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: Aniline **CAS REGISTRY NUMBER:** 62-53-3

AMBIENT WATER QUALITY VALUE: 5 ug/L

BASIS: Surface Water: Principal Organic Contaminant Classes

Groundwater: Former Reference to 10 NYCRR Subpart 5-1 Principal Organic Contaminant (POC) General Maximum Contaminant Level (MCL)

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 1 ug/L (NYS, 1985). Available information on aniline was examined as described in "Scope of Review," below. Potential water quality values are derived below, and the value of 5 ug/L selected as described under "Selection of Value."

II PRINCIPAL ORGANIC CONTAMINANT CLASSES AND SPECIFIC MCL (702.3)

A. Discussion

Aniline does not have a Specific MCL as defined in 700.1. Aniline is in principal organic contaminant class iv 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 aniline.

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 aniline in drinking water.

B. Derivation of Water Quality Value

Because aniline 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

Genotoxicity

Aniline or aniline hydrochloride have been mostly inactive in genotoxicity tests with a few exceptions. In the presence of norharman and hepatic microsomes from Aroclor-treated rats, aniline was mutagenic for Salmonella TA98 (Nagao et al., 1977). The hydrochloride induced an increase in sister chromatid exchanges in cultured chinese hamster pseudodiploid (Don) cells (Abe and Sasaki, 1977) and lung fibroblasts (Kawachi et al., 1980). Aniline was reported slightly, but significantly, mutagenic for the thymidine kinase locus of L5178Y mouse lymphoma cells in the presence of liver microsomes from Aroclor-treated rats (Amacher et al., 1980)

Oncogenicity

U.S. EPA (1994) classifies aniline as "B2: probable human carcinogen on the basis of induction of tumor of the spleen in two strains of rat and supporting genetic toxicology data." IARC considers there to be limited evidence of aniline's carcinogenicity to humans (IARC, 1982).

In an epidemiolgic study of men employed more than six months, Case et al. (1954) found no evidence that 1233 workers exposed to aniline had an increased risk of developing bladder tumors (1 case observed vs. 0.83 expected). In a retrospective cohort study of workers (Ruder et al., 1992; Ward et al., 1991) exposed to aniline and o-toluidine in a New York State chemical plant, it was not possible to separate workers exposed to o-toluidine and aniline from those exposed to aniline alone on the basis of work

history records. An increased incidence of bladder tumors was found in the study population.

Aniline has been shown at high concentrations in the diet to induce hemangio- and fibrosarcomas in the spleens of Fischer 344 rats in two long-term bioassays (CIIT, 1982; NCI, 1978).

Aniline hydrochloride was administered in the diet for 2 years to CD-F rats (130 rats/sex/group) at levels of 200, 600 and 2000 ppm (7.2, 21.6, 72 mg/kg/day aniline) (CIIT, 1982). An increased incidence of primary splenic sarcomas, hemangiosarcoma of the spleen and stromal sarcoma was observed in male rats in the high dose groups. Stromal hyperplasia and fibrosis of the splenic red pulp, which may represent a precursor lesion of sarcoma, was also observed in the high-dose males and, to a lesser degree, in the female rats.

Aniline hydrochloride was administered in the diet at 0, 3,000 or 6,000 ppm (0, 108, 216 mg/kg/day aniline) to 50 male and 50 female Fischer 344 rats for 103 weeks (NCI, 1978). The animals were sacrificed at 107-110 weeks. The male rats showed statistically significant dose-related trends in incidence of hemangiosarcomas and sarcomas or fibrosarcomas. The males also had statistically significantly increased incidences of hemangiosarcoma in the spleen, fibrosarcoma and sarcoma (not otherwise specified) in the body cavity and spleen, and a significant dose-related trend in incidence of malignant pheochromocytoma. According to the authors, there was a possible association in the female rats between aniline hydrochloride treatment and the increased incidence of fibrosarcoma and sarcoma in multiple organs of the body cavity. None of the pooled control groups of 249 females and 250 male rats were observed to have fibrosarcoma or sarcoma in the spleen or multiple organs of the body cavity. Male and female mice were exposed to food containing 0, 6,000 or 12,000 ppm aniline hydrochloride (0, 216, 432 mg/kg aniline) for 103 weeks (NCI, 1978). No statistically significant increase in any type of tumor in male or female mice was observed.

