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NEW YORK STATE
- HUMAN HEALTH FACT SHEET -

Ambient Water Quality Value for Protection of Sources of Potable Water

SUBSTANCE(S): *NITRILOTRIACETIC ACID* **CAS REGISTRY NUMBER(S):** 139-13-9

AMBIENT WATER QUALITY VALUE: 3 ug/L

BASIS: Oncogenic effects (702.4)

SUMMARY OF INFORMATION:

The toxicology of nitrilotriacetic acid (NTA) has been the subject of a number of reviews (UAREP, 1985; USEPA, 1980; IJC, 1977). An evaluation of human health effects of exposure to NTA in drinking water was prepared by the New York State Department of Health (DOH) for the Environmental Impact Statement on the regulation banning the use of NTA in household cleaning products (NYSDEC, 1986, 1985). The following is a brief summary of the toxicity information regarding potential human health effects associated with exposure to NTA in drinking water.

I. Pharmacokinetics

NTA is absorbed from the digestive tract at rates that vary widely within and between species, and rodents appear to have a higher absorption rate than humans (Budny, 1972). NTA absorption appears to be affected by composition of the diet, and evidence suggests that absorption rates are greater when NTA is dissolved in water rather than when incorporated in food (NYSDEC, 1985).

Absorbed NTA is rapidly distributed throughout the body, primarily to the kidney, bladder and bone. Highest levels occur in the bone, where concentrations have been observed to reach a steady state at 5 mg/g bone tissue (USEPA, 1980). Excretion of NTA occurs at a relatively constant rate, with most of the substance excreted within 24 hours in animals tested. No metabolites or biotransformation products of ingested NTA have been identified in either laboratory-animal or human studies.

2. Acute/Chronic Toxicity

Oral LD_{50} values have been reported for NTA that range from 750 mg/kg for the rhesus monkey to 5000 mg/kg for dogs and 1100 to 5270 mg/kg for rats (NYSDEC, 1984). Symptoms associated with high doses of NTA include decrease in motor activity, vomiting, and stomach irritation and hemorrhage.

Animal studies based upon chronic low-dose exposure to NTA indicate that the urinary system is the primary target for NTA toxicity. Non-carcinogenic effects observed in rodents include nephritis and nephrosis. Hypoglycemia was observed in rats that consumed NTA in drinking water in a study reported by Mahaffey and Goyer (1972) who concluded that persons with latent or preclinical diabetes could be significantly affected if chronically exposed to low concentrations of NTA in drinking water. Because NTA binds to bone tissue, its effect on bone structure and function have been examined. Only one study, using skeletally mature dogs, showed any abnormalities in bone structure, but these were considered minimal (Anderson and Danylchuck, 1980).

3. Synergism/Antagonism

Initial concern regarding the safety of NTA was focussed on the reported enhancement by NTA of the teratogenic effects of cadmium and mercury (Chernoff and Courtney, 1970), but subsequent studies have been unable to corroborate these findings (NYSDEC, 1984). Diabetes-like symptoms have been observed in laboratory animals injected with high doses of iron-NTA. Ebina et al. (1984) concluded from their study of rats injected with aluminum-NTA that small doses of aluminum can produce toxicosis when given with NTA, based upon observations of urinary system effects and atrophy and demyelination of nerve cells in the brain. NTA has been observed to enhance the activity of several mutagens and carcinogens (see sections 5. and 6. below).

4. Teratogenicity

NTA is not considered to be teratogenic or embryotoxic either alone or in the presence of heavy metals (NYSDEC, 1984).

5. Mutagenicity

NTA has been tested in a variety of mutagenicity or genotoxicity assays including microbial, plant and mammalian systems. With a few exceptions, the results have indicated that NTA alone is not mutagenic or genotoxic. Ved Brat and Williams (1984) found no evidence that NTA increases the frequency of sister chromatid exchange (SCE) in mammalian cell cultures, but Montaldi et al. (1985) observed that NTA increased the frequency of SCE induced by insoluble salts of heavy metals. NTA was found effective in inducing mutations in a human cell line bioassay using selection for diphtheria-toxin

resistance (Grilli and Capucci, 1985). When tested in the Salmonella assay, NTA increased the mutagenicity of chromium compounds that were inactive or slightly mutagenic when tested alone (Loprieno et al., 1985).

