NITRILOTRIACETIC ACID AND ITS SALTS

This substance was considered by a previous working group, in 1989 (IARC, 1990). Since that time, new data have become available, and these have been incorporated into the monograph and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Chemical and physical data

1.1.1 *Nomenclature*

Nitrilotriacetic acid

Chem. Abstr. Serv. Reg. No.: 139-13-9
Deleted CAS Reg. No.: 26627-44-1; 26627-45-2; 80751-51-5
Chem. Abstr. Name: *N*,*N*-Bis(carboxymethyl)glycine
IUPAC Systematic Name: Nitrilotriacetic acid
Synonyms: Nitrilo-2,2′,2″-triacetic acid; nitrilotris(methylenecarboxylic acid); NTA; triglycine; triglycollamic acid; α,α′,α″-trimethylaminetricarboxylic acid

Nitrilotriacetic acid, sodium salt

Chem. Abstr. Serv. Reg. No.: 10042-84-9
Chem. Abstr. Name: *N*,*N*-Bis(carboxymethyl)glycine, sodium salt
IUPAC Systematic Name: Nitrilotriacetic acid, sodium salt
Synonyms: Nitrilotriacetic acid sodium salt; NTA sodium salt; NTA, sodium salt; sodium aminotriacetate; sodium nitriloacetate; sodium nitrilotriacetate; sodium NTA

Nitrilotriacetic acid, monosodium salt

Chem. Abstr. Serv. Reg. No.: 18994-66-6
Chem. Abstr. Name: *N*,*N*-Bis(carboxymethyl)glycine, monosodium salt
IUPAC Systematic Name: Nitrilotriacetic acid, monosodium salt
Synonyms: Monosodium nitrilotriacetate; NTA, monosodium salt

Nitrilotriacetic acid, disodium salt

Chem. Abstr. Serv. Reg. No.: 15467-20-6
Chem. Abstr. Name: *N*,*N*-Bis(carboxymethyl)glycine, disodium salt
IUPAC Systematic Name: Nitrilotriacetic acid, disodium salt
Synonyms: Disodium hydrogen nitrilotriacetate; disodium nitrilotriacetate; nitrilotriacetic acid disodium salt; NTA, disodium salt

Nitrilotriacetic acid, disodium salt, monohydrate

Chem. Abstr. Serv. Reg. No.: 23255-03-0
Chem. Abstr. Name: *N*,*N*-Bis(carboxymethyl)glycine, disodium salt, monohydrate
IUPAC Systematic Name: Nitrilotriacetic acid, disodium salt, monohydrate
Synonyms: Disodium nitrilotriacetic acid monohydrate; NTA, disodium salt, monohydrate

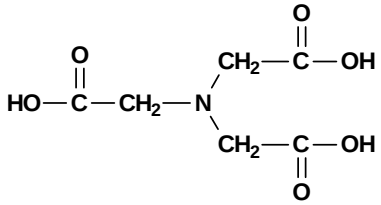
Nitrilotriacetic acid, trisodium salt

Chem. Abstr. Serv. Reg. No.: 5064-31-3
Deleted CAS Reg. No.: 37291-81-9
Chem. Abstr. Name: *N*,*N*-Bis(carboxymethyl)glycine, trisodium salt
IUPAC Systematic Name: Nitrilotriacetic acid, trisodium salt
Synonyms: Nitrilotriacetic acid trisodium salt; NTA trisodium salt; NTA, trisodium salt; trisodium nitrilotriacetate; trisodium 2,2′,2″-nitrilotriacetate; trisodium NTA

Nitrilotriacetic acid, trisodium salt, monohydrate

Chem. Abstr. Serv. Reg. No.: 18662-53-8
Chem. Abstr. Name: *N*,*N*-Bis(carboxymethyl)glycine, trisodium salt, monohydrate
IUPAC Systematic Name: Nitrilotriacetic acid, trisodium salt, monohydrate
Synonyms: NTA, trisodium salt, monohydrate; trisodium nitrilotriacetate monohydrate

