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NEW YORK STATE
- HUMAN HEALTH FACT SHEET -

Ambient Water Quality Value for Protection of Sources of Potable Water

SUBSTANCE: beta-Hexachlorocyclohexane **CAS REGISTRY NUMBER:** 319-85-7

AMBIENT WATER QUALITY VALUE: 0.04 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. New York State previously prepared a fact sheet that supported a value of 0.02 ug/L for hexachlorocyclohexane (HCH) and the isomers alpha-HCH, beta-HCH, gamma-HCH, delta-HCH and epsilon-HCH (NYS, 1985). Available information on beta-HCH was examined as described in "Scope of Review," below. Potential water quality values are derived below, and the value of 0.04 ug/L selected as described under "Selection of Value."

II PRINCIPAL ORGANIC CONTAMINANT CLASSES AND SPECIFIC MCL (702.3)

A. Discussion

beta-HCH does not have a Specific MCL as defined in 700.1.

However, beta-HCH is in a principal organic contaminant class (vi) 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 beta-HCH.

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 beta-HCH in drinking water.

B. Derivation of Water Quality Value

Because beta-HCH 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 beta-HCH as class C (possible human carcinogen) on the basis of increase in benign liver tumors in CF1 mice fed beta-HCH. IARC (1987) classifies hexachlorocyclohexanes in Group 2B (possibly carcinogenic to humans) but lists no separate entry for beta-HCH.

Thorpe and Walker (1973) fed 30 each male and female CF1 mice dietary beta-HCH at 200 ppm (26 mg/kg/day) for 110 weeks. This resulted in 12% mortality of males and 25% of females during the first 3 months. A significantly increased incidence of liver tumors was observed in treated males and females. Goto et al. (1972) maintained male ICR-JCL mice on a diet containing 600 ppm (78 mg/kg/day) beta-HCH for 26 weeks. Relative liver weight was increased in the treated animals, and there was histologic evidence of benign neoplasms.

Chromosome aberrations were reported in bone marrow cells of rats exposed to beta-HCH (Shimaza et al. 1972).

No statistically significant increased tumor incidence as a consequence of beta-HCH feeding was seen in several small (5-20 animals per group) studies with male and female mice fed 0-600 ppm for 24-32 weeks (Nagasaki et al. 1972; Hanada et al. 1973; Ito et al., 1973) or in male Wistar rats fed 0-1000 ppm for more than 72 weeks (Ito et al., 1975; Fitzhugh et al., 1950).

B. Derivation of Water Quality Value

1. Oncogenic Definition

The evidence of oncogenic activity in one mammalian species, after beta-HCH exposure in Thorpe and Walker (1973) and independently

reproduced by Goto et al. (1972) fulfills the definition of an oncogenic effect in 700.1 for beta-HCH.

2. Selection of Data

The Thorpe and Walker (1973) study is selected 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 Table I. It was conducted with adequate number of animals and for the lifetime of the animal. A significant weakness of the study is that it was carried out with one dose group. U.S. EPA (1995) used these data as the basis of a water value. NYS (1985) presented these data and calculated a value for beta-HCH and gamma-HCH. Since the gamma-HCH was the lower value, the ambient water value was based on gamma-HCH.

Table I. Incidence of Hepatic Tumors in Mice Fed Beta-HCH - Thorpe and Walker (1973)

Animal	Dose (mg/kg/day)*	Tumor Site	Tumor Incidence
male mouse	0		11/45
	26	liver	22/24

* Dose = ppm x 0.13 food consumption.

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 pharmacokinetic data were found that would warrant the use of another model.

The GLOBAL82 model (Crump, 1982) is used to provide the LMS extrapolation from test results to the risk level required by regulation. The model derives both the 95% lower confidence limit (LCL) on the 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. The MLE, when compared to the 95% LCL, provides a measure of goodness-of-fit of the data and thus one indication of uncertainty. The agreement between the 95%

LCL and MLE is very good indicating a low degree of uncertainty of the fit of the LMS model to the data.