6. Carcinogenicity

Studies conducted prior to 1977 indicated that NTA was not a carcinogen (Lijinsky et al., 1973; Nixon et al., 1972), but the conclusions of these studies have been generally discounted for a number of reasons. NTA was subsequently shown to be carcinogenic in rats and mice, with the highest tumorigenic responses observed in the urinary system (Goyer et al., 1981; NCI, 1977). A dietary study of NTA carcinogenesis, sponsored by the National Cancer Institute (NCI) and conducted at two laboratories, Stanford Research Institute (SRI) and Litton Bionetics Incorporated (LBI), reported a statistically significant increase in tumors in the urinary system in Fischer 344 rats and B6C3F1 mice fed H_3NTA and Na_3NTA in the diet at highest doses tested (NCI, 1977). The NCI data were subsequently re-evaluated by Tarone et al. (1981), who determined that the increases in tumor incidences at other organ sites (i.e., lungs, adrenals and liver) should also be considered significant. Goyer et al. (1981) reported results of a National Institute of Environmental Health Sciences study which showed that NTA is tumorigenic to kidneys of Sprague-Dawley rats exposed to NTA in drinking water at a dose lower than those associated with induction of tumors in the NCI study. Studies by Hiasa et al. (1984) and Lipsky (1984) have shown that NTA enhances the carcinogencity of other known carcinogens. Recently, it has been shown that NTA acts as a promoter in a two-stage urinary bladder carcinogenesis bioassay using rats pretreated with an initiator (Kitahori et al., 1985).

7. Epidemiology

No epidemiological data are available from either occupational exposure or exposure via drinking water. Occupational exposure to NTA occurs during manufacture and shipping of NTA as well as formulation of cleaning products containing NTA. It has been estimated that worker exposures range from 32 to 3400 ug/da (USEPA, 1980; Procter & Gamble, 1982), but studies examining effects related to such exposures have not been reported.

NTA has been used in cleaning products in Canada for over 10 years, and a survey of Canadian drinking water supplies reported a mean NTA concentration of 2.83±1.53 ug/l in finished drinking water. Due to the Canadian widespread pattern of use of NTA and its occurrence in drinking water, as well as the long latency period for induction of any carcinogenic response that might be correlated with such exposure, any epidemiological evidence associated with NTA exposure in Canada is probably not forthcoming.

DERIVATION OF VALUES:

The toxicological information summarized above was evaluated with respect to deriving an ambient water quality value pursuant to the Part 701 (proposed Part 702) methodologies. Evidence from several independently conducted studies that NTA induces tumors at several sites and in two mammalian species satisfies the criteria set forth in the definition of an oncogenic chemical in subdivision 701.1(p) (proposed Part 700). Therefore, a value should be derived for NTA using the section 701.4 (proposed section 702.3) procedure which is based upon oncogenic effects. This value would be more stringent than any derived by other procedures based upon protection of human health.

I. Other Quantitative Risk Assessments

Carcinogenicity data from the NCI (1977) and Goyer et al. (1981) studies have previously been used to derive drinking water values for NTA (Table 1). These values range from 2 to 1840 ug/l when based on urinary system tumor data and from 7 to 28 ug/l using tumor data from other organ sites. All values given are the 95 percent lower confidence limits on the dose corresponding to a 1×10^{-6} excess cancer risk as estimated by either one-hit or linear multi-stage models. Values derived by the Environmental Protection Agency (EPA), National Toxicology Program (NTP), and DOH are all based upon the most sensitive data set in the NCI or Goyer studies.

2. Selection of Data

Data from the NCI (1977) dietary study are selected to calculate a range of values for consideration in the establishment of an ambient water quality value. This study, which appears to be the most comprehensive of all the carcinogenicity bioassays, reports data from two independent laboratories for both sexes of two mammalian species exposed to multiple dose levels. Although the Goyer et al. (1981) drinking water study represents a more relevant exposure route, this investigation reported data for only male rats exposed at only one dose level.

