

# Nitritotriacetic acid in Drinking-water

Background document for development of  
WHO *Guidelines for Drinking-water Quality*

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## Preface

One of the primary goals of WHO and its member states is that “all people, whatever their stage of development and their social and economic conditions, have the right to have access to an adequate supply of safe drinking water.” A major WHO function to achieve such goals is the responsibility “to propose regulations, and to make recommendations with respect to international health matters ....”

The first WHO document dealing specifically with public drinking-water quality was published in 1958 as International Standards for Drinking-Water. It was subsequently revised in 1963 and in 1971 under the same title. In 1984–1985, the first edition of the WHO Guidelines for drinking-water quality (GDWQ) was published in three volumes: Volume 1, Recommendations; Volume 2, Health criteria and other supporting information; and Volume 3, Surveillance and control of community supplies. Second editions of these volumes were published in 1993, 1996 and 1997, respectively. Addenda to Volumes 1 and 2 of the second edition were published in 1998, addressing selected chemicals. An addendum on microbiological aspects reviewing selected microorganisms was published in 2002.

The GDWQ are subject to a rolling revision process. Through this process, microbial, chemical and radiological aspects of drinking-water are subject to periodic review, and documentation related to aspects of protection and control of public drinking-water quality is accordingly prepared/updated.

Since the first edition of the GDWQ, WHO has published information on health criteria and other supporting information to the GDWQ, describing the approaches used in deriving guideline values and presenting critical reviews and evaluations of the effects on human health of the substances or contaminants examined in drinking-water.

For each chemical contaminant or substance considered, a lead institution prepared a health criteria document evaluating the risks for human health from exposure to the particular chemical in drinking-water. Institutions from Canada, Denmark, Finland, France, Germany, Italy, Japan, Netherlands, Norway, Poland, Sweden, United Kingdom and United States of America prepared the requested health criteria documents.

Under the responsibility of the coordinators for a group of chemicals considered in the guidelines, the draft health criteria documents were submitted to a number of scientific institutions and selected experts for peer review. Comments were taken into consideration by the coordinators and authors before the documents were submitted for final evaluation by the experts meetings. A “final task force” meeting reviewed the health risk assessments and public and peer review comments and, where appropriate, decided upon guideline values. During preparation of the third edition of the GDWQ, it was decided to include a public review via the world wide web in the process of development of the health criteria documents.

During the preparation of health criteria documents and at experts meetings, careful consideration was given to information available in previous risk assessments carried out by the International Programme on Chemical Safety, in its Environmental Health

Criteria monographs and Concise International Chemical Assessment Documents, the International Agency for Research on Cancer, the joint FAO/WHO Meetings on Pesticide Residues, and the joint FAO/WHO Expert Committee on Food Additives (which evaluates contaminants such as lead, cadmium, nitrate and nitrite in addition to food additives).

Further up-to-date information on the GDWQ and the process of their development is available on the WHO internet site and in the current edition of the GDWQ.

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*Headquarters:*

- H. Galal-Gorchev, International Programme on Chemical Safety
- R. Helmer, Division of Environmental Health

*Regional Office for Europe:*

- X. Bonnefoy, Environment and Health
- O. Espinoza, Environment and Health

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## GENERAL DESCRIPTION

### *Identity*

CAS no: 139-13-9

Molecular formula: C<sub>6</sub>H<sub>9</sub>NO<sub>6</sub>

### *Physicochemical properties (1)*

<i>Property</i>	<i>Value</i>
Physical state	Needles or prismatic crystals in the undissociated acid form
Melting point	241.5 °C
Water solubility	1.28 g/l at 22.5 °C
pH of saturated solution	2–3

### *Major uses*

The trisodium salt of nitrilotriacetic acid (NTA) is used in laundry detergents as a "builder" to replace phosphates because of its ability to chelate calcium and magnesium ions (1). NTA is used extensively in the treatment of boiler water to prevent the accumulation of mineral scale and, to a lesser extent, in photography, textile manufacture, paper and cellulose production, and metal plating and cleaning operations. Its use as a therapeutic chelating agent for the treatment of manganese poisoning (2) and iron overloading has been suggested (3).