B. Derivation of Water Quality Value

1. Oncogenic Definition

The evidence of oncogenic activity in one mammalian species (rats), independently reproduced after aniline exposure in CIIT (1982) and NCI (1978) bioassays fulfills the definition of an oncogenic effect in 700.1 for aniline. U.S. EPA (1994) classifies aniline as "B2, probable human carcinogen based on tumors in two strains of rat and supporting toxicological evidence".

2. Selection of Data

U.S. EPA (1994) selected CIIT (1982) as the basis for calculating a slope factor and drinking water concentration.

New York State reviewed IRIS and the original bioassay CIIT (1982) and NCI (1978) and concurs with EPA's choice of data. The CIIT study was conducted at lower doses than the NCI study, which reduces the influence of "high-dose only" phenomena on estimates of potency at low doses.

The CIIT (1982) bioassay is selected as the most appropriate dose-response data for deriving a water quality value. The CIIT study used more dose groups than the NCI study and found an increase in tumor incidence at a lower dose (72 mg/kg/day) than the NCI study and used more animals per dose group (USEPA 1994). A summary of the data sets showing statistically and biologically significant increases in tumor response is presented in Table I.

Table I. Splenic Tumor Incidence in Male Rats in CIIT (1982) Aniline Bioassay

Dose* (mg/kg/day)	Tumor Type	Tumor Incidence
0	--	0/64
7.2	--	0/90
21.6	spleen sarcoma	1/90
72	spleen sarcoma, stromal sarcoma, capsular sarcoma and hemangiosarcoma	31/90

* Dose = ppm in food x .05 food consumption x 0.72 aniline/aniline HCl.

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. In its investigation, New York State did not find any information 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 output of the model, i.e. both the animal dose 95% LCL and MLE, is shown in Table II. The difference between the 95% LCL and MLE is relatively large indicating higher uncertainty.

Table II. Animal Doses Corresponding to 10^{-6} Risk

Data Set		Animal Dose (ug/kg/day) GLOBAL82	
Animal	Tumor Site	95% LCL	MLE
male rat	spleen	1.02	960

4. Calculation of Human Dose

The animal dose is converted as shown below to a human dose, as in proposed 702.4.

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

$$\text{Human dose} = \left(\frac{0.430\ \text{kg}}{70\ \text{kg}}\right)^{0.25} \times 1.02\ \text{ug/kg/day} = 0.29\ \text{ug/kg/day}$$

Table III. Human Dose

Data Set		Conversion Factor	95% LCL Human Dose (ug/kg/day)
Animal	Site		
male rat	spleen	0.28	0.29

5. Selection of Human Dose and Discussion of Uncertainties

With appropriate, reproducible data in a multi-dose study on one mammalian species, the data are adequate as the basis for the water quality value. Thus, the human dose derived from the male rat, 0.29 ug/kg/day, will be used 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:

$$\text{Water Quality Value} = \left(\frac{0.29 \text{ ug}}{\text{Kg} \cdot \text{day}} \right) \frac{(70 \text{ kg})}{(2 \text{ L/day})} = 10 \text{ ug/L}$$

IV NON-ONCOGENIC EFFECTS (702.5)

A. Data

In an eight week feeding study, Fischer rats and $B_6C_3F_1$ mice were given up to 1% aniline hydrochloride. No effect was seen in mice. Male and female rats at the highest dose (500 mg/kg) had a 25% reduction in body weight gain. Rats given 0.3 and 0.6% (150 and 300 mg/kg/day) in the diet showed fatty metamorphosis, fibrosis and papillary hyperplasia for the spleen as well as hemosiderosis of the liver and kidney and endometrial stromal polyps (NCI, 1978). The LOAEL for rats is 150 mg/kg/day.

