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: Hexachlorobutadiene **CAS REGISTRY NUMBER:** 87-68-3

AMBIENT WATER QUALITY VALUE: 0.5 ug/L

BASIS: Non-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. New York State previously prepared a fact sheet that supported a value of 0.5 ug/L for hexachlorobutadiene (HCBD) (NYS, 1985). Much of that derivation is included in the present fact sheet. New information on HCBD since then was examined as described in "Scope of Review," below. Potential water quality values are derived below, and the value of 0.5 ug/L selected as described under "Selection of Value."

II PRINCIPAL ORGANIC CONTAMINANT CLASSES AND SPECIFIC MCL (702.3)

A. Discussion

HCBD does not have a Specific MCL as defined in 700.1. HCBD is in principal organic contaminant class v as defined in 700.1.

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

B. Derivation of Water Quality Value

Because HCBD 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 (1994) classifies HCBD as C, possible human carcinogen, based on observation of renal neoplasms in male and female rats in one study (Kociba et al., 1977). IARC (1987) classifies HCBD in Group 3, not classifiable as to human carcinogenicity. Both groups agree that HBCD caused kidney tumors in male and female rats.

Kociba et al. (1977) exposed groups of 39 or 40 Sprague-Dawley male and female rats to 0, 0.2, 2 or 20 mg HCBD/kg/day in the diet for 22 to 24 months. Combined incidences of renal tubular neoplasms increased ($p<0.05$) over controls at 20 mg/kg/day in both sexes. The tumor incidence was not increased in the 0.2 and 2 mg/kg/day dose groups but there was some indication of hyperplasia in animals exposed to 2 mg/kg/day.

Genotoxicity

Results of testing HCBD metabolic conjugates in bacterial assays (S. typhimurium) are mixed with positive results in strains TA100, 98 and 2638 with activation (Vamvakas et al. 1988; Reichert et al., 1984; Wild et al., 1986; Dekant et al., 1986) and induced unscheduled DNA synthesis and transformation in Syriam hamster embryo fibroblasts (Schiffman et al., 1984). HCBD did not induce unscheduled DNA synthesis in rat hepatocytes (Stott et al., 1981).

B. Derivation of Water Quality Value

1. Oncogenic Definition

The evidence of oncogenic activity in both sexes of one mammalian species after HCBD exposure in Kociba et al. (1977) supported by positive results in short-term tests that are indicative of potential

oncogenic activity (ATSDR, 1994) fulfills the definition of an oncogenic effect in 700.1 for HCBD.

2. Selection of Data

Dose-response data from the Kociba et al. (1977) bioassay are appropriate for deriving a water quality value. The dose-response data for kidney tumors in male rats (Table I) represent the most sensitive response in rats (NYS, 1985; U.S. EPA, 1994).

U.S. EPA (1994) evaluated these data and calculated a human potency factor of 7.8×10^{-2} $(mg/kg/day)^{-1}$ and a drinking water concentration of 0.5 ug/L at the 10^{-6} risk level on the basis of the male rat tumor incidence.

Table I

Dose-Response Data for Kidney Tumors in Male Rats

Sex/Species	Administered Dose (mg/kg)/day	Tumor Type	Tumor Incidence
male rats	0	renal adenomas	1/90
	0.2	and carcinomas	0/40
	2.0		0/40
	20.0		9/39

3. 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. No information that would warrant the use of another model was found.

The low-dose extrapolation from experimental results to the risk level required by regulation (1 x 10E-6) was done with the GLOBAL82 LMS model (Crump, 1982). The model derives both the 95% lower confidence limit (LCL) on the dose and the maximum likelihood estimate (MLE) of the dose. The MLE, when compared to the 95% LCL, provides a measure of goodness-of-fit of the data to the LMS model.

There is a substantial difference between the 95% lower bound estimate (0.068 ug/kg/day) and the MLE (310 ug/kg/day) of the dose associated with an extra cancer risk of 1 x 10E-6 indicating very poor goodness-of-fit. Although a difference of this magnitude is not typical, it will occur on occasion. The very poor fit reflects an inherent limitation of the LMS model to describe dose-response functions that are initially flat but curve steeply upwards at higher doses, such as the observed dose-response data for kidney tumors in male rats. The output of the model i.e. the 95% LCL and the MLE are shown in Table II. Part 702 specifies the 95% LCL as the basis of the water quality value.

