxide.

In its Reregistration Eligibility Document (RED) for heptachlor, U.S. EPA (1992) presents a RfD for heptachlor epoxide of 0.000013 mg/kg/day, based on what is evidently the same study on dogs as described above. That document also lists a NOEL of 0.025 mg/kg/day based on [absence of] liver effects in pups, from dogs treated with heptachlor epoxide in the diet at that level for an unspecified amount of time.

B. Derivation of Water Quality Value

1. Selection of Data

   Despite some concerns, the study by Dow (1958) was selected for deriving a potential water quality value based on non-oncogenic effects.

2. Calculation of Acceptable Daily Intake (ADI)

   An ADI is calculated from the study of Dow (1958) by dividing the LEL of 0.0125 mg/kg/day by a total uncertainty factor of 1000 as follows:

   $$\text{ADI} = \frac{0.0125 \text{ mg/kg/day}}{1000} = 0.0000125 \text{ mg/kg/day}$$

   This uncertainty factor was selected to account for interspecies differences (10), potential sensitive individuals (10), and for using a LEL instead of a no-observed-effect level (NOEL) (10).

3. Calculation of Water Quality Value

   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 come from drinking water, as follows:

$$\text{Water Quality Value} = \frac{(0.0000125 \text{ mg/kg/day})(1000 \text{ ug/mg})(70 \text{ kg})(0.2)}{2 \text{ L/day}}$$

$$= 0.0875 \text{ ug/L, rounded to } 0.09 \text{ ug/L}$$

We note that this value is less stringent than the value based on oncogenic effects, ameliorating the concerns mentioned above.

V CHEMICAL CORRELATION (702.7)

A value based on chemical correlation was not derived because of the extensive data base on the oncogenic and non-oncogenic effects of this substance.

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 oncogenic value of 0.03 ug/L (6 NYCRR 702.4) is the most stringent value derived by these procedures and is the ambient water quality value for heptachlor epoxide.

Not only does this value differ numerically from the one presented previously (NYS, 1984) but it applies to heptachlor epoxide alone, instead of the sum of heptachlor and heptachlor epoxide. This approach is judged appropriate and is consistent with that of U.S. EPA.

VII REFERENCES

ATSDR (Agency for Toxic Substances and Disease Registry). 1993. Toxicological Profile for Heptachlor/Heptachlor Epoxide. Update. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service.

Bogdan, K. 1995. New York State Department of Health. Personal Communication.

Davis, K.J. 1965. Pathology Report on Mice Fed Aldrin, Dieldrin, Heptachlor and Heptachlor Epoxide for Two Years. Internal FDA memorandum to Dr. A.J. Lehman, July 19. [As cited by U.S. EPA, 1995].

Dow Chemical Company. 1958. MRID No. 00061912. Available from EPA. Write to FOI, EPA, Washington, D.C. 20460. [As cited by U.S. EPA, 1995].

Epstein, S.S. 1976. Carcinogenicity of heptachlor and chlordane. Sci. Total Environ. 6: 103-154.

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.

NYS (New York State). 1984. Ambient Surface Water Quality Standards Documentation. Heptachlor and Heptachlor epoxide. Albany, NY: Department of Health.

Reuber, M.D. 1977. Histopathology of carcinomas of the liver in mice ingesting heptachlor or heptachlor epoxide. Exp. Cell Biol. 45:147-157. [As cited by U.S. EPA, 1995].

U.S. EPA (Environmental Protection Agency). 1992. Reregistration Eligibility Document (RED): Heptachlor. PB92-191105. Washington, D.C.

U.S. EPA (Environmental Protection Agency). 1995. Heptachlor epoxide. On-line. Integrated Risk Information System (IRIS). Cincinnati, OH: Office of Research and Development, Environmental Criteria and Assessment Office.

Velsicol Chemical Corporation. 1973. MRID No. 00062678. Available from EPA. Write to FOI, EPA, Washington, D.C. 20460. [As cited by U.S. EPA, 1995].

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 heptachlor epoxide; 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 (substance not on CCRIS).
- ATSDR (Agency for Toxic Substances and Disease Registry) toxicological profile.

- IARC (International Agency for Research on Cancer) Monographs Supplement 7 (substance not listed).

- U.S. EPA health advisory.

- U.S. EPA drinking water criteria document.

The sources below were reviewed by NYS (1984).

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

- NAS (National Academy of Sciences). 1982. An Assessment of the Health Risks of Seven Pesticides used for Termite Control. National Academy Press. Washington, D.C.

- IARC (International Agency for Research on Cancer). 1974. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. 5:173-191.

- IARC (International Agency for Research on Cancer). 1979. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. 20: 129-155.

- USEPA (U.S. Environmental Protection Agency). 1980. Ambient water quality criteria for heptachlor. NTIS No. PB81-117632.

The sources above are deemed adequate to assess the literature through 1989.Coverage of more recent literature was provided by a New York State Library on-line search of the databases listed below.

- NTIS (National Technical Information Service)

- TOXLINE

- BIOSIS

In addition, a public notice soliciting information on the toxicity of this substance was placed in the New York State Register and the Environmental Notice Bulletin.

SJS
February 5, 1997