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: alpha-Hexachlorocyclohexane **CAS REGISTRY NUMBER:** 319-84-6

AMBIENT WATER QUALITY VALUE: 0.01 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 the sum of the isomers alpha-HCH, beta-HCH, gamma-HCH, delta-HCH and epsilon-HCH (NYS, 1985). Available information on alpha-HCH published after 1985 was examined as described in "Scope of Review," below. Potential water quality values are derived below, and the value of 0.01 ug/L selected as described under "Selection of Value."

II PRINCIPAL ORGANIC CONTAMINANT CLASSES AND SPECIFIC MCL (702.3)

A. Discussion

alpha-HCH does not have a Specific MCL as defined in 700.1. However, alpha-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 alpha-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 alpha-HCH in drinking water.

B. Derivation of Water Quality Value

Because alpha-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 alpha-HCH as B2 (probable human carcinogen). IARC (1987) classifies hexachlorocyclohexanes in group 2B (possible human carcinogen) but has no specific entry for alpha-HCH.

Dietary alpha-HCH has been shown to cause increased incidences of liver tumors in males and females of five mouse strains (Ito et al., 1973, 1976; Nagasaki et al., 1972, 1975; Goto et al., 1972; Hanada et al., 1973) and in Wistar rats (Ito et al. 1975; Schulte-Hermann and Parzefall, 1981; Nagasaki et al., 1975) after varying exposure periods.

Ito et al. (1973) and Nagasaki et al. (1972) treated groups of 20-40 male dd mice with 0, 100, 250 or 500 ppm alpha-HCH in the diet for 24 weeks. They observed liver nodules and hepatocellular carcinomas in the 250 and 500 ppm dose groups. Hanada et al. (1973) found increased tumor incidence in both sexes of dd mice fed 300 and 600 ppm alpha-HCH for 32 weeks and basal diet for 5 to 6 weeks. Greater activity was seen from exposure to alpha-HCH than beta- or gamma-HCH.

Ito et al. (1976) maintained male DDY mice on a diet containing 500 ppm alpha-HCH for 16, 20, 24 or 36 weeks, followed by basal diet for 4, 8, 12, 16, 24 or 36 weeks, respectively, to examine the effects of length of dosing and length of observation on tumor incidence. Incidence of liver tumors increased with continuous alpha-HCH administration. Incidence decreased, however, with recovery time. At 24 weeks most lesions were nodules, but by 60 or 72 weeks the tumors were primarily hepatocellular carcinomas (USEPA, 1995). (See B.2. Selection of Data for further discussion). Nagasaki et al. (1975) found increased incidence of carcinomas in 4 of 5 strains of mice exposed to 500 ppm alpha-HCH for 24 weeks. In a feeding study using male ICR-JCL mice exposed to 600 mg/kg alpha-HCH for 26 weeks, alpha-HCH produced hepatomas in 100% of the animals (Goto

et al., 1972). Male DDY mice were found to be the most sensitive at these time spans.

Ito et al. (1975) found increased nodular hyperplasia and hepatocellular carcinomas in 12-16 male W rats exposed to 1000 and 1500 ppm (50 and 75 mg/kg/day) alpha-HCH for 72 weeks, to 1000 ppm for 48 weeks, and 5 rats to 500 ppm for 48 weeks. Shulte-Hermann and Parzefell found 100% (6/6) nodule or carcinoma incidence in female Wistar rats fed alpha-HCH at 20 mg/kg/day continuously or 88% (7/8) incidence in rats fed, at 3-week intervals, a dose of approximately 20 mg/kg/day for their lifetimes.

Except for the last mentioned study, none were conducted for the animals' lifetime. Others conducted for a significant portion of lifetime (>50%) were one-dose.