1.1.2 *Structural and molecular formulae and relative molecular mass*



$C_6H_9NO_6$ Relative molecular mass: 191.14

Monosodium salt

$C_6H_8NO_6.Na$ Relative molecular mass: 213.14

Disodium salt

$C_6H_7NO_6.2Na$ Relative molecular mass: 235.13

Disodium salt, monohydrate

$C_6H_7NO_6.2Na.H_2O$ Relative molecular mass: 253.11

Trisodium salt

$C_6H_6NO_6.3Na$ Relative molecular mass: 257.13

Trisodium salt, monohydrate

$C_6H_6NO_6.3Na.H_2O$ Relative molecular mass: 275.11

1.1.3 *Chemical and physical properties of the pure substance*

(*a*) *Description*: White crystalline powder (Lewis, 1993)

(*b*) *Melting-point*: 242°C (decomposes) (Lide, 1997)

(*c*) *Solubility*: Slightly soluble in water; soluble in ethanol (Lide, 1997)

(*d*) *Conversion factor*: $mg/m^3 = 7.82 \times ppm$

1.2 Production and use

Information available in 1995 indicated that nitrilotriacetic acid was produced in 10 countries (Chemical Information Services, 1995).

Nitrilotriacetic acid is used as a chelating and sequestering agent, and as a builder in synthetic detergents (Budavari, 1996). It is also used as an eluting agent in the purification of rare earth elements (Lewis, 1993), as a boiler feedwater additive, in water and textile treatment, in metal plating and cleaning and in pulp and paper processing (National Toxicology Program, 1991).

1.3 Occurrence

1.3.1 *Natural occurrence*

Nitrilotriacetic acid and its salts and complexes are not known to occur naturally.

1.3.2 *Occupational exposure*

According to the 1981–83 National Occupational Exposure Survey (National Institute for Occupational Safety and Health, 1998), approximately 270 000 workers in the United States were potentially exposed to nitrilotriacetic acid and its trisodium salts. Occupational exposure to these compounds may occur in their production and use. Workers involved in detergent formulation were estimated to be exposed to concentrations up to 4.6 µg/kg bw per day (Universities Associated for Research and Education in Pathology, 1985), and lifetime average daily doses were estimated to be less than 1 µg/kg bw for all workers formulating or using nitrilotriacetic acid-containing products (CanTox, 1996).

1.3.3 *Environmental occurrence*

Four major assessments have been conducted of exposure to nitrilotriacetic acid: by the Midwest Research Institute (1979), the Environmental Protection Agency (1980), the Universities Associated for Research and Education in Pathology (1985) and CanTox (1996). Although different methods were used and slightly different results were obtained, all four studies indicate that daily exposure of consumers to all possible sources of nitrilotriacetic

acid is generally < 1 μg/kg bw. Among the sources specifically considered were drinking-water, showering and bathing, wearing clothes washed with nitrilotriacetic acid-containing detergents, inhalation of detergents, skin contact with washwater from laundry or dishes and ingestion of residues on hand-washed dishes.

According to the Environmental Protection Agency Toxic Chemical Release Inventory for 1987, 800 kg of nitrilotriacetic acid were released into the air, 2300 kg were discharged into water, 860 000 kg were disposed of by underground injection and 2300 kg were released onto the land from manufacturing and processing facilities in the United States. By 1996, the levels were 5 kg released into the air, 35 kg released into water and 680 kg disposed of by underground injection (National Library of Medicine, 1998).

1.4 Regulations and guidelines

WHO (1993) has established an international drinking-water guideline for nitrilotriacetic acid of 200 μg/L.

2. Studies of Cancer in Humans

No data were available to the Working Group.

3. Studies of Cancer in Experimental Animals

Previous evaluation

Nitrilotriacetic acid was tested for carcinogenicity by oral administration in the diet in mice and rats. It induced renal-cell adenocarcinomas in mice of each sex, renal-cell tumours in male rats and transitional-cell and squamous-cell carcinomas of the urinary bladder, hepatocellular adenomas and adrenal phaeochromocytomas in female rats.

Nitrilotriacetic acid, trisodium salt was tested for carcinogenicity in mice and rats by oral administration. When administered in the diet as the monohydrate, it induced haematopoietic tumours in male mice and benign and malignant tumours of the urinary system (kidney, ureter and bladder) in rats of each sex. When administered in drinking-water to male rats, it induced renal adenomas and adenocarcinomas.

In two-stage carcinogenicity studies in male rats by oral administration, nitrilotriacetic acid and its trisodium salt increased the incidence of urinary-tract tumours after pretreatment with various *N*-nitrosamines (IARC, 1990).