### *Environmental fate*

NTA is degraded principally by microorganisms by carbon–nitrogen cleavage with the formation of such intermediates as iminodiacetate, glyoxylate, glycerate, glycine, and ammonia (4–6); the metabolic end-products are carbon dioxide, water, ammonia, and nitrate (7). NTA mobilizes heavy metals from aquatic sediments (8) and is present in water primarily in the form of metal complexes (9), most of which degrade rapidly. Under certain conditions, it is broken down by photochemical and chemical reactions (7).

The half-life for biodegradation of NTA in groundwater at 1–100 µg/litre is approximately 31 h (10). Concentrations of 5–50 mg/litre completely disappeared from river water containing acclimatized microorganisms in 2–6 days; concentrations below 5 mg/litre are expected to degrade within 1 day (11,12). Acclimatization of microorganisms in two lake waters resulted in the reduction of the disappearance time of up to 10 mg of NTA per litre from 6 and 11 days to 4 and 3 days, respectively (13). Sand-associated bacteria adapt more quickly to NTA and degrade it more actively than do plankton and algae (14).

## ANALYTICAL METHODS

NTA concentrations in water may be determined by gas chromatography with a nitrogen-specific detector. This method is suitable for the detection of levels as low as 0.2 µg/litre (15).

## ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

### *Water*

NTA has been detected in both raw and treated water. In a national survey of 70 Canadian municipalities, the mean concentrations of NTA in drinking-water and raw water samples were 2.82 µg/litre (range <0.2–30.4 µg/litre) and 3.9 µg/litre (range <0.2–33.5 µg/litre),

respectively. Concentrations exceeded 10 µg/litre in only 14% of the locations (15). In a survey of tapwater in eight cities in New York State, 68% of the samples contained no detectable levels of NTA (detection limit 1 µg/litre); the remaining samples contained an average of 2.1 µg/litre (16). Mean concentrations in surface water ranged from 0.3 to 4.7 µg/litre in Germany (17) and from 1.0 to 12.0 µg/litre in Switzerland (18).

### ***Other routes of exposure***

No information on NTA concentrations in food or ambient air has been found. For a very small proportion of the population in households in which dishes are washed with detergents containing NTA, residues present on unrinsed dishes left to drip dry may be a source of exposure. Intake from this source may approximate 0.0025 mg/kg of body weight per day (0.15 mg for a 60-kg adult) (19).

### ***Estimated total exposure and relative contribution of drinking-water***

The daily intake of NTA in drinking-water can be calculated to be 5.64 µg, using the mean concentration in drinking-water reported in the Canadian national survey (2.82 µg/litre) (15) and assuming an average daily water consumption of 2 litres.

## **KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS**

Absorption of NTA from the gastrointestinal tract is rapid; however, there is considerable variation among species in the proportion of NTA eliminated in the urine. It does not appear to be metabolized by mammals: this conclusion is based on studies in mice, rats, dogs, and humans in which unchanged NTA is excreted in the urine (20–23).

NTA accumulates in bone because it forms complexes with divalent cations such as calcium; its turnover time in bone is similar to that of calcium (7). Deposition of NTA in the kidney has also been reported, although this may be an artefact associated with the retention of urine in the kidney rather than uptake by renal tissue (7).

## **EFFECTS ON LABORATORY ANIMALS AND *IN VITRO* TEST SYSTEMS**

### ***Acute exposure***

NTA does not appear to be highly acutely toxic to mammals. Oral LD<sub>50</sub>s in rats and mice of 1470 mg/kg of body weight and 3160 mg/kg of body weight, respectively, have been reported (24). The oral LD<sub>50</sub> of Na<sub>3</sub>NTA·H<sub>2</sub>O in rodents is about 2000 mg/kg of body weight (7). The oral LD<sub>50</sub>s in rats for the metal complexes of NTA commonly found in drinking-water range from 810 mg/kg of body weight for CuNaNTA to over 22 500 mg/kg of body weight for NiNaNTA (7).