Mechanism of Action- Evidence suggests that alpha-hexachlorocyclohexane is a promoter of carcinogenesis. It is a non-genotoxic chemical, showing insignificant activity in short-term tests of bacterial or mammalian mutagenesis or chromosome damage and does not show DNA-damaging activity in animals tested after gavage exposure to alpha-hexachlorocyclohexane. (Kitchin et al., 1993). The ability of alpha-hexachlorocyclohexane to promote tumorigenesis in female mice, pretreated with the tumor-initiating chemical, diethylnitrosamine, correlates with its ability to induce DNA synthesis in hepatocellar foci of B6C3F1 mice (Siglin et al. 1995). Like the model promoter, phenobarbital, short-term exposure to alpha-hexachlorocyclohexane in rats or rat hepatic cell cultures induces increases in liver cell growth concurrent with increases in DNA replication (Edwards et al. 1985; Schulte-Hermann and Parzefall, 1981), increases in rat hepatic ornithine decarboxylase and microsomal P-450 cytochrome drug-metabolizing activities (Kitchin et al. 1993; Schubert et al. 1980; Seifert and Buchar, 1978; Schulte-Hermann and Parzefall, 1981), and increases in smooth endoplasmic reticulum, the site of the microsomal mono-oxygenase enzymes (Lembowicz et al. 1991). Human hepatocytes in culture, however, did not show these responses to alpha-hexachlorocyclohexane (Parzefall et al. 1991).

B. Derivation of Water Quality Value

1. Definition

The evidence of oncogenic activity in two mammalian species after alpha-HCH exposure in Ito et al. (1973, 1975, 1976); Nagasaki et al. (1972; 1975); Hanada et al., 1973; Schulte-Hermann and Parzefall, (1981) fulfills the definition of an oncogenic effect in 700.1 for apha-HCH.

2. Selection of Data

The Ito et al. (1973) study is selected as the most appropriate dose-response data for deriving a water quality value. The data support the use of mice data over rat data as the most sensitive species, and indicate that the alpha isomer is more potent than other hexachlorocyclohexane isomers in causing liver tumors in mice and rats. Although the study has the deficiency of a very short exposure period, relative to the lifetime of the animal, it has adequate numbers of animals per group and it was conducted with 4 dose groups, including controls. Other studies suffer from small numbers of animals and less than 50% of lifetime dosing/observation.

Because the Ito et al. (1973) was a short-term study, it was considered important to investigate the effect of length of dosing on tumor response and cancer potency slopes in mice. The Department of Health (1995) obtained this information by calculating cancer slope factors from data on the mice exposed to 500 ppm in for varying dosing lengths in Ito et al. (1976). The slopes from all the DDY mice data range from 0.43 to 4.3 per(mg/kg)/day. Although conducted for varying periods of dosing and observation, the study appears to give consistent results for tumor incidence. This supports the idea that adjustment factors used to determine time-weighted average dosing do not have a profound effect on the calculations of potency slopes. This fact allows confidence in using a significantly less-than-lifetime study to project effects for a longer term. Among the short-term studies, Ito et al. (1973) has the best protocol, and it was selected by USEPA for a drinking water value calculation (USEPA, 1995). A summary of the data sets showing statistically and biologically significant increases in tumor response is presented in Table 1.

Table I. Incidence of tumors in male mice exposed to alpha-HCH (Ito et al. 1973)

Dose ug/kg/day	Tumors	Tumor Incidence
0	--	0/20
156	--	0/20
400	hyperplastic nodules, hepatocellular carcinoma	30/38
790	hyerplastic nodules heptacellular carcinoma	20/20

* Dose = ppm x 0.13 food consumption x (24 week dose/104 week life)^3

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 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 output of the model, i.e. both the animal dose 95% LCL and MLE, is shown in Table II. 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 LMS model to the data and thus one indication of uncertainty. The MLE and 95% LCL are in poor agreement indicating a higher degree of uncertainty.

Table II. Output of Model-Animal Dose at 10^{-6} Risk		
	Dose (ug/kg/day)	
Male Mice	95% LCL	MLE
liver tumors	.00204	0.306

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 on the basis of the 3/4 power of relative body weights as proposed in Part 702.

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

$$\text{Human dose} = \left(\frac{0.03}{70}\right)^{0.25} \times 0.00204 \text{ ug/kg/day} = 2.94 \times 10^{-4} \text{ ug/kg/day}$$

5. Selection of Human Dose and Discussion of Uncertainties

For both the male and female mice and rats, the critical site is the liver. A human dose of 2.94 x 10^{-4} ug/kg/day was calculated from the male mouse dose as shown above.

