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: Octachlorostyrene **CAS REGISTRY NUMBER:** 29082-74-4

AMBIENT WATER QUALITY VALUE: 0.2 ug/L

BASIS: Non-oncogenic, Chronic

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. Available information on octachlorostyrene (OCS) was examined as described in "Scope of Review," below. Potential water quality values are derived below, and the value of 0.2 ug/L selected as described under "Selection of Value."

II PRINCIPAL ORGANIC CONTAMINANT CLASSES AND SPECIFIC MCL (702.3)

A. Discussion

OCS does not have a Specific MCL as defined in 700.1, but is in principal organic contaminant class iii 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 OCS.

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 OCS in drinking water.

B. Derivation of Water Quality Value

Because OCS is in a principal organic contaminant class and has no Specific MCL, regulations require that the water quality value not exceed 5 ug/L.

III ONCOGENIC EFFECTS (702.4)

A. Data

Little information was found as to the oncogenicity of OCS. Chu et al. (1986) found no treatment-related tumors in a 12-month dietary study, but as they pointed out, the short duration of the study precludes its interpretation as a negative carcinogenic response. RTECS had no information on carcinogenicity or mutagenicity studies on this substance.

OCS was negative in Salmonella typhimurium TA98 and TA100, with and without metabolic activation in each strain (CCRIS, 1994). However, a liver 9000 x g supernatant fraction from rats pretreated with OCS was shown to increase the bacterial mutagenicity of 2-acetylaminofluorene and 2-amino-fluorene compared to controls (Holme and Dybing, 1983).

Smith et al. (1994) examined the influence of iron overload on the potential of OCS to cause tumors of the liver in mice. Male C57BL/10 ScSn mice were administered dextran or iron-dextran (600 mg Fe/kg), then placed on a control or 0.01% OCS diet for 18 months. All surviving OCS-treated mice exhibited hypertrophy of hepatocytes in the centrilobular region with increased number of cells with enlarged hyperchromatic nuclei. Liver-to-body weight was increased in the iron-pretreated OCS group only (significantly different from all other groups, $p < 0.05$). One mouse in the non-iron, OCS group had a histiocytic sarcoma infiltrating the liver, but nodular hyperplasias were not observed. For animals pretreated with iron and fed OCS, two mice (out of 10/11 survivors), had single nodular hyperplasias (one per liver). There were no livers with nodules reported in the controls (with or without iron treatment). There is no indication that the animals were maintained beyond the 18-month exposure period. Smith et al. concluded that OCS has the potential to induce neoplastic changes in the liver of this strain of mice, when potentiated by iron overload.

Chu et al. (1986) reported the incidence of tumors in rats exposed to dietary levels of OCS of 0, 0.005, 0.05, 0.5, 5.0 or 50 ppm for 12 months. Adenomas of the pituitary were found in 4/20, 2/19, 1/19, 5/20, 0/19 and 5/20 animals from these groups, respectively. Chu et al. reported "a few" mammary and skin tumors in females but stated that "all of the tumors observed in the present study were considered to be incidental and not treatment related."

Chu et al. (1982a) studied the tissue distribution, metabolism and excretion of radiolabeled OCS in the rat and concluded that it is a stable substance that is slowly eliminated and/or metabolized in this species. It was absorbed in the gastrointestinal tract following oral administration and widely distributed. OCS was most concentrated in fat, followed by adrenal glands, skin and lungs. OCS was also given intravenously (iv), with similar results. Levels of radioactivity in the tissues decayed along first-order kinetics. During 7 days following iv administration, roughly 8% of the dose was excreted in the feces, over 90% as the parent compound. The remaining 10% consisted of equal amounts of pentachloro-phenyldichloroacetic acid and heptachlorostyrene.

B. Derivation of Water Quality Value

Insufficient information to evaluate the oncogenicity of OCS was found. Although Smith et al. (1994) did conclude of its potential to cause tumors, that was only in an iron overload situation. The existence of one histiocytic sarcoma in OCS-fed, non iron-treated animals at the single treatment dose in a study with very few animals is not considered adequate evidence of oncogenicity. Furthermore, the limited in-vitro test results are negative.

At the same time, there is insufficient evidence to conclude that OCS is <u>not</u> oncogenic. Its similarity to other, oncogenic substances warrants concern and further testing.

At the present time, a value cannot be derived for OCS based on oncogenic effects.

