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NEW YORK STATE
- HUMAN HEALTH FACT SHEET -

Ambient Water Quality Value for
Protection of Sources of Potable Water

SUBSTANCE: gamma-Hexachlorocyclohexane (lindane) **CAS REGISTRY NUMBER:** 58-89-9

AMBIENT WATER QUALITY VALUE: 0.05 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 0.02 ug/L for hexachlorocyclohexane (HCH) and its isomers, alpha-HCH, beta-HCH, gamma-HCH, delta-HCH, epsilon-HCH (NYS, 1985). Available information on gamma-HCH (lindane) published after 1985 was examined as described in "Scope of Review," below. Potential water quality values are derived below, and the value of 0.05 ug/L selected as described under "Selection of Value."

II PRINCIPAL ORGANIC CONTAMINANT CLASSES AND SPECIFIC MCL (702.3)

A. Discussion

gamma-HCH (lindane) has a Specific MCL of 0.2 ug/L as defined in 700.1. This is a maximum contaminant level for drinking water established by the New York State

Department of Health under the State Sanitary Code (10 NYCRR Part 5, Public Water Supplies).

However, gamma-HCH is also in a 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 0.2 ug/L and a MCL of 0.2 ug/L for drinking water for gamma-HCH.

B. Derivation of Water Quality Value

Although gamma-HCH is in a principal organic contaminant class, regulations require that the water quality value based on 702.3 be equal to the Specific MCL of 0.2 ug/L.

III ONCOGENIC EFFECTS (702.4)

A. Data

In 1987, USEPA classified gamma-HCH between B2 and C (probable human carcinogen and possible carcinogen). This issue has yet to be resolved (Cogliano, 1995). IARC (1987) classifies hexachlorocyclohexanes in group 2B, (possibly carcinogenic to humans) but lists no separate classification for gamma-HCH.

Thorpe and Walker (1973) fed male and female mice 0 or 400 ppm gamma-HCH (0 or 52 mg/kg/day) for 110 weeks and noted a significant increase in the incidence of liver tumors in both sexes. Mortality was higher in treated females than treated males. Only 17% of males and 3% of females survived 110 weeks. Goto et al. (1972) reported benign liver tumors in 5 of 10 IRC-JCL male mice fed gamma-HCH at 600 ppm 78 mg/kg/day, for six months. This is too short an observation period to detect malignant tumors. NCI (1977) fed male and female mice 0, 80 or 160 ppm (0, 10.4 or 20.8 mg/kg/day) gamma-HCH and reported a significant increase in tumors only in low-dose males. NCI concluded that the occurrence of liver tumors in high-dose males could not be related to the administration of the chemical due to high spontaneous incidence (20.8%) of the tumors.

Gamma-HCH is embryotoxic and induced chromatid breaks in human lymphocytes in vitro (IARC, 1979; Sircar and Lahiri, 1993). Roux et al. (1979) found that gamma-HCH inhibited protein, RNA and DNA synthesis in cultured

lymphocytes either in the unstimulated, phytohemagglutinin-stimulated or lymphoblast state.

Risk estimates were calculated by USEPA's Carcinogen Assessment Group (1980) and the National Academy of Sciences (NAS, 1977) based on oncogenic effects observed in the liver of CF1 mice fed gamma-HCH (Thorpe and Walker, 1973). The estimated water levels that would result in increased lifetime risks of 10^{-6} are: CAG, 0.026 ug/L; NAS, 0.055 ug/L (USEPA, 1987). The Great Lakes Initiative (USEPA 1993) used the same data to calculate a cancer slope factor of 1.3 (mg/kg)/day and a human cancer value of 0.02 ug/L that takes into account both water and fish consumption.

B. Derivation of Water Quality Value

1. Oncogenic Definition

The evidence of oncogenic activity in one mammalian species, independently reproduced after gamma-HCH (lindane) exposure in Thorpe and Walker (1973) and Goto et al. (1972) fulfills the definition of an oncogenic effect in 700.1 for gamma-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.

Table I. Liver Tumor Response in Male Mice After Exposure to gamma-HCH

Dose* (mg/kg/day)	Animals with Tumors	Animals Exposed
0	11	45
52	27	28

*Dose = ppm x 0.13 consumption by mice per body weight.

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 information was 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 95% LCL and MLE are in close agreement indicating a lower degree of uncertainty.

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

Table II

		Animal Dose (ug/kg/day)	
Animal	Tumor Site	95% LCL	MLE
male mouse	liver	0.0098	0.0170

4. Calculation of Human Doses

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

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

$$\text{Human dose} = \left(\frac{0.03}{70} \right)^{0.25} \times 0.0098 \text{ ug/kg/day} = 1.41 \times 10^{-3} \text{ ug/kg/day}$$

5. Selection of Human Dose and Discussion of Uncertainties

For the male mouse, the critical site is the liver, with a human dose of 1.41×10^{-3} ug/kg/day calculated from the animal dose as shown above.

