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: N,N-Dimethylaniline **CAS REGISTRY NUMBER:** 121-69-7

AMBIENT WATER QUALITY VALUE: 1 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 1 ug/L for N,N-dimethylaniline (NYS 1985). Available information on N,N-dimethylaniline published after the 1985 fact sheet was examined as described in "Scope of Review," below. Potential water quality values are derived below, and the value of 1 ug/L selected as described under "Selection of Value."

II PRINCIPAL ORGANIC CONTAMINANT CLASSES AND SPECIFIC MCL (702.3)

A. Discussion

N,N-Dimethylaniline does not have a Specific MCL as defined in 700.1. N,N-Dimethylaniline is in principal organic contaminant, class iv, as defined in 700.1.

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 N,N-dimethylaniline in drinking water.

The U.S. Environmental Protection Agency has not established a maximum contaminant level goal (MCLG) or a MCL for drinking water for N,N-dimethylaniline.

B. Derivation of Water Quality Value

Because N,N-dimethylaniline 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

Evidence of oncogenicity in animals is considered limited and in humans inadequate according to IARC (1993). RTECs (1994) considers the evidence for oncogenicity of N,N-dimethylaniline equivocal in both rats and mice.

Abdo (1989) found some evidence of oncogenicity of N,N-dimethylaniline in male rats in a NTP bioassay in which rats were exposed by a gavage to 0, 3 or 30 mg/kg/day and mice were exposed to 0, 15 or 30 mg/kg/day for 103 weeks. There was no increase in tumors in female rats given 3 or 30 mg/kg. A positive trend of occurrence of spleen sarcomas were found in male rats. Equivocal evidence of oncogenicity was described in female mice on the basis of squamous cell papillomas of the forestomach. Ashby and Tennant (1991) consider N,N-dimethylaniline to contain a structural alert for oncogenicity in the CH_3-N-CH_3 portion of the molecule.

Genotoxicology evidence exists for gene mutation chromosomonal abberration and primary DNA damage (Tanningher et al. 1993; Abdo, 1989). The sites of carcinogenic response and the sex differences in response to dosing with N,N-dimethylaniline were generally similar to that of aniline and other structurally related chemicals (Abdo, 1989).

In vivo, the primary transformations observed with N,N-dimethylaniline are N-demethylation and ring hydroxylation (Kiese 1974). Hydroxylation of the ring to form the urinary metabolites 4-aminophenol, 4-dimethylaminophenol and 2-aminophenol could involve an electrophilic arene/oxide binding to macromolecules. N,N-dimethylaniline is demethylated to N-methylaniline and aniline. Both compounds cause methemoglobinemia. N,N-Dimethyl-aniline may be less potent (Kiese, 1974).

N,N-Dimethylaniline, although negative in Salmonella tests, was clastogenic in cultured mammalian cells (Tanningher et al. 1993). The clastogenic response is increased in the presence of Aroclor-enhanced bacterial microsomes and

is observed at lower doses than aniline. These observations are consistent with the hypothesis that a DNA-reactive arene oxide intermediate may be involved in clastogenic action of N,N-dimethylaniline.

B. Derivation of Water Quality Value

1. Oncogenic Definition

The evidence of oncogenic activity in one mammalian species supported by positive results in short-term tests that are indicative of potential oncogenic activity after N,N-dimethylaniline exposure (Abdo, 1989) fulfills the definition of an oncogenic effect in 700.1 for N,N-dimethyl-aniline.

2. Selection of Data

NYS (1985) selected the method of chemical correlation to derive a value of 1 ug/L by correlation with aniline. With specific data available, a value based on chemical correlation is not appropriate.

The Abdo (1989) assay is the only long term assay in rats and is selected as the most appropriate dose-response data for deriving a water quality value. A summary of the data set showing statistically and biologically significant increases in tumor response is presented in Table I.

TABLE I. Splenic Sarcomas or Osteosarcoma (Combined) Incidences in Male Rats from Exposure to N,N-dimethylaniline

Dose* (mg/kg/day)	Tumor Incidence
0	0/49
2.1	0/49
21.4	4/50

* Dose = mg/kg/day x 5 days exposed/7days per week

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. 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 high difference between the female MLE and the 95% LCL indicate a high degree of uncertainty.