IV NON-ONCOGENIC EFFECTS (702.5)

A. Data

OCS causes liver, thyroid, kidney and hematological effects in experimental animals. It has been the subject of a number of studies, for up to 18 months. Pharmacokinetics are described under "Oncogenic Effects," above. Several experiments by Chu and co-workers are described below, followed by other studies.

1. Studies by Chu et al.

Chu et al. (1982b; 1984; 1986) conducted 28-day, 90-day and 12-month studies on OCS in the rat.

a. 28-Day Rat Study

Chu et al. (1982b) fed groups of weanling Sprague-Dawley rats containing 0, 0.5, 5.0, 50 or 500 ppm OCS for 28 days. Effects reported include hepatomegaly in males at 50 and 500 ppm, and a dose-dependent increase in hepatic microsomal aminopyrine demethylase activities (APDM) in males at 5.0 ppm and higher. Total protein in serum was also elevated at 5.0 ppm and up ($p \leq 0.05$ compared to controls). These authors also noted a dose-dependent increase in both prevalence and severity of liver injury in both sexes, but did not present any statistical evidence of significant effects at the 0.5 ppm dietary level. However, four female rats (4/10) at this level had liver lesions, as compared to 0/10 controls. Chu et al. noted that these lesions were very mild and that more pronounced changes to the liver and to the thyroid were seen at the next (5.0 ppm) dietary level. They suggest 0.5 ppm as the maximum no-effect level, which they present as equivalent to 0.034 and 0.043 mg/kg/day in males and females, respectively.

b. 90-Day Rat Study

Chu et al. (1984) conducted a 90-day subchronic rat study on OCS. Groups of 15 male and 15 female weanling Sprague-Dawley rats were given diets with 0, 0.05, 0.5, 5.0, 50 or 500 ppm OCS. Effects in both sexes included increases in liver weights (50 ppm and up) and spleen and kidney weight (500 ppm). Biochemical changes in serum were seen in males down to 5.0 ppm, with elevated cholesterol and increased aminopyrine demethylase activity (both $p \leq 0.05$). Hematological effects appear to be the most sensitive. Based on cytological evaluation of bone marrow smears, males at all treatment levels showed decreased erythroid cell numbers ($p \leq 0.05$). In females, this effect was only noted at the 0.5 and 50 ppm levels.

Histopathology revealed lesions of the liver, kidney and thyroid. Changes in the liver were described as moderate to severe. At 0.05 or 0.5 ppm, animals showed a mild anisokaryosis, which became progressively more severe with higher dose, with marked anisokaryosis and nuclear necrosis at 500 ppm. Although a statistical treatment was

not provided, Table 1 shows the prevalence of microscopic lesions in male rats.

Table 1

Microscopic Lesions in Male Rats: 90-Day Study
(Chu et al., 1984)

(No. of Animals Showing Lesions/Number of Animals Examined)

Organ	0 (Control)	0.05 ppm
Thyroid	8/14	13/14
Liver	2/14	13/14
Kidney	4/14	12/14

Based on decreased erythroid cell numbers and supported by the presence of lesions in the thyroid, liver and kidney, one would conclude that 0.05 ppm (0.0036 mg/kg/day) represents a LOAEL in this 90-day study.

c. 12-Month Rat Study

Chu et al. (1986) also conducted a 12-month dietary study on OCS in rats. Groups of 20 male and 20 female weanling Sprague-Dawley rats were given diets that contained 0, 0.005, 0.05, 0.5, 5.0 or 50 ppm OCS. These investigators describe their results as "in general agreement with those of" their 28-day and 90-day studies, except that erythroid cell depression and meyloid [sic] hypertrophy observed in the 90-day experiment were not seen in the year-long study. Specific effects noted in the 12-month study include hepatomegaly (50 ppm), increased wet liver and kidney weights ($p \leq .05$ for liver for all doses in males) but significant only at the high dose when expressed in relation to body weight. Tabulated results of biochemical parameters were not provided, but Chu et al. did note elevated serum cholesterol at 50 ppm ($p \leq .05$), decreased SGOT (presumably serum glutamic oxalacetic transaminase) levels were noted in males at 0.05 or 0.5 ppm, with decreased alkaline phosphatase in females at 50 ppm. Increased aniline hydroxylase activity was noted in males at both the 5.0 and 50

ppm levels. In contrast to the 90-day study, the only hematological effect noted was decreased hemoglobin (p = 0.02) in females at 50 ppm.