The NCI (1977) study reported increases in tumor incidence for the urinary system of rats and mice, the adrenal gland, lung and liver of the female rat and the hematopoietic system of male mice. Tumor incidences observed in the urinary tract of dosed animals are of particular significance, because these tumors are not observed in controls and only rarely develop spontaneously in the strains of animals used. The SRI data are presented for both sexes of Fischer 344 rats administered the tri-sodium salt of NTA. The LBI data are reported for both sexes of Fischer 344 rats and B6C3F1 mice exposed to the tri-sodium salt as well as to the free acid form of NTA. Of the ten subsets, five show a statistically significant increase in tumors relative to the controls at the p 0.01 level, and these dose-response data are therefore considered the most appropriate for deriving a water quality value (Table 2.).

Table 1. Summary of Drinking Water Values Derived for NTA Based on 1 x 10-6 Excess Cancer Risks

Source	Drinking Water Value (ug/l)	Data Base
United States Environmental Protection Agency (1980) (DOH, 1984)	5	Urinary system tumors in rats fed Na_3NTA in the diet (NCI, 1977)
National Toxicology Program (1980), (DOH, 1984)	2	Urinary system tumors in rats exposed to Na_3NTA in drinking water (Goyer et al., 1981)
	5	Urinary system tumors in rats fed Na_3NTA in the diet (NCI, 1977)
Procter & Gamble (1983)	14-77 (mean = 40)	Kidney tumors in rodents fed either Na_3NTA or H_3NTA in the diet (NCI, 1977)
	14-101 (mean = 60)	Kidney tumors in rodents fed either Na_3NTA or H_3NTA in the diet (NCI, 1977); data sets pooled within species
NYS Department of Health (1984)	3-18	Urinary system tumors in rodents fed either Na_3NTA or H_3NTA in diet (NCI, 1977)
	12	Lung tumors in female rats fed H_3NTA in the diet (NCI, 1977)
	28	Adrenal gland tumors in female rats fed H_3NTA in the diet (NCI, 1977)
	7	Liver tumors in female rats fed H_3NTA in the diet (NCI, 1977)
Crump (1984)	477 and 455	Malignant tumors in mice and rats (NCI, 1977)
	1840 and 935	Urinary system tumors in mice and rats (NCI, 1977)

The urinary system tumor data employed in the calculations consist of the combined incidence of tubular-cell and transitional-cell neoplasms of the kidney, bladder, and ureter. The overall contribution of malignant tumors to the total incidence of urinary system tumors was approximately 80 percent in both rats and mice. Most of the tumors were found in the kidneys of males, bladders of females, and ureters of both sexes. All urinary system tumor data sets that show a statistically significant dose-response relationship are individually employed in the derivations. In addition, data sets that might be considered part of one large experiment are combined to provide a larger data base for the low-dose extrapolation.

3. Selection of Model

For derivation of a water quality value, Part 701 (proposed Part 702) specifies use of a linear multi-stage (LMS) low-dose extrapolation model unless there is sufficient scientific evidence that supports use of another extrapolation procedure. The results of several models were compared by Munro and Krewski (1981), and although the one-hit and LMS models produce similar results for NTA, other models predict doses that are nearly four orders of magnitude higher at the 1 x 10-6 risk level. The authors attributed this large discrepancy to the manner in which the relatively steep slope of the NTA dose-response curve is handled by the different parameters of each model.

Table 2. Urinary System Tumor Incidence in Rodents Fed NTA (NCI, 1977)

Lab[1]	Species[2]	NTA(3)	Dose[4] mg/kg/da)	Incidence Male	Female
SRI	Rat	NA_3NTA	0	0/24	0/24
			6.9	0/23	0/24
			69	0/24	1/24 (4%)
			690	14/24 (58%)*	13/24 (54%)*
LBI	Rat	H_3NTA	0	0/20	0/20
			280	1/49 (2%)	2/50 (4%)
			560	7/43 (16%)*	14/50 (28%)*
LBI	Rat	Na_3NTA	0	0/20	0/20
			190	2/49 (4%)	4/50 (8%)
			390	2/50 (4%)	2/49 (4%)
LBI	Mouse	H_3NTA	0	0/20	0/20
			640	5/49 (10%)	0/39
			1300	24/49 (49%)*	4/50 (8%)
LBI	Mouse	Na_3NTA	0	0/20	0/18
			150	0/48	0/46
			300	0/50	0/47