### ***Short-term exposure***

Results of short-term studies in which NTA was administered orally indicate that the kidney is the target organ and that damage is dose-dependent and rapidly induced. In two studies in which male Sprague-Dawley rats and Charles River CD rats consumed drinking-water containing between 0.01 and 0.1% Na<sub>3</sub>NTA for 10 weeks, elevated blood glucose levels were observed at all dose levels. Six of the nine Sprague-Dawley rats in the high-dose group died by the fourth week; animals in this group showed marked vacuolization of renal tubules, and glycosuria was present in five rats (25). In a bioassay in which groups of weanling rats were fed diets containing 0, 2000, 7500, 10 000, or 20 000 mg of the trisodium salt per kg of diet for 90 days, hydronephrosis was observed in 63% of the animals in the group given 20 000 mg/kg; hydropic degeneration of the kidney tubular cells, tubular atrophy, and dilatation were

reported in the groups given 7500 and 10 000 mg/kg; no adverse effects were observed at 2000 mg/kg (26). In a limited investigation in which two skeletally mature dogs were administered 2.5 mg of trisodium salt per kg of body weight per day in their drinking-water for 7 months, radial closure rates and the percentage of osteoid seams taking a fluorescent label were decreased, suggesting interference with the mineralization process (27).

### ***Long-term exposure***

Weanling Charles River CD rats (50 per sex per dose) were fed diets containing 0.03, 0.15, or 0.5% of the trisodium salt or 0.5% of the calcium chelate of NTA for 2 years. A dose-dependent increase in urinary zinc was reported in the groups receiving 0.15 and 0.5% Na<sub>3</sub>NTA, accompanied by a dose-dependent increase in renal tubular cell toxicity. Mild nephrosis consisting of hydropic degeneration of tubular cells and the minor tubule was observed at 6 months at 0.15 and 0.5% Na<sub>3</sub>NTA; its incidence and severity became more pronounced as the study continued. Renal effects at 0.5% for the trisodium salt and 0.5% for the calcium chelate were severe. The NOAEL for nephrosis or nephritis in rats was considered to be 0.03% for the trisodium salt, equivalent to 30 mg/kg of body weight per day in young rats and 15 mg/kg of body weight per day as they grew older (or 10 and 20 mg of NTA per kg of body weight per day, respectively) (19).

### ***Reproductive toxicity, embryotoxicity, and teratogenicity***

NTA may be beneficial in neonatal development because it increases the bioavailability of essential elements (28).

NTA was not teratogenic or embryotoxic in studies with mice (0.2% NTA) (29), rats (0.1 or 0.5% trisodium salt) (30), or rabbits (250 mg of trisodium salt per kg of body weight) (30).

### ***Mutagenicity and related end-points***

The mutagenic and clastogenic potential of NTA has been investigated both *in vivo* and *in vitro*, but the results of the assays conducted to date have been largely negative (1,7,31,32). It enhances the induction of sister chromatid exchange in Chinese hamster cells by insoluble salts of some heavy metals (33,34), and some insoluble salts of chromium(VI) are mutagenic in the *Salmonella* microsome assay in the presence of NTA (35).

### ***Carcinogenicity***

There was no evidence of carcinogenicity in studies in which weanling Charles River CD rats were fed diets containing 0.03, 0.15, or 0.5% of the trisodium salt or 0.5% of the calcium chelate of NTA for 2 years (19), groups of 80 Swiss mice were given drinking-water containing 5 g of NTA per litre or 5 g of NTA plus 1 g of sodium nitrite per litre for 26 weeks (36), or groups of 15 male and 15 female MRC rats were exposed to the same levels for 84 weeks (37).

In an experiment in which groups of 24 male and 24 female Fischer 344 rats were fed diets containing 200, 2000, or 20 000 mg of Na<sub>3</sub>NTA·H<sub>2</sub>O per kg of diet for 2 years, a significant increase in primary neoplasms of the urinary tract was reported in both males and females in the highest dose group; in addition, five males and five females in this group developed metastatic transitional cell carcinomas, which appeared most frequently in the lung and often in the lymph nodes, pancreas, adrenal gland, and seminal vesicle (38).