In terms of histopathology, the liver, thyroid and kidney were affected by the treatment, with the more severe morphological changes noted in males. In all three organs, more severe changes were noted at 5.0 and 50 ppm.

In the liver, very mild changes were noted at 0.005 - 0.5 ppm, including cytoplasmic vacuolation and an increased ground-glass appearance of the cytoplasm in the perivenous and midzone areas. At 5.0 and 50 ppm, observations of moderate to marked cytoplasmic vacuolation along with periportal eosinophilia and aggregated basophilia in the periphery of the hepatocytes; changes considered to be moderate to severe.

In the thyroid, very mild reduction in colloid density and scattered collapse of follicles were noted at the 0.005 - 0.5 ppm range. Reduction of colloid dnsity [sic] of a moderate degree, along with thickening of epithelial cells to columnar form were noted. Morphological changes in the kidney were described as less severe than those found in the liver and thyroid.

Chu et al. report histological evaluation as the most sensitive index of OCS exposure, but that changes in the 0.005 - 0.5 ppm range "are considered to be mild and adaptive in nature" and that significant histological changes only occurred at and above 5.0 ppm. They also suggest that the erythroid depression in the 90-day study may be "adaptive changes." These investigators judge the dietary no-observed-adverse-effect level (NOAEL), to be 0.5 ppm (0.03 mg/kg body wt/day) based on their 12-month, 90-day and 28-day studies.

However, there are histologic changes even at the lowest dose levels in the 90-day and 12-month studies. There are substantial increases in the percentage of rats with histological changes in the liver, thyroid or kidney at 0.005 ppm in the 12-month study and 0.05 ppm in the 90-day study. In the longer study, in 11 of 26 comparisons, the difference between incidences of control males or females with histological changes and the incidences in males or females at 0.005 ppm were statistically significant ($p < 0.05$ by the Fisher exact test). This issue is further discussed under "Derivation of Water Quality Value," below.

2. Additional Studies

Smith et al. (1986) fed mice and rats OCS (267 ppm) in the diet for 6 and 12 weeks respectively. Mice also received an injection of iron prior to being fed the OCS. In both species, liver weight and liver weight as a percentage of body weight were elevated over controls ($p < 0.001$).

In a study described under "Oncogenic Effects," Smith et al. (1994) reported hypertrophy of hepatocytes in all surviving OCS-treated mice, and increased liver to body weight in only the iron-pretreated group.

Strik and Koeman (1975) fed male Wistar rats with 0 or 400 ppm OCS for 8-12 weeks. No porphyrin accumulation in the liver was detected. The treated group showed increased 5-aminolaevulinic acid synthase (ALAS) activity at 8 weeks, and increased N-demethylation of aminopyrene, p-hydroxylation of aniline at both 8 and 12 weeks (all $p < 0.01$). The p-450 content was elevated at 12 weeks ($p < 0.01$). Histological effects noted in the liver of treated animals but not controls included megalocytosis (predominantly centrilobular), basophilic spots in cytoplasm and whorl formation. Also reported from the liver of treated animals (unknown result in controls) was a pronounced hypertrophy of hepatocytes. A lowest-observed-adverse-effect level (LOAEL) of 20 mg/kg/day (assuming a 5% of body weight daily food consumption at 400 ppm) can be derived from this study.

Kacew et al. administered OCS via gavage to Sprague-Dawley rats on days 6 through 15 of gestation. The dose levels were 0, 50, 100, 200 and 400 mg/kg/day. An increase in maternal mortality was noted about 8.8 days after dosing begun, especially in the two higher groups. All groups exhibited a significant increase in liver weight to body weight.

Pups from all treatment groups exhibited hydronephrotic kidney (no statistics). From the two highest groups, there was decreased density of the bone marrow and a decrease in erythropoiesis. In the highest group, the pups were undersized.

B. Derivation of Water Quality Value

1. Selection of Data

Both the 12-month and 90-day studies by Chu et al. showed effects at the lowest dose tested. In the 90-day study, there was an adverse effect at 0.05 ppm; the longer study showed adverse effects at 5 ppm, and less severe effects as low as 0.005 ppm.