New studies

No new data on nitriloacetic acid and its salts were available to the Working Group.

4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

No new data were available to the Working Group.

4.1.2 *Experimental systems*

Nitrilotriacetic acid and its sodium salt are absorbed in mammals; the parent compound is not metabolized and is excreted rapidly by filtration in the kidney. The information on the absorption, distribution and excretion of nitrilotriacetic acid and its salts has been reviewed previously (IARC, 1990).

4.2 Toxic effects

The toxic effects of nitrilotriacetic acid and its salts have been reviewed previously (IARC, 1990).

4.2.1 *Humans*

No data were available to the Working Group.

4.2.2 *Experimental systems*

Renal tubular cells show evidence of toxicity in rats and mice given high doses of nitrilotriacetic acid or its sodium salt corresponding to the doses that produce renal-cell tumours in these species. Regenerative proliferation ensues. The toxicity correlates with plasma and urinary accumulation of Zn^{++}, considered to occur secondary to the chelating properties of nitrilotriacetic acid. Administration of zinc nitrilotriacetic acid or co-administration of zinc salts with nitrilotriacetic acid accentuates this effect (Anderson *et al.*, 1985).

The urothelial effects of nitrilotriacetic acid and its sodium salt occur in rats but not in mice, and sex differences are seen, depending on the experimental treatment. Urothelial tumours (renal pelvis, ureters, bladder) occur in animals of each sex. In contrast to the effect in renal tubules, the urothelial effects are not due to accumulation of zinc but rather appear to be related to depletion of calcium. This occurs at doses higher than those required for the nephrotoxicity produced by nitrilotriacetic acid, and the doses correspond to those that produce urothelial toxicity and regenerative hyperplasia. Although nitrilotriacetic acid-containing microcrystalluria occurs, this was not considered to be a sufficient explanation for the urothelial toxic and regenerative effects (Anderson *et al.*, 1985).

Nitrilotriacetic acid did not mediate efficient oxidative production of single- and double-strand breaks in DNA *in vitro* in supercoiled plasmid pZ189 (Toyokuni & Sagripanti, 1993).

It increased the incidence of liver-cell nodules but not carcinomas in female rats (IARC, 1990).

4.3 Reproductive and developmental effects

4.3.1 *Humans*

No data were available to the Working Group.

4.3.2 *Experimental systems*

The developmental and reproductive effects of nitrilotriacetic acid have been reviewed (Anderson *et al*., 1985). No significant maternal, embryonic or fetal effects were reported in rats exposed to up to 0.5% in the diet, rabbits exposed by oral gavage to up to 250 mg/kg bw per day or in mice exposed via the drinking-water at 0.2%. Addition of heavy metals such as mercury and cadmium did not change the response. Similarly, studies of reproductive toxicity did not indicate an effect on neonatal development.

Nitrilotriacetic acid was used to assess the predictive value of two assays for mammalian teratogenesis *in vitro*: an assay for inhibition of the growth of embryonic palatal mesenchymal cells, which evaluates effects on proliferative potential, and an assay for inhibition of the attachment of mouse ascites tumour cells to concanavalin A-coated surfaces. The concentrations of nitrilotriacetic acid that inhibited growth or attachment by 50% were > 1 mmol/L in both assays, and the authors considered the results to be negative (Steele *et al*., 1988).

Exposure of developing *Drosophila* larvae to nitrilotriacetic acid caused a dose-related increase in gross wing defects and extra bristles in adults, but the authors did not consider these effects predictive of developmental toxicity in mammals (Lynch *et al*., 1991).

Nitrilotriacetic acid was evaluated for effects on amphibian embryogenesis in the frog embryo teratogenesis assay *Xenopus laevis* (FETAX) assay. The concentration that caused the deaths of 50% of the embryos was reported to be 540 mg/L, the concentration that induced terata in 50% of the surviving embryos was 530 mg/mL, and the teratogenic index was 1.0 mg/mL. The authors considered the effects to be due to disruption and osmoregulation and not to teratogenic potential (Dawson *et al.*, 1989).

4.4 Genetic and related effects

4.4.1 *Humans*

No data were available to the Working Group.