TABLE II

Data Animal Site	Animal Dose 95% LCL (ug/kg/day)	MLE GLOBAL82 (ug/kg/day)
Male Rat Spleen	0.150	74

4. Calculation of Human Dose

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

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

$$\text{Human dose} = \left(\frac{0.45}{70} \right)^{0.25} \times 0.150 = 0.0425 \text{ ug/kg/day}$$

5. Selection of Human Dose and Discussion of Uncertainties

With suitable data in a multi-dose study on one mammalian species, data are adequate as the basis of the water quality value. The critical site for exposure to N,N-dimethylaniline is the spleen. Thus, the male rat data is selected for calculation of the water quality value from the human dose of 0.0425 ug/kg/day.

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:

$$\text{Water Quality Value} = \left(\frac{0.0425 \text{ ug}}{\text{kg/day}}\right)\left(\frac{70 \text{ kg}}{2 \text{ L/day}}\right) = 1.49 \text{ ug/L rounded to, } 1 \text{ ug/L}$$

IV NON-ONCOGENIC EFFECTS (702.5)

A. Data

N,N-Dimethylaniline, as well as several other aniline derivatives, induce methemoglobin formation in rats and mice (Abdo, 1989). Its reported toxicity is similar to that of aniline in that they both cause central nervous system effects (headache, weakness and paralysis and convulsions) and hematoxic effects (methemoglobinemia, anemia, Heinz bodies) (Sax 1975).

The chronic toxicity of N,N-dimethylaniline was studied by administration in corn oil gavage at doses of 0, 3 and 30 mg/kg bodyweight to groups of male and female F344 rats 5 days per week for 103 weeks (Abdo, 1989). Clinical signs of toxicity (cyanosis) and decrease in motor activity occurred in a dose-dependent fashion. Splenomegaly, hemosiderin, bone marrow hyperplasia and hematopoiesis were increased in the spleen and liver of treated rats. A lowest observed adverse effect level (LOAEL) of 3 mg/kg was estimated for rats.

B. Derivation of Water Quality Value

1. Selection of Data

The study by Abdo (1989) is chosen as the only study with adequate dosing and number of animals and was judged the most appropriate for deriving a water quality value based on non-oncogenic effects. The authors consider the lowest dose, 3 mg/kg, to be a LOAEL.

2. Calculation of Acceptable Daily Intake (ADI)

An ADI is calculated from the study of Abdo (1989) by dividing the LOAEL of 3 mg/kg/day, by a total uncertainty factor of 1000 and adjusting for 5 day/week administration:

$$ADI = \left(\frac{3 \times 5/7}{1000} \right) \text{ mg/kg/day} = 2 \text{ ug/kg/day}$$

This uncertainty factor accounts for intra-(10) and inter-species(10) variation and 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:

$$\text{Water Quality Value} = \frac{2 \text{ ug/kg/day } (70 \text{ kg})(0.2)}{2 \text{ L/day}} = 14 \text{ ug/L, rounded to } 10 \text{ ug/L}$$

V CHEMICAL CORRELATION (702.7)

Because values can be derived using 702.4 and 5, deriving a water quality value for N,N-dimethylaniline 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 class value of 1 ug/L 6 NYCRR 702.4 is the most stringent value derived by these procedures and is the ambient water quality value for N,N-dimethylaniline.

VII REFERENCES

Abdo, K. 1989. Toxicology and Carcinogenesis Studies of N,N-dimethylaniline (CAS No. 121-69-7) in F344 rats and B6C3F1 mice (gavage studies). National Toxicology Program, Research Triangle Park, NC.

Ashby, J. and R.W. Tennent. 1991. Definitive relationships among chemical structures carcinogenicity and mutagenicity for 301 chemicals tested by the NTP. Mutat. Res. 257:299-306.

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

IARC (International Agency for Research on Cancer). 1993. IARC Monograph on Evaluation of Carcinogenic Risks to Man. 57:337.

Kiese, M. 1974. Methemoglobinemia: A Comprehensive Treatise. Cleveland, OH: CRC Press.

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 for N,N-Dimethylaniline. Albany, New York.

Sax, N.T. 1975. Dangerous Properties of Industrial Materials. Fifth Edition. New York: Van Nostrand Rheinhold Company.

Tanningher, M., R. Pasquini and S. Bonati. 1993. Genotoxicity Analysis of N,N-dimethylaniline and N,N-dimethyl-p-toluidine. Environ. Mol. Mutag. 21:349-356.

U.S. EPA (Environmental Protection Agency). 1994. Integrated Risk Information System. N,N-dimethylaniline on-line. Cincinnati, OH: Office of Research and Development, Environmental Criteria and Assessment Office.

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 N,N-dimethylaniline; 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 (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.

The sources above are deemed adequate to assess the literature through 1985. 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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