The 12-month study was judged the most appropriate for deriving a water quality value because:

- longer duration
- lower dose was tested
- both a LOAEL and NOAEL were identified

The NOAEL of 0.5 ppm (0.03 mg/kg/day) from this study is selected as the basis for the water quality value for OCS. A no-observed-effect level (NOEL), preferred as the basis for a non-oncogenic value under 702.5, was not identified from this study. Consideration was given to basing a value on the minimal effect level of 0.005 ppm, but this was not done given the mild nature of the effects. However, the question of significance of effects below 5 ppm was considered in selecting the uncertainty factor.

2. Calculation of Acceptable Daily Intake (ADI)

An ADI is calculated from the study of Chu et al. (1986) by dividing the NOAEL of 0.03 mg/kg/day by a total uncertainty factor (UF) of 1000 as follows:

$$\text{ADI} = \frac{0.03 \text{ mg/kg/day}}{1000} = 0.00003 \text{ mg/kg/day}$$

This uncertainty factor was selected as follows:

- 10 for intraspecies (human) variability
- 10 for the uncertainty of extrapolation across species
- 10 for the combination of less-than-lifetime duration and uncertainty over the severity of effects below 5 ppm.

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:

$$\text{Water Quality Value} = \frac{(0.00003 \text{ mg/kg/day})(1000 \text{ ug/mg})(70 \text{ kg})(0.2)}{2 \text{ L/day}} = 0.2 \text{ ug/L}$$

V CHEMICAL CORRELATION (702.7)

Given the limited database on OCS along with its general structural similarity to oncogenic substances such as 2,3,7,8-TCDD and hexachlorobenzene (HCB), the issue of correlation was carefully considered.

Smith et al. (1986) highlight a similarity of effects in rat liver, kidney and thyroid between OCS and HCB. The porphyrinogenic effects and potential to induce liver microsomal ethoxyphenoxazone deethylation were compared between these two substances; the latter caused greater effects. According to Smith et al. "if these effects are mediated through binding to the aromatic hydrocarbon responsiveness (Ah) receptor, HCB would appear to have a much greater affinity than OCS despite the fact that neither chemical possesses a structure currently considered to be necessary for efficient binding."

Believing ethoxyresorufin deethylase to be a more specific and sensitive marker for Ah locus regulated activity than aryl hydrocarbon hydroxylase (AHH) activity, Smith and Francis (1986) measured its activity five days after dosing with OCS and HCB. Both substances induced the activity of this enzyme in male C57BL/6 mice but OCS significantly less than HCB and less than following three daily doses of 60 mg/kg phenobarbital.

Insufficient evidence was found to warrant deriving a value for OCS based on chemical correlation.

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 non-oncogenic, chronic value of 0.2 ug/L (6 NYCRR 702.5) is the most stringent value derived from these procedures and is the ambient water quality value for octachlorostyrene.

VII REFERENCES

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Holme, J.A. and E. Dybing. 1983. Increased cytochrome P-450 independent drug metabolism and mutagen activation in rat liver by octachlorostyrene. Acta Pharacol. et Toxicol. 53:325-332.

Kacew, S., J.A. Ruddick, M.R. Parulekar, D.C. Villeneuve and V.E. Valli. An assessment of octachlorostyrene toxicity in the pregnant rat. In press. [As cited by Kitchin and Kacew, 1987].

Kitchin, K.T. and S. Kacew. 1987. Some pharmacokinetic and metabolic factors affecting the neonatal toxicity of chlorinated hydrocarbons found in the Great Lakes. Research Triangle Park, NC: U.S. Environmental Protection Agency. Report No. EPA/600/D-87/004. January 1987. PB87-147104.

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.

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Strik, J.J.T.W.A. and J.H. Koeman. 1975. Porphyrinogenic action of hexachlorobenzene and octachlorostyrene. pp. 418-423. In: Porphyrins in Human Diseases (M. Doss, Ed.) Basel, Karger. 1976.

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 octachlorostyrene; where none was found it is so noted.

- IRIS (U.S. EPA's Integrated Risk Information System). On-line database. (Not on IRIS).
- 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 (document not found).
- 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).
- IARC (International Agency for Research on Cancer) Monographs Supplement 7 (substance not listed).

No comprehensive review document was found for octachlorostyrene. Therefore, an on-line search of the literature was conducted by the New York State Library from 1994 back to the 1960's on the databases listed below.

- NTIS (National Technical Information Service)
- TOXLINE
- BIOSIS

New York State Department of Environmental Conservation
Division of Water
SJS
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