4.4.2 *Experimental systems* (see Table 1 for references)

Nitrilotriacetic acid did not induce reverse mutation in *Escherichia coli* and did not induce gene mutation in either *Saccharomyces cerevisiae* or *Schizosaccharomyces pombe*. It did not induce sex-linked recessive lethal mutation or dominant lethal mutation but induced aneuploidy in *Drosophila melanogaster*. It did not induce sister chromatid exchange or chromosomal aberrations in Chinese hamster cells *in vitro*. It did not induce dominant lethal mutation but induced aneuploidy in mice *in vivo*.

Table 1. Genetic and related effects of nitrilotriacetic acid and its salts

Test system	Results[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Nitrilotriacetic acid				
Escherichia coli WP2, reverse mutation	–	NT	4000	Zetterberg (1970)
Saccharomyces cerevisiae, forward mutation	–	NT	4000	Zetterberg (1970)
Saccharomyces cerevisiae, reverse mutation	–	NT	4000	Zetterberg (1970)
Schizosaccharomyces pombe, reverse mutation	–	NT	4000	Zetterberg (1970)
Drosophila melanogaster, sex-linked recessive lethal mutations	–		1900 inj	Kramers (1976)
Drosophila melanogaster, sex-linked recessive lethal mutations	–		4000	Woodruff *et al.* (1985)
Drosophila melanogaster, dominant lethal mutations	–		1900 inj	Kramers (1976)
Drosophila melanogaster, aneuploidy, germ cells	+		9600	Costa *et al.* (1988)
Drosophila melanogaster, aneuploidy, germ cells	+		4000	Ramel & Magnusson (1979)
Sister chromatid exchange, Chinese hamster ovary cells *in vitro*	–	–	5	Loveday *et al.* (1989)
Chromosomal aberrations, Chinese hamster ovary cells *in vitro*	–	–	5	Loveday *et al.* (1989)
Dominant lethal mutation, mice *in vivo*	–		125	Epstein *et al.* (1972)
Aneuploidy, mouse germ cells *in vivo*	+		275	Costa *et al.* (1988)
Nitrilotriacetic acid, disodium salt				
Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	–	NT	941	Toyokuni *et al.* (1995)
Sister chromatid exchange, Chinese hamster lung V79 cells *in vitro*	–	NT	358	Hartwig *et al.* (1993)
DNA damage (8-hydroxydeoxyguanosine formation), rat kidney *in vivo*	–		100 ip × 1	Umemura *et al.* (1990)
Nitrilotriacetic acid, trisodium salt				
Echerichia coli PQ37, SOS chromotest	–	–	NR	Venier *et al.* (1987)
Escherichia coli WP2, differential toxicity	+	+	250	Venier *et al.* (1987)
Salmonella typhimurium TA100, TA98, TA1535, TA1537, TA1538, reverse mutation	–	–	10 000 µg/plate	Dunkel *et al.* (1985)

Table 1 (contd)

Test system	Results[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Nitrilotriacetic acid, trisodium salt (contd)				
Salmonella typhimurium TA100, TA98, TA1535, TA1537, TA1538, reverse mutation	–	–	870 µg/plate	Loprieno *et al.* (1985)
Salmonella typhimurium TA100, reverse mutation	–	–	870 µg/plate	Venier *et al.* (1987)
Escherichia coli WP2 *uvr*A, reverse mutation	–	–	10 000 µg/plate	Dunkel *et al* (1985)
Escherichia coli WP2 *uvr*A, reverse mutation (fluctuation test)	–	–	100 000	Venier *et al.* (1987)
Saccharomyces cerevisiae, gene conversion	–	–	40	Loprieno *et al.* (1985)
Aspergillus nidulans, genetic crossing-over	–	NT	10 930	Crebelli *et al.* (1986)
Schizosaccharomyces pombe, forward mutation	–	–	40	Loprieno *et al.* (1985)
Aspergillus nidulans, forward mutation	–	NT	18 510	Crebelli *et al.* (1986)
Aspergillus nidulans, aneuploidy	–	NT	10 930	Crebelli *et al.* (1986)
Allium cepa, micronuclei	+	NT	550	De Marco *et al.* (1986)
Vicia faba, chromosomal aberrations	+	NT	1375	Kihlman & Sturelid (1970)
Drosophila melanogaster, somatic mutation (and recombination)	(+)		1336	Zordan *et al.* (1991)
Micronucleus formation, Chinese hamster lung Cl-1 cells *in vitro*	+	NT	514	Modesti *et al.* (1995)
Unscheduled DNA synthesis, rat primary hepatocytes *in vitro*	–	NT	1000	Williams *et al.* (1982)
Gene mutation, Chinese hamster lung V79 cells, *hprt* locus *in vitro*	–	NT	1.5	Celotti *et al.* (1987)
Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	–	–	2350	Mitchell *et al.* (1988)
Sister chromatid exchange, Chinese hamster ovary cells *in vitro*	–	NT	1.9	Loprieno *et al.* (1985)
Sister chromatid exchange, Chinese hamster ovary cells *in vitro*	–	NT	1.0	Venier *et al.* (1985)
Sister chromatid exchange, Chinese hamster ovary cells *in vitro*	–	NT	275	Ved Brat & Williams (1984)
Sister chromatid exchange, Chinese hamster ovary cells *in vitro*	–	NT	514	Montaldi *et al.* (1985)
Sister chromatid exchange, mouse lymphocytes *in vitro*	–	NT	257	Montaldi *et al.* (1985)
Chromosomal aberrations, rat kangaroo kidney PT K1 cells *in vitro*	+	NT	688	Kihlman & Sturelid (1970)
Gene mutation, human EUE cells DT^R, *in vitro*	+	NT	3	Grilli & Capucci (1985)