With data on more than one mammalian species, the one that provides the best data and best model for human response to a substance should be selected as the basis for the water quality value. The male mice are clearly more sensitive to the effects of alpha-hexachlorocyclohexane. Thus, the male mice data are selected for calculation of the water quality value.

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:

$$\text{Water Quality Value} = \left(\frac{2.94 \times 10^{-4} \text{ ug}}{\text{kg} \cdot \text{day}}\right)\left(\frac{70 \text{ kg}}{2 \text{ L/day}}\right) = 0.0103 \text{ ug/L, rounded to } 0.01 \text{ ug/L}$$

As discussed in Selection of Data, USEPA (1995) used mice data (Ito et al., 1973) to calculate a slope factor of 6.3 per (mg/kg)/day and a water quality value of 0.006 ug/L. USEPA (1995) calculated a slope factor of 1.3 per (mg/kg)/day on the basis of the rat data in Schulte-Hermann and Parzefell (1981) and 4.7 per (mg/kg)/day on the basis of Nagasaki et al. (1972). These are in close agreement with the value calculated from Ito et al. (1973), giving support to the selection of the final water quality value.

IV NON-ONCOGENIC EFFECTS (702.5)

A. Data

Liver effects were reported in rats and mice after exposure to alpha-HCH in the diet. In rats fatty degeneration and focal necrosis were reported by Fitzhugh et al. (1950) and dose-related liver cell hypertrophy and hyperplasia by Ito et al. (1975). In mice, hypertrophied liver cells, oval cells, and bile duct proliferation were reported by Ito et al. (1973) and Nagasaki et al. (1975).

Shulte-Hermann and Parzefell (1981) exposed female Wistar rats to 20 mg/kg/day alpha-HCH for their lifetime. The size of the liver, as well as the content of protein, RNA and DNA were significantly increased at all time points studied (one-third, 1 and 2 years of treatment). Microsomal cytochrome P-450 content, monooxygenase activities and cytosolic glutathione transferase activity were enhanced at all time points studied. Livers of alpha-HCH treated rats exhibited centrolobular hypertrophy and increased eosinophilia. Both control and treated rats exhibited foci of altered cells.

Fitzhugh et al. (1950) exposed groups of ten female and ten male rats to 0, 10, 100, 800 ppm (0, 0.5, 2.5, 5, 40 mg/kg/day) alpha HCH in their diet. Mean age at death was 56 weeks. Hepatic cell alterations characteristic of chlorinated cyclic compounds were evident at 2.5 and 5 mg/kg/day. Hepatic cell enlargement, hepatic cell atrophy, fatty degeneration and focal necrosis were evident at 5 and 40 mg/kg/day. Accumulation of the isomer was greatest in fat followed by kidney, brain and liver. The authors described a NOEL (no-observed effect level) of 0.5 mg/kg/day.

B. Derivation of Water Quality Value

1. Selection of Data

The study by Fitzhugh et al. (1950) was judged the most appropriate for deriving a water quality value based on non-oncogenic effects. It was selected because it used several dose groups and demonstrated a dose-related response, although it was a less-than-lifetime study.

2. Calculation of Acceptable Daily Intake (ADI)

An ADI is calculated from the study of Fitzhugh et al. (1950) by dividing the NOEL of 0.5 mg/kg/day by a total uncertainty factor of 1000 as follows:

ADI = (0.5/1000) mg/kg/day = 5×10^{-4} 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).

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:

$$\text{Water Quality Value} = \frac{(5 \times 10^{-4} \text{ mg/kg/day})(1000\text{ug/mg})(70\text{kg})(0.2)}{(2 \text{ L/day})} = 3.5 \text{ ug/L}$$

V CHEMICAL CORRELATION (702.7)

Because values can be derived using 702.4 and 702.5, deriving a water quality value for alpha-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 0.01 ug/L (6 NYCRR 702.4) is the most stringent value derived by these procedures and is the ambient water quality value for alpha-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.