In an 18-month study, Fischer 344 rats were fed diets containing 7500 or 15 000 mg of NTA per kg of diet or 7500 or 15 000 mg of Na<sub>3</sub>NTA·H<sub>2</sub>O per kg of diet, and B6C3F<sub>1</sub> mice were fed diets containing 7500 or 15 000 mg of NTA per kg of diet or 2500 or 5000 mg of

$\text{Na}_3\text{NTA}\cdot\text{H}_2\text{O}$  per kg of diet. Several carcinogenic effects were observed in both rats and mice. In rats, these included a significant increase in the incidence of a variety of neoplastic lesions of the urinary tract in those exposed to 15 000 mg of NTA per kg of diet, a slight increase in the incidence of neoplasms of the urinary system in those exposed to 7500 and 15 000 mg/kg of the trisodium salt, a positive dose–response relationship for the incidence of tumours of the endocrine system, and a dose-related increase in the incidence of neoplastic nodules of the liver in female rats consuming NTA. In mice, effects included a statistically significant increase in tumours of the kidney, especially tubular-cell adenocarcinomas, in males ingesting 15 000 mg of NTA per kg and a dose-related increase in the incidence of tumours of the haematopoietic system in males consuming  $\text{Na}_3\text{NTA}\cdot\text{H}_2\text{O}$  (38). In a study in which male Sprague-Dawley albino rats were exposed to drinking-water containing 1000 mg of trisodium salt per litre for 2 years, the incidence of renal tumours, including renal adenomas and adenocarcinomas, was significantly increased in the exposed animals (39).

The induction of tumours is considered to be due to cytotoxicity resulting from the chelation of divalent cations such as zinc and calcium in the urinary tract, leading to the development of hyperplasia and neoplasia. It has been observed, for example, that only NTA doses that increase urinary calcium are associated with transitional epithelial cell tumours, leading to the hypothesis that uncomplexed NTA in urine extracts extracellular calcium from the transitional epithelial cells of the urinary tract faster than it can be replenished (7).

## **EFFECTS ON HUMANS**

There is little information on the toxicity of NTA in humans. On the basis of physical examination, blood chemistry analysis, and urinalysis, no adverse health effects were reported in a metabolism study in which volunteers ingested a single dose of 10 mg of NTA (23).

## **GUIDELINE VALUE**

NTA is poorly absorbed in humans as compared with experimental animals and does not appear to be metabolized in mammals. It has not been shown to be teratogenic or genotoxic in the studies conducted to date but has induced urinary tract tumours in rats and mice at high doses (38,39). IARC has placed NTA in Group 2B (40).

The reported induction of tumours in rodents is considered to be due to cytotoxicity resulting from the chelation of divalent cations such as zinc and calcium in the urinary tract, leading to the development of hyperplasia and subsequently neoplasia. In general, neoplasms have occurred only following long-term ingestion of NTA at concentrations greater than 100 mg/kg of body weight per day, whereas nephrotoxicity occurs at a lower level, between 10 and 60 mg/kg of body weight per day (7).

Because NTA is nongenotoxic and induces tumours only after prolonged exposure to doses higher than those that produce nephrotoxicity, the guideline value is derived on the basis of a NOAEL for nephrotoxic effects but incorporating a larger uncertainty factor to account for the evidence of urinary tumour induction at high doses. A TDI of 10  $\mu\text{g}/\text{kg}$  of body weight was calculated by applying an uncertainty factor of 1000 (100 for inter- and intraspecies variation and 10 for carcinogenic potential at high doses) to the NOAEL of 10 mg/kg of body weight per day for nephritis and nephrosis in a 2-year study in rats (19). In view of the higher absorption of NTA in rats than in humans, it should be noted that this TDI is probably conservative. Because there is no substantial exposure from other sources, 50% of the TDI was allocated to drinking-water, resulting in a guideline value of 200  $\mu\text{g}/\text{litre}$  (rounded figure).

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