The output of the model, i.e. both the animal dose 95% LCL and MLE, is shown in Table II.

Table II

Animal	Tumor Site	Animal Dose (ug/kg/day) 95% LCL	MLE
male mouse	liver	0.0072	0.012

4. Calculation of Human Doses

The animal dose associated with a 1×10^{-6} excess cancer risk, is converted as shown below to human dose on the basis of the 3/4 power of relative body weights as proposed in Part 702.

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

$$\text{Human dose} = \left(\frac{0.030 \text{ kg}}{70 \text{ kg}} \right)^{0.25} \times 0.0072 \text{ ug/kg/day} = 1.04 \times 10^{-3} \text{ ug/kg/day}$$

5. Selection of Human Dose and Discussion of Uncertainties

For the male mouse, the critical site is the liver. A human dose of 1.04×10^{-3} ug/kg/day as shown above was calculated from an animal dose of 0.0072 ug/kg/day.

The risk estimate was calculated on data from only one non-zero dose group.

6. Calculation of Water Quality Value

The human dose 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:

$$\text{Water Quality Value} = \frac{1.04 \times 10^{-3} \text{ ug}}{70 \text{ kg}} = 0.0364 \text{ ug/L},$$

$\left(\text{kg} \cdot \text{day}\right)\left(\text{2 L/day}\right)$ rounded to 0.04 ug/L

IV NON-ONCOGENIC EFFECTS (702.5)

A. Data

Adverse effects in the hepatic, renal, neurological and reproductive systems have been found in animals exposed to beta-HCH chronically or subchronically. A dose-dependent increase in liver weight was noted in rats exposed for 13 weeks to 0.1 - 12.5 mg beta-HCH/kg/day, as well as an increase in cellular hypertrophy and an increase in eosinophils (Van Velsen et al., 1986). Kidney weights in female rats exposed to 0.1 mg beta-HCH/kg/day for 13 weeks and in males exposed to 0.25 mg/kg/day increased significantly (Van Velsen et al., 1986). Muller et al. (1981) reported a significant delay in tail nerve conduction velocity in rats fed 66.3 mg beta-HCH/kg/day for 30 days. Van Velsen et al. (1986) reported coma in rats exposed to 12.5 mg/kg/day for 13 weeks. Significantly increased ovary and uterus weights were reported with 13 week exposure to 0.5 mg beta-HCH/kg/day in female rats. Atrophy was observed in the uterus and ovary of rats fed 12.5 mg/kg/day. Exposure to 12.5 mg beta-HCH/kg/day resulted in severe effects in male rats including degeneration of seminiferous tubules and disruption of spermatogenesis (Van Velsen et al., 1986). The LOAEL for this study is 0.1 mg/kg/day.

B. Derivation of Water Quality Value

1. Selection of Data

The study by Van Velsen et al. (1986) was judged the most appropriate for deriving a water quality value based on non-oncogenic effects. It was selected because the study was conducted using several dose levels and several endpoints were examined.

2. Calculation of Acceptable Daily Intake (ADI)

An ADI is calculated from the study of Van Velsen et al. (1986) by dividing the LOAEL of 0.1 mg/kg/day by a total uncertainty factor of 1000 as follows:

$$\text{ADI} = \left(\frac{0.1 \text{ mg/kg/day}}{10{,}000}\right) = 1 \times 10^{-5} \text{ mg/kg/day}$$

This uncertainty factor was selected to account for intra- and interspecies differences (10 x 10) and the use of a LOAEL (10) from a subchronic 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:

$$\text{Water Quality Value} = \frac{(1 \times 10^{-5}\ \text{mg/kg/day})(1000\ \text{ug/mg})(70\ \text{kg})(0.2)}{(2\ \text{L/day})} = 0.07\ \text{ug/L}$$

V CHEMICAL CORRELATION (702.7)

Because values can be derived using 702.4 and 5, deriving a water quality value for beta-HCH using chemical correlation was not considered.