Table 1 (contd)

Test system	Results[a]		Dose[b] (LED or HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Nitrilotriacetic acid, trisodium salt (contd)				
Sister chromatid exchange, human lymphocytes *in vitro*	–	NT	275	Ved Brat & Williams (1984)
Chromosomal aberrations, human lymphocytes *in vitro*	–	NT	2063	Montaldi *et al.* (1988)
Sister chromatid exchange, mouse bone-marrow cells *in vivo*	–		275 ip × 1	Russo *et al.* (1989)
Aneuploidy, mouse bone-marrow cells *in vivo*	–		275 ip × 1	Russo *et al.* (1989)
Micronucleus formation, mouse bone-marrow cells *in vivo*	–		400 ip × 1	Montaldi *et al.* (1988)

[a] +, positive; (+), weakly positive; –, negative; NT, not tested

[b] LED, lowest effective dose; HID, highest ineffective dose; unless otherwise stated, in-vitro test, µg/mL; in-vivo test, mg/kg bw per day; inj, injection; ip, intraperitoneal; NR, not reported

Nitrilotriacetic acid, disodium salt did not induce gene mutation in mouse lymphoma L5178Y *tk*$^{+/-}$ cells or sister chromatid exchange in Chinese hamster lung V79 cells *in vitro*. It did not induce oxidative DNA damage in rat kidney cells *in vivo*.

Nitrilotriacetic acid, trisodium salt gave negative results in the bacterial SOS DNA repair assay but induced differential toxicity in various repair-deficient *Escherichia coli* WP2 strains. It did not induce gene mutation in *Salmonella typhimurium* TA100, TA1535, TA1537, TA1538 or TA98 or in *E. coli* WP2 *uvrA* with or without exogenous metabolic activation. It did not induce gene conversion, crossing-over, forward mutation or aneuploidy in yeast and fungi without exogenous metabolic activation or gene conversion or forward mutation with exogenous metabolic activation. Nitrilotriacetic acid, trisodium salt induced micronuclei and chromosomal aberrations in plant cells, but it did not give rise to micronuclei in Chinese hamster lung cells *in vitro*. It weakly induced somatic mutation in *D. melanogaster*. It did not induce unscheduled DNA synthesis in rat primary hepatocytes in the absence of metabolic activation. Nitrilotriacetic acid, trisodium salt did not induce gene mutation at the *hprt* locus of Chinese hamster lung V79 cells without exogenous metabolic activation or at the *tk* locus of mouse lymphoma L5178Y cells with or without exogenous metabolic activation. It did not induce sister chromatid exchange in Chinese hamster ovary cells or mouse lymphocytes *in vitro*. Nitrilotriacetic acid, trisodium salt induced chromosomal aberrations in rat-kangaroo kidney cells *in vitro* without exogenous metabolic activation and gene mutation in human cells *in vitro*. It did not induce sister chromatid exchange or chromosomal aberration in human lymphocytes *in vitro*. It did not induce micronuclei or aneuploidy *in vivo* in mice treated with a single intraperitoneal injection.