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:

$$\text{Water Quality Value} = \left(\frac{1.41 \times 10^{-3} \text{ ug}}{\text{kg day}}\right)\left(\frac{70 \text{ kg}}{2 \text{ L/day}}\right) = 0.0494 \text{ ug/L, rounded to } 0.05 \text{ ug/L}$$

IV NON-ONCOGENIC EFFECTS (702.5)

A. Data

Twenty male and 20 female Wistar KFM-Han outbred SPF rats/treatment group were fed 0, 0.2, 0.8, 4, 20 or 100 ppm gamma-HCH (99.85%) in the diet (Zoecon Corporation, 1983). After 12 weeks, 15 animals/sex/group were sacrificed. The remaining rats were fed the control diet for an additional 6 weeks before sacrifice. No treatment related effects were noted on mortality, hematology, clinical chemistry, or urinalysis. Rats receiving 20 and 100 ppm lindane were observed to have greater-than-control incidence of the following: liver hypertrophy, kidney tubular degeneration, hyaline droplets, tubular distension, interstitial nephritis, and basophilic tubules. Since these effects were mild or rare in animals receiving 4 ppm, this represents a NOAEL. The reviewers of the study calculated the dose to be 0.29 mg/kg/day for males and 0.33 mg/kg/day for females, based on food intake (USEPA, 1995).

USEPA (1987) calculated an RfD (reference dose) of 3×10^{-4} mg/kg/day based on the NOAEL of 0.33 mg/kg/day in the Zoecon Corp. (1983) study and an uncertainty factor of 1000. USEPA (1991) promulgated an MCL of 0.2 ug/L, using an additional uncertainty factor of 10 for category II (class C) chemicals, having limited evidence of carcinogenicity. The Great Lakes Initiative (USEPA, 1993) calculated a Human Noncancer value for the protection of human health from both water and fish consumption of 0.7 ug/L based on the Zoecon Corp. data.

B. Derivation of Water Quality Value

1. Selection of Data

The study by Zoecon Corp. (1983) was judged the most appropriate for deriving a water quality value based on non-oncogenic effects. It was selected because it used an adequate number of animals and measured multiple endpoints.

2. Calculation of Acceptable Daily Intake (ADI)

An ADI is calculated from the study of Zoecon Corp. (1983) by dividing the NOAEL of 0.33 mg/kg/day by a total uncertainty factor of 1000 as follows:

$$ADI = \left(\frac{0.33}{1000}\right) \text{ mg/kg/day} = 3.3 \times 10^{-4} \text{ mg/kg/day}$$

This uncertainty factor was selected to account for intra- and interspecies differences (10 x 10) and the use of a less-than-lifetime study (10). These are the same data used by USEPA (1995).

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:

$$\text{Water Quality Value} = \frac{(3.3 \times 10^{-4} \text{ mg/kg/day})(1000 \text{ ug/mg})(70 \text{ kg})(0.2)}{(2 \text{ L/day})} = 2 \text{ ug/L}$$

USEPA derived a drinking water MCL of 0.2 ug/L using an additional factor of 10 for a chemical with carcinogenicity evidence.

V CHEMICAL CORRELATION (702.7)

Because values can be derived using 702.4 and 702.5, deriving a water quality value for gamma-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 0.05 ug/L (6 NYCRR 702.4) is the most stringent value derived by these procedures and is the ambient water quality value for gamma-HCH.

VII REFERENCES

ATSDR (Agency for Toxic Substances and Disease Registry). 1994. Alpha-, Beta-, Gamma- and Delta-Hexachlorocyclohexanes. Washington, D.C.: U.S. Public Health Service.

Cogliano, J. 1995. Personal Communication.

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

Goto, M., M. Hattori and T. Mizagawa. 1972. Contributions to ecology. II. Hepatoma development in mice after administration of HCH isomers in high doses. Chemosphere 1: 279-282.

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. Hexachlorocyclohexane and the isomers alpha-HCH, beta-HCH, gamma-HCH (lindane), delta-HCH and epsilon-HCH. Albany, N.Y.

Roux, F., I. Treich, C. Brun et al. 1979. Effect of lindane on human lymphocyte responses to phytohemagglutinin. Biochem. Pharmacol. 28(16):2419-2426.

Sircar, S. and P. Lahiri. 1993. Lindane (gamma-HCH) causes reproductive failure and fetotoxicity in mice. Toxicology 59:171-177.

Thorpe, E. and A.I.T. Walker. 1973. The toxicity 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. EPA (Environmental Protection Agency). 1987. Lindane Health Advisory. Washington, D.C.: Office of Drinking Water.

U.S. EPA (Environmental Protection Agency). 1993. Great Lakes Initiative Human Health Criteria for Lindane. CAS No. 58-89-9.

U.S. EPA (Environmental Protection Agency). 1991. Federal Register 56:3545. January 30, 1991.

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

Zoecon Corporation. 1983. Lindane: Subchronic oral dosing (rat) study. MRID No. 00128356. FOI EPA, Washington, D.C.

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 gamma-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 (substance not listed).
- 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).

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

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

! International Agency for Research on Cancer. 1979. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. 20:195-223.

! National Academy of Sciences. 1977. Drinking Water and Health, Vol. 1. National Academy of Sciences. Washington, D.C.

! National Academy of Sciences. 1980. Drinking Water and Health, Vol. 3. National Academy Press. Washington, D.C.

! 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 1993-94. 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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