(l) SRI = Stanford Research Institute; LBI = Litton Bionetics Incorporated

(2) Fischer 344 rat and $B6C3F_1$ mouse

(3) Form of NTA administered in diet

(4) Time-weighted average daily dose of NTA over animal lifetime

* Statistically significant increase ($p < 0.01$) by the Fisher-Irwin one-tail test

The GLOBAL82 LMS model (Howe and Crump, 1982) is chosen to estimate the dose from which the NTA values are derived, because available evidence suggesting that NTA is a non-genotoxic or threshold carcinogen is not strong enough to support use of a non-linear model for setting a value. Both the 95 percent lower confidence limit and maximum likelihood estimate (MLE) are calculated for the dose associated with a 1×10^{-6} lifetime excess cancer risk. The confidence limit provides a value that is 95 percent certain to be more stringent than the value associated with the true risk. The maximum likelihood estimate should have the best association with true risk, which may be as low as zero.

4. Conversions

The output of the GLOBAL82 extrapolation, which is the animal dose associated with a 1×10^{-6} excess cancer risk (Table 3), is converted to a human dose by the surface-area conversion rule as specified in Part 701 (proposed Part 702). This is a more conservative approach than the body-weight conversion procedure used by Crump (1984) and Procter and Gamble (1983). Use of the surface-area conversion, however, is consistent with the available pharmacokinetic information on NTA, and there appear to be no compelling reasons to use an alternative conversion procedure. Human daily doses are converted to drinking water values that are based upon lifetime exposure of a 70-kg human consuming 2 liters of water per day (see Table 3).

5. Values and Their Uncertainties

Results of the quantitative risk assessment based on urinary system tumor data from the NCI (1977) studies are presented in Table 3. Values based on both the 95 percent confidence limit and the MLE are provided, although only the former meet the Part 701 (proposed Part 702) requirements as a basis for the value. Values based on the confidence limit of individual data sets range from 3 to 20 ug/l and of combined data from 6 to 40 ug/l. Values based on the MLE range from 10 to 40,000 ug/l and 30 to 7,000 ug/l when based on individual and combined data sets, respectively. The broad range in MLE values and the sizes of the confidence intervals suggest there is a considerable amount of uncertainty regarding the ability of the model to predict NTA risk at the 1×10^{-6} risk level using both individual and combined NCI data sets.

A number of factors related to the NCI studies can be identified that may affect the bioassay results and their use in risk assessment. These factors are discussed below with respect to their contribution to the uncertainty of the derived values: (1) number and concentration of dose levels and number of animals per dose group; (2) form of NTA administered; (3) length of exposure period; (4) sex and species of animals; and (5) biological and statistical significance of tumors at various organ sites.

Table 3. Ambient Water Quality Values for NTA Derived by Section 701.4 (Proposed Section 702.3) Procedures Using NCI (1977) Urinary System Tumor Data

Data Set [1]	Animal Dose [2] (ug/kg/da) MLE	95% LCL	Value (ug/l)[3] MLE	95% LCL
Individual:				
SRI male rat	7200	1.3	40000	8
SRI female rat	2.0	0.65	10	3
LBI male rat	1400	3.4	9000	20
LBI female rat	1000	2.8	6000	20
LBI male mice	1600	5.0	4000	10
Combined:				
SRI and LBI female rats	5.8	2.5	30	10
SRI and LBI male rats	44	6.8	300	40
SRI male and female rats	5.8	1.0	30	6
LBI male and female rats	1200	5.5	7000	30
SRI and LBI rats	11	4.8	60	30

(1) Male rat = 0.35 kg; female rat = 0.25 kg; male mouse = 0.035 kg

(2) Animal dose as determined by GLOBAL82 for 1 x 10-6 excess cancer risk; LCL = lower confidence limit; MLE = maximum likelihood extimate

(3) Drinking water value = animal dose (ug/kg/da) $\times$ $\frac{\text{animal body weight}}{\text{human body weight}}$ $\frac{0.33}{2\,l} \times \frac{70\ kg}{}$

Differences in study design that control the data base have implications with respect to the statistical nature of quantitative risk assessment. Although it cannot be quantified, some of the uncertainty in risk assessment can be reduced by using data from larger or adjusted animal group sizes and a greater number of well-spaced dose levels. The SRI study dosed 24 animals per group as compared with 50 in the LBI study. Three experimental doses spaced at order-of-magnitude levels were used in the SRI study, while the LBI study used only the maximum tolerated dose and half that level. Although neither of the studies employed a dosing regime that was clearly the better one, it should be recognized that the risk assessment results based on the SRI and LBI rat data may differ simply because of differences between dose rates and sample sizes. The size and distribution of the data base should also be considered with respect to the effects of pooling data for risk assessment calculations.