Table II

GLOBAL82 Outputs

Sex/Species	Tumor Site	Animal Dose ug/kg/day	
		95% LCL	MLE
male rat	kidney	0.068	310

4. Calculation of Human Doses

The animal dose associated with a 1 x 10^{-6} excess cancer risk is converted as shown below to a human dose by a transpecies scaling factor as proposed in Part 702.

$$\text{Human dose} = \left(\frac{\text{animal body weight}}{\text{human body weight}}\right)^{0.25} \times \text{animal dose}$$

$$\text{Human dose} = \left(\frac{0.610\ \text{kg}}{70\ \text{kg}}\right)^{0.25} \times 0.068\ \text{ug/kg/day} = 0.0208\ \text{ug/kg/day}$$

5. Selection of Human Dose and Discussion of Uncertainties

An adequate number of animals were exposed to an adequate number of doses for their lifetime. The doses are widely spaced, in order-of-magnitude steps. Response data are zero at 2.0 mg/kg/day and absent between 2.0 mg/kg/day and 20 mg/kg/day. Nevertheless the shorter

term NTP (1991) results support the kidney as the primary target organ at this dose range (see Section IV Non-Oncogenic Effects).

For the male rat, the critical site is the kidney, with an equivalent human dose of 0.0208 ug/kg/day at the 10^{-6} risk level. The human dose derived 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 a 1 x 10^{-6} risk level in the section above is converted to a water quality value based on a 70 kg adult consuming 2 liters of water per day as follows:

$$\text{Water Quality Value} = \left(\frac{0.0208 \text{ ug}}{\text{kg day}}\right) \frac{(70 \text{ kg})}{(2 \text{ L/day})} = 0.728 \text{ ug/L}, \text{ rounded to } 0.7 \text{ ug/L}$$

IV NON-ONCOGENIC EFFECTS (702.5)

A. Data

The kidney is the primary target organ following oral exposure to HCBD. Lifetime exposure of Sprague-Dawley rats to diets containing HCBD at 0, 0.2, 2.0 or 20 mg/kg/day (Kociba et al., 1977) resulted in increased urinary excretion of coproporphyrin, increased kidney weight and increased renal tubular epithelial hyperplasia at 20 mg/kg/day, an increase in renal tubular epithelial hyperplasia at 2 mg/kg/day and no treatment-related effects at 0.2 mg/kg/day. The no-observed-adverse-effect-level (NOAEL) is 0.2 mg/kg/day.

The NTP (1991) conducted thirteen week studies in which groups of 10 mice per sex received 0, 1, 3, 10, 30 or 100 ppm HCBD in feed (corresponding to doses of 0, 0.1, 0.4, 1.5, 4.9 or 16.8 mg/kg/day for males and 0.2, 0.5, 1.8, 4.5 or 19.2 mg/kg/day for females). Kidney weights were reduced in males receiving 4.9 or 16.8 mg/kg/day and in females receiving 19.2 mg/kg/day. A compound related increase in tubular cell regeneration in the renal cortex occurred in male and female mice. This lesion increased in severity with dose. Female mice were more sensitive to the effects of HCBD exposure. The NOAEL for male mice was 1.5 mg/kg/day. A lowest-observed-effect-level (LOEL) for female mice was 0.2 mg/kg/day (in 1 out of 10 mice).

When HCBD was administered orally to rats, the glutathione conjugate of HCBD, its mercapturic acid derivative, and bile containing HCBD metabolites were all nephrotoxic (Nash et al., 1984). However, when the rats' bile ducts

were blocked they were completely protected from kidney damage, indicating that hepatic metabolites were solely responsible for the nephrotoxicity of HCBD.

Reproductive and Developmental Toxicity

Schwetz et al. (1977) conducted a 148-day study in which groups of 10 to 17 male and 20 to 34 female adult rats/group were exposed to HCBD at 0, 0.2, 2.0 or 20 mg/kg/day in their diet for 90 days prior to mating, 15 days during mating and throughout gestation (22 days) and lactation (21 days). There were no treatment-related effects on pregnancy or neonatal survival. Body weight of 21-day-old weanlings in the high-dose group was slightly but significantly ($p < 0.05$) less than controls. No toxic effects were observed in neonates at doses of 0.2 or 2.0 mg/kg/day.