Single oral doses of 25-65 mg/person of aniline caused a dose-dependent increase in methemoglobin formation. Doses of 45-65 mg/person also produced a slight increase in serum bilirubin in two subjects (Jenkins et al., 1972).

Pharmacokinetics

In experimental animals, aniline is rapidly absorbed after oral administration, dermal application or inhalation (Carpenter et al. 1949; Kiese 1966). After intravenous administration to rats, radiolabelled aniline concentrations were highest in blood, liver, kidney, bladder and gut (Irons et al., 1980). All species tested (rabbit, rat, mouse, guinea pig, gerbil, hamster, cat and dog) oxidize aniline to ortho- and para-aminophenol, which are excreted in the urine as various conjugates (Parke, 1960). Small amounts of aniline, phenylsulfamic acid, aniline N-glucuronide and meta-aminophenol have been found in the urine of some species. Ortho- and para-aminophenyl and para-acetylaminophenyl mercapturic acids are also excreted in rats (Boyland, et al., 1963; Baranowska-Dutkiewiez, 1982). Phenylhydroxylamine and nitrosobenzene appear in the blood of treated dogs and cats (Kiese, 1966). Phenylhydroxylamine formation appears to be the major cause of the methemoglobinemia that follows aniline administration.

B. Derivation of Water Quality Value

1. Selection of Data

   Of the few studies available, the study by NCI (1978) was judged appropriate for deriving a water quality value based on non-oncogenic effects.

2. Calculation of Acceptable Daily Intake (ADI)

   An ADI is calculated from the study of NCI (1978) by dividing the lowest observed adverse effect level (LOAEL) of 150 mg/kg/day by a total uncertainty factor of 1000 as follows:

$$\text{ADI} = \left(\frac{150}{1000} \right) \text{ mg/kg/day} = 0.150 \text{ mg/kg/day}$$

   This uncertainty factor was selected to account for intra-(10) and inter-species variation (10) and the use of a LOAEL (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:

$$\text{Water Quality Value} = \frac{(0.150 \text{ mg/kg/day})(1000 \text{ ug/mg})(70 \text{ kg})(0.2)}{2 \text{ L/day}} = 1000 \text{ ug/L}$$

V CHEMICAL CORRELATION (702.7)

No basis was found for deriving a water quality value for aniline using 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 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 principal organic contaminant class value of 5 ug/L 6 NYCRR 702.3(b) is the most stringent value derived by these procedures and is the ambient water quality value for aniline.

It should be noted that the principal organic contaminant (POC) value of 5 ug/L became a standard for groundwater (6 NYCRR 703.5) effective on January 9, 1989 by reference to 10 NYCRR Subpart 5-1 standards. The basis and derivation of this POC standard are described in a separate fact sheet.

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VIII SCOPE OF REVIEW

The widely-recognized sources listed below can often provide a comprehensive review of the toxicity of a substance and, in some cases, the derivation of a value. These sources were searched for their availability and, if found, examined. Where they were not found, it is so noted.

- IRIS (U.S. EPA's Integrated Risk Information System) (on-line).
- RTECS (Registry of Toxic Effects of Chemical Substances) (on-line).
- CCRIS (Chemical Carcinogenesis Research Information System) (on-line).
- ATSDR (Agency for Toxic Substances and Disease Registry) toxicological profile (not found).
- U.S. EPA ambient water quality criteria document (not found).
- U.S. EPA health advisory (not found).
- U.S. EPA drinking water criteria document (not found).
- U.S. EPA Drinking Water Regulations and Health Advisories, Office of Water, May 1994 (not found).
- IARC (International Agency for Research on Cancer) Monographs Supplement 7. 1987.

The sources above are deemed adequate to assess the literature through 1982. 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 System)
- TOXLINE
- BIOSIS

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