4.5 Mechanistic considerations

The nephrocarcinogenic effects of nitrilotriacetic acid in rats and mice appear to be related to dose-dependent changes in Zn^{++} homeostasis. Orally administered nitrilotriacetic acid and its trisodium salt were nephrotoxic to rats and mice of each sex. The toxicity occurs at high doses and appears to be due to Zn^{++} accumulation secondary to the chelating properties of nitrilotriacetic acid. Administration of zinc nitrilotriacetic acid or Zn^{++} accentuated the nephrotoxicity of nitrilotriacetic acid.

Nitrilotriacetic acid has urothelial effects only in rats and at doses higher than those required for nephrotoxicity and proliferative effects. Although the mechanism of induction of the urothelial effects is not known, they are not related to Zn^{++} homeostasis but rather correlate with depletion of cellular calcium and possibly the formation of nitrilotriacetic acid-containing microcrystals.

The renal and urothelial effects of nitrilotriacetic acid are associated with cellular toxicity and regenerative hyperplasia. Its toxic, regenerative proliferative and tumorigenic effects occur only at high doses. No direct genotoxic effect appears to be involved.

None of 12 renal-cell carcinomas in rats treated with ferric nitrilotriacetate acid had mutations in codons 12, 13 or 61 of the H-, K- and N-*ras* genes. Only one high-grade

tumour contained a CGC→CTC transversion in codon 246 of the *p53* gene (Nishiyama *et al*., 1995).

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Exposure to nitrilotriacetic acid and its salts occurs during their production, formulation and use in synthetic laundry and dishwashing detergents and related products as metal chelating and sequestering agents.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

Nitrilotriacetic acid was tested for carcinogenicity by oral administration in the diet to mice and rats. It induced renal tubular tumours (adenomas and adenocarcinomas) in mice of each sex and in male rats and transitional-cell and squamous-cell carcinomas of the urinary bladder, hepatocellular adenomas and adrenal phaeochromocytomas in female rats.

The trisodium salt was tested for carcinogenicity in mice and rats by oral administration. When administered in the diet as the monohydrate, it induced haematopoietic tumours in male mice and benign and malignant tumours of the urinary system (kidney, ureter and bladder) in rats of each sex. When administered in drinking-water to male rats, it induced renal tubular adenomas and adenocarcinomas.

In two-stage studies of carcinogenicity in male rats treated by oral administration, nitrilotriacetic acid and its trisodium salt increased the incidence of urinary-tract tumours after pretreatment with various *N*-nitrosamines.

5.4 Other relevant data

Nitrilotriacetic acid is absorbed in mammals, but it is not metabolized and is excreted rapidly by filtration in the kidney.

Orally administered nitrilotriacetic acid and its trisodium salt were nephrotoxic to rats and mice of each sex. Toxicity occurs at high doses and appears to be due to Zn^{++} accumulation secondary to the chelating properties of nitrilotriacetic acid; administration of Zn^{++} accentuated the nephrotoxicity of the acid. Urothelial cytotoxicity and regenerative hyperplasia were seen in male and female rats but not in mice, and only at doses higher than those that produced nephrotoxicity. The mechanism is unclear but appears to involve cellular Ca^{++} depletion secondary to the chelating effect of nitrilotriacetic acid. Urinary microcrystals were also produced.

Nitrilotriacetic acid does not induce developmental toxicity in rats, rabbits or mice exposed during gestation and gave negative results in short-term assays to screen for teratogenesis in two cellular assays in *Drosophila* larvae and frog embryos.

No data were available on the genetic and related effects of nitrilotriacetic acid or its salts in humans. Nitrilotriacetic acid and its disodium and trisodium salts were not genotoxic in experimental systems *in vivo*, except that the acid induced aneuploidy in mouse germ cells. Neither the acid nor its salts were genotoxic in mammalian cells *in vitro* and they were not mutagenic to bacteria.

5.5 Evaluation

There is *inadequate evidence* in humans for the carcinogenicity of nitrilotriacetic acid and its salts.

There is *sufficient evidence* in experimental animals for the carcinogenicity of nitrilotriacetic acid and its salts.

Overall evaluation

Nitrilotriacetic acid and its salts *are possibly carcinogenic to humans (Group 2B)*.

6. References

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