It is possible that the form of NTA administered to test animals may have had an effect on the tumor response rates. Establishment of ambient water quality values involves consideration of the toxicity of the most environmentally relevant chemical form of NTA. Because NTA occurs in drinking water as a salt of any of a number of metal ions, drinking water values based on data from the SRI study, which used the tri-sodium salt of NTA, may be more appropriate than the LBI study which used the free acid form.

The relationship between dose and tumor response may have been affected by the length of the exposure period, which was 104 weeks in the SRI study and only 72 weeks in the LBI study. Considering that section 701.4 incorporates human lifetime exposure into the derivation of the value, use of values based on actual lifetime exposure data from the SRI study would be more appropriate than those adjusted for lifetime from the LBI study. Use of the LBI results requires an additional assumption that effects of larger doses administered over the shorter exposure period are equivalent to those of smaller doses over the animal lifetime.

It is generally assumed that due to genetic differences, tumor response rates may vary with sex, strain, and species of test animals. In the NCI studies, a statistically significant increase in tumor incidence was observed in four organ systems in the rat and in only two in the mouse. With the exception of essentially equal tumor rates that were observed in the urinary system of both sexes of LBI rats, female rats exhibited greater sensitivity than males, while in the mice only males had significant increases in tumor incidence.

The biological and statistical significance of tumor occurrence varies with the organ system of test animals. The response rates observed for urinary system tumors is highly significant ($p < 0.01$) for five data sets, and the spontaneous tumor occurrence was less than 1 percent. On the other hand, the statistical significance of response rates reported for the other organ systems relative to controls was not as great, and the reported spontaneous tumor occurrence at those sites is high enough to potentially contribute to false positive errors.

6. Selection of Value(s)

All risk-estimate based values for NTA derived from the NCI studies (Table 3) are considered scientifically justifiable, because they are derived from biologically and statistically acceptable data sets. The values presented within the 3 to 40 ug/l range, which are based on the 95 percent confidence limits, meet the requirements of Part 701 (proposed Part 702) as the basis for an ambient water quality value for NTA in Class A waters. There is no clear-cut scientific evidence that would immediately support selection of any single value as the most appropriate for promulgation as the standard for NTA. As a result, an ambient water quality value for NTA in Class A waters may be based upon any value within the range of 3 to 40 ug/l.

Although there is no established procedure for selecting among these recommended values, the associated uncertainties and assumptions, which were discussed previously, may be weighed along with the degree of conservatism imposed by the proposed standard. The following criteria and assumptions required may be considered as support for either a low-, mid-, or high-range value.

Selection of the most conservative value requires the assumption that human sensitivity may be as great as the most sensitive animal group tested. Based on this assumption and using the individual data sets reported by the NCI, a value of 3 ug/l would be selected as an ambient water quality value for NTA. An additional assumption is required, however, that the response rate from which the 3 ug/l value was derived is different from other response rates because of actual differences in animal sensitivity to NTA. While this may be true, it is more likely a consequence of biological and statistical variability inherent in the results of animal bioassays for carcinogenesis.

Different assumptions can be made regarding the NCI bioassay results that would allow combining of data sets and use of two other criteria as support for the NTA value. Based on these assumptions, use of the most sensitive sex and species as the criteria for value selection leads to a value of 10 ug/l, while use of the most sensitive species as the criterion supports a 30 ug/l value. Although both sets of assumptions required for combining data sets can be considered reasonable, given the bioassay response rates and the related toxicological information, neither is judged to be the more plausible.

Although as discussed above, there are uncertainties associated with all of the values within the range of 3-40 ug/l and it is possible to support any of them, a value of 3 ug/l is selected on the basis of providing the greatest degree of protection.

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