Edwards, A.M., and C.M. Lucas. 1985. Phenobarbital and some other liver tumor promoters stimulate DNA synthesis in cultured rat hepatocytes. Biochem. Biophys. Res. Comm. 131(1): 103-108.

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

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

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

Kitchin, K.T. and J.L. Brown. 1993. Biochemical Studies of Promoters of Carcinogenesis in the liver. Teratog. Carcinog. Mutag. 9: 273-285.

Kitchin K.T., J.L. Brown, A.P. Kulkarni. 1993. Predicting Rodent Carcinogenicity of halogenated halocarbons by in vivo biochemical parameters. Teratopg. Carcinog. Mutag. 13: 167-184.

IARC (International Agency for Research on Cancer). 1987. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Supplement 7. Lyon, France. p. 45, 220-222.

Ito, N., H. Nagasaki, M. Arai, S. Sugihara and S. Makiura. 1973. Histologic and ultrastructural studies on the hepatocarcinogenicity of benzene hexachloride in mice. J. Natl. Cancer Inst. 51(3):817-826.

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

Ito, N., M. Hananouchi, S. Sugihara, et al. 1976. Reversibility and irreversibility of liver tumors in mice induced by the alpha isomer of 1,2,3,4,5,6-hexachlorocyclohexane. Cancer Res. 36: 2227-2234.

Lembowicz , K. E. Sitarska, T. Gorska, J. Ludwicki. 1991. The effect of organic chlorine compounds and their metabolites present in human milk on newborn mice. Toxicol. Lett. 57: 215-226.

Nagasaki, H., S. Tomii, T. Mega, M. Marugami and N. Ito. 1972. Hepatocarcinogenic effect of alpha-, beta-, gamma-, and delta- isomers of benzene hexachloride in mice. Gann. 63(3):393.

Nagasaki, H., H. Kawabata, Y. Miyata, et al. 1975. Effect of various factors on induction of liver tumors in animals by the alpha-isomer of benzene hexachloride. Gann. 66(2):185-191.

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 (HCH) and the sum of the isomers alpha-HCH, beta-HCH, gamma-HCH, delta-HCH and epsilon-HCH. Albany, N.Y.: Department of Health.

NYS (New York State). 1995. Technical comments on draft fact sheets for hexachlorocyclohexanes. Bureau of Toxic Substances Assessment. Albany, NY: Department of Health.

Parzefall, W., E. Erber, R. Sedivy, R. Schulte-Hermann. 1991. Testing for in duction of DNA synthesis in human hepatocyte primary cultures by rat liver tumor promoters. Cancer Research 51: 1143-1147.

Schubert, I., and K.J. Netter. 1980. Perinatal inducibility of microsomal monooxygenase activities in rats. Naunyn-Schmiedebergs Arch. Pharmacol. 311(suppl.): R10.

Schulte-Hermann, R. and W. Parzefall. 1981. Failure to determine initiation from promotion of liver tumors in a long-term study with the phenobarbital- type inducer alpha-hexachlorocyclohexane and the role of sustained stimulation of hepatic growth and monooxygenases. Cancer Res. 41:4140-4146.

Seifert, J., and E. Buchar. 1978. The biosynthesis of pyrimidine nucleotides and cytochrome P-450 content in rat liver microsomes after the administration of alpha-hexachlorocyclohexane in vivo. Toxicology 11: 37-44.

Siglin, J.C., C.M. Weghorst, D.E. Rodwell, J.E. Klaunig. 1995. Gender-dependent differences in hepatic tumor promotion in diethylnitrosamine initiated infant B6C3F1 mice by alpha-hexachlorocyclohexane. J. Toxicol. Environ. Helath. 44: 235-245.

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

U.S. EPA (Environmental Protection Agency). 1980. Ambient Water Quality Criteria for Hexacholorocyclohexane.

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 alpha-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 (document not found).
- U.S. EPA health advisory (document not found).
- U.S. EPA drinking water criteria document (document not found).
- 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 and 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.

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