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 value of 0.04 ug/L (6 NYCRR 702.4) is the most stringent value derived by these procedures and is the ambient water quality value for beta-HCH.

VII REFERENCES

ATSDR (Agency for Toxic Substances and Disease Registry). 1994. Toxicological Profile for alpha-, beta-, gamma- and delta-hexachlorocyclohexane. Washington, D.C.: Public Health Service, U.S. Department of Health and Human Services.

Crump, K.S. 1982. GLOBAL82. Ruston, LA: K.S. Crump and Company, Inc.

Fitzhugh, O.G., A.A. Nelson and J.P. Frawley. 1950. The chronic toxicities of technical benzene hexachloride and its alpha, beta, and gamma isomers. J. Pharmacol. Exp. Ther. 100:59-66.

Goto, M., M. Hattori and T. Miyagawa. 1972. Contribution on ecological chemistry. II. Formation of hepatoma in mice after ingestion of HCH isomers in high doses. Chemosphere 6:279-282.

Hanada, M., C. Yutani and T. Miyaji. 1973. Induction of hepatoma in mice by benzene hexachloride. Gann 64:511-513.

Ito, N., H. Nagasaki, M. Arai et al. 1973. Histologic and ultrastrutural studies on the hepatocarcinogenicity of benzene hexachloride in mice. J. Natl Cancer Inst. 51:817-826.

Ito, N., H. Nagasaki, H. Aoe et al. 1975. Development of hepatocellular carcinomas in rats treated with benzene hexachloride. J. Natl Cancer Inst. 54:801-805.

Muller, D., H. Klepel, R.M. Macholz et al. 1981. Electroneurophysiological studies on neurotoxic effects of hexachlorocyclohexane isomers and gamma-pentachlorohexane. Bull. Environ. Contam. Toxicol. 27:704-706.

Nagasaki, H., S. Tomii, T. Mega et al. 1972. Hepatocarcinogenic effect of alpha, beta, gamma and delta isomers of benzene hexachloride in mice. Gann 63:805-807.

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). 1985. Ambient Surface Water Quality Standards Documentation. Hexachlorocyclohexane (HCH) and the isomers alpha-HCH, beta-HCH, gamma-HCH, delta-HCH and epsilon-HCH. Albany, N.Y.

Shimazu, H., N. Shiraishi, T. Akematsu et al. 1972. Carcinogenicity screening tests on induction of chromosomal aberrations in rat bone marrow cells in vivo. MURE 38:347.

Thorpe, E. and A.I.T. Walker. 1973. The toxicology of dieldrin (HEOD): II. Comparative long-term oral toxicity studies in mice with dieldrin, DDT, phenobarbitone, beta-BHC, and gamma-BHC. Food Cosmet. Toxicol. 11:433-442.

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

Van Velsen, F.L., L.H.J.C. Danse, F.X.R. Van Leeuwen et al. 1986. The subchronic oral toxicity of the beta-isomer of hexachlorocyclohexane in rats. Fund. Appl. Toxicol. 6:697-712.

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 beta-HCH; 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 (document not found).
- U.S. EPA drinking water criteria document (document not found).

The sources below were reviewed by NYS (1985).

- Howe, R.B. and K.S. Crump. 1982. GLOBAL82 Computer Program. Science Research Systems, Inc., Ruston, LA.

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- International Agency for Research on Cancer. 1974. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. 5:47-74.

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- Thorpe, E. and A.I.T. Walker. 1973. The toxicology of dieldrin (HEOD). II. Comparative long-term oral toxicity studies in mice with dieldrin, DDT, phenobarbitone, beta-BHC and gamma-BHC. Fd. Cosmet. Toxicol. 11:433-442.

- U.S. Environmental Protection Agency. 1980. Ambient water quality criteria for hexachlorocyclohexane. NTIS No. PB81-117659.

The sources above are deemed adequate to assess the literature through 1994.

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