B. Derivation of Water Quality Value

1. Selection of Data

The study by NTP (1991) was judged the most appropriate for deriving a water quality value based on non-oncogenic effects. It was selected because it demonstrates differences in response to several increasing doses of HCBD, defining clear dose-response curves. A NOAEL in male mice and a LOEL in female mice were defined. However, only 10 animals were used per group.

The effects are similar to those in rats in Kociba et al. (1977). However, NTP (1991) found tubular regeneration in one female mouse at the dose equivalent to the Kociba et al. rat NOAEL. The LOEL is 0.2 mg/kg/day.

2. Calculation of Acceptable Daily Intake (ADI)

An ADI is calculated from the study of NTP (1991) by dividing the female LOEL of 0.2 mg/kg/day by a total uncertainty factor (UF) of 3000 as follows:

$$ADI = \left(\frac{0.2}{3000} \right) \text{ mg/kg/day} = 6.7 \times 10^{-5} \text{ mg/kg/day}$$

This uncertainty factor was selected to account for intra-(10) and interspecies(10) differences and the use of a less-than-lifetime study(10). Due to the nature of the lesion in only one out of 10 female mice an uncertainty factor of 3 is chosen for the use of a minimal effect

LOEL. No pharmacokinetic information was found to warrant the use of a different conversion.

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 drinking water:

$$\text{Water Quality Value} = \frac{(6.7\times10^{-5}\ \text{mg/kg/day})(1000\ \text{ug/mg})(70\ \text{kg})(0.2)}{(2\ \text{L/day})} = 0.47\ \text{ug/L, rounded to } 0.5\ \text{ug/L}$$

V CHEMICAL CORRELATION (702.7)

A value based on chemical correlation was not derived because data are sufficient for deriving a value using sections 6 NYCRR 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 non oncogenic value of 0.5 ug/L (6 NYCRR 702.5) is the most stringent value derived by these procedures and is the ambient water quality value for HCBD.

VIII REFERENCES

ATSDR (Agency for Toxic Substances and Disease Registry). 1994. Toxicological Profile for Hexachlorobutadiene. Washington, D.C.: U.S. Public Health Service.

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NTP (National Toxicology Program). 1991. Toxicity studies of Hexachloro-1,3-butadiene in B6C3F1 mice (feed studies). R.S.H. Yang. Research Triangle Park, NC: National Institute of Environmental Health Sciences.

Nash, J.A., L.J. King, E.A. Lock, T. Green. 1984. The metabolism and nephrotoxicity of hexachlorobutadiene in the rat and its relevance to nephrotoxicity. Toxicol. Appl. Pharmacol. 73:124-137. (As cited in NTP, 1991).

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 Water Supply Protection.

NYS (New York State). 1985. Ambient Surface Water Quality Standards Documentation. Hexachlorobutadiene. Albany, N.Y.: New York State Department of Health.

Reichert, D., T. Neudecker, S. Schulz. 1984. Mutagenicity of hexachlorobutadiene, perchlorobutenoic acid and perchlorobutenoic acid chloride. Mutat. Res. 137:89-93. [As cited in ATSDR, 1994].

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USEPA (Environmental Protection Agency). 1989. Hexachlorobutadiene. Drinking Water Health Advisory. Washington, D.C.: Office of Water.

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Wild, D., S. Schutz, D. Reichert. 1986. Mutagenicity of the mercapturic acid and other S-containing derivatives of hexachloro-1,3-butadiene. Carcinogenesis. 7:431-434. [As cited in ATSDR, 1994]

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 HCBD; 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.
- U.S. EPA health advisory.
- U.S. EPA drinking water criteria document.
- Verschueren, K. 1983. Handbook of Environmental Data on Organic Chemicals, 2nd Edition. New York, NY: Van Nostrand Reinhold Company, Inc.

The sources below were reviewed by NYS (1985).

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- International Agency for Research on Cancer. 1979. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. 20:179-193.

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- U.S. EPA (Environmental Protection Agency). 1980. Ambient water quality criteria for hexachlorobutadiene. NTIS No. PB81-117640.

The sources above are deemed adequate to assess the literature through 1984. 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

New York State Department of Environmental Conservation
Division of Water
AS
November, 1995
Revised SJS January 28, 1997