Nitrilotriacetic acid and salts: Human health tier II assessment

10 March 2017

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Glycine, N,N-bis(carboxymethyl)-	139-13-9
Glycine, N,N-bis(carboxymethyl)-, tripotassium salt	2399-85-1
Glycine, N,N-bis(carboxymethyl)-, trisodium salt	5064-31-3

Preface

This assessment was carried out by staff of the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) using the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework.

The IMAP framework addresses the human health and environmental impacts of previously unassessed industrial chemicals listed on the Australian Inventory of Chemical Substances (the Inventory).

The framework was developed with significant input from stakeholders and provides a more rapid, flexible and transparent approach for the assessment of chemicals listed on the Inventory.

Stage One of the implementation of this framework, which lasted four years from 1 July 2012, examined 3000 chemicals meeting characteristics identified by stakeholders as needing priority assessment. This included chemicals for which NICNAS already held exposure information, chemicals identified as a concern or for which regulatory action had been taken overseas, and chemicals detected in international studies analysing chemicals present in babies' umbilical cord blood.

Stage Two of IMAP began in July 2016. We are continuing to assess chemicals on the Inventory, including chemicals identified as a concern for which action has been taken overseas and chemicals that can be rapidly identified and assessed by using Stage One information. We are also continuing to publish information for chemicals on the Inventory that pose a low risk to human health or the environment or both. This work provides efficiencies and enables us to identify higher risk chemicals requiring assessment.

The IMAP framework is a science and risk-based model designed to align the assessment effort with the human health and environmental impacts of chemicals. It has three tiers of assessment, with the assessment effort increasing with each tier. The Tier I assessment is a high throughput approach using tabulated electronic data. The Tier II assessment is an evaluation of risk on a substance-by-substance or chemical category-by-category basis. Tier III assessments are conducted to address specific concerns that could not be resolved during the Tier II assessment.

These assessments are carried out by staff employed by the Australian Government Department of Health and the Australian Government Department of the Environment and Energy. The human health and environment risk assessments are conducted and published separately, using information available at the time, and may be undertaken at different tiers.

This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

For more detail on this program please visit:**www.nicnas.gov.au**

Disclaimer

ACRONYMS & ABBREVIATIONS

Grouping Rationale

The chemicals in this group are known as nitrilotriacetic acid (NTA) and its trisodium and tripotassium salts, trisodium nitrilotriacetate (trisodium NTA) and tripotassium nitrilotriacetate (tripotassium NTA). The trisodium salt also occurs as its monohydrate form (trisodium nitrilotriacetate monohydrate; CAS No. 18662-53-8). The chemical NTA is an aminocarboxylic acid with three functional carboxylate groups. The chemical forms water-soluble complexes with multivalent metal ions. The chemical NTA and trisodium NTA dissociate to form a common moiety, nitrilotriacetate ion. Thus the systemic toxicity of these chemicals is similar (Health Canada, 2010; SCCS 2010). Tripotassium NTA is considered to be functionally similar to trisodium NTA.

The chemicals, NTA and trisodium NTA are used to soften water and to remove traces of heavy metals. These chemicals are commonly used as chelating and sequestering agents, and as builders in detergent and cleaning formulations for domestic and commercial use (EU RAR, 2008; SCCS, 2010).

Import, Manufacture and Use

Australian

The National Pollutant Inventory (NPI) holds data for all sources of trisodium NTA in Australia.

The chemical NTA has reported commercial use as a chelating agent (to replace phosphate) in laundry detergents as identified in Australia by the National Health and Medical Research Council (NHMRC, 2011).

Trisodium NTA has reported non-industrial use as a listed medicine, approved for topical use only in concentrations not exceeding 0.005 % by Australia's Therapeutic Goods Administration (TGA, 2007).

No specific use, importation, or manufacturing information has been identified for tripotassium NTA.

International

The following international uses have been identified through Galleria Chemica; the European Union (EU) Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) dossiers; the Substances and Preparations in Nordic countries (SPIN) database; the United States (US) Department of Health and Human Services Household Products Database (US HHPD); the US Environmental Protection Agency's Aggregated Computer Toxicology Resource (ACToR); the US National Library of Medicine's Hazardous Substances Data Bank (HSDB); and various international assessments including World Health Organisation - Drinking water report (WHO, 1996); Health Canada Screening Report (Health Canada, 2010); the EU Risk Assessment Report (EU RAR, 2008); and the US National Toxicology Program (NTP, 1977).

Trisodium NTA has reported cosmetic uses as an ingredient in:

- makeup;
- fragrances;
- hair shampoo; and
- skin cleanser for body and face.

The chemicals, NTA and trisodium NTA have reported domestic uses as ingredients in:

- phosphate-free laundry detergents; and
- soaps.

The chemicals, NTA and trisodium NTA have reported commercial uses, including:

- as boiler feed-water additives;
- as chelating agents;
- in textile processing; and
- in water treatment.

The chemicals, NTA and trisodium NTA have reported site-limited uses:

- as sequestering agents;
- as eluting agents;
- in processing rubber;
- in emulsion polymerisation; and
- in paper and pulp processing.

No specific international use, importation, or manufacturing information has been identified for tripotassium NTA. Tripotassium NTA is most likely to have similar uses as trisodium NTA. However, tripotassium NTA is not listed on the INCI directory.

Restrictions

Australian

No known restrictions have been identified.

International

No known restrictions have been identified.

Existing Worker Health and Safety Controls

Hazard Classification

Trisodium NTA is classified as hazardous, with the following risk phrases for human health in the Hazardous Chemicals Information System (HCIS) (Safe Work Australia):

Acute toxicity – category 4; H302 (Harmful if swallowed)

Eye irritation – category 2; H319 (Causes serious eye irritation)

Carcinogenicity – category 2; H351 (Suspected of causing cancer).

NTA and tripotassium NTA are not listed on HCIS.

Exposure Standards

Australian

The chemical NTA has an Australian drinking water guideline value of 0.2 mg/L (NHMRC, 2011; FSANZ).

International

The following exposure standards are identified (Galleria Chemica; Protective Action Criteria (PAC)):

Temporary Emergency exposure limits (TEELs) defined by the US Department of Energy (DOE):

TEEL-1= 3.7 - 9.2 mg/m^3;

TEEL-2= 40 - 100 mg/m^3;

TEEL-3= 220 - 110 mg/m^3.

Health Hazard Information

The chemicals dissociate to form the nitrilotriacetate ion, considered to be the moiety responsible for systemic toxicity. The systemic toxicity of all three chemicals is expected to be similar, however; the chemical NTA will have different local toxicity to trisodium NTA and tripotassium NTA due to their differing pH. Local effects associated with the alkaline trisodium NTA are not applicable to NTA.

Toxicokinetics

The chemicals, NTA and trisodium NTA are rapidly absorbed from the gastrointestinal tract and eliminated in the urine at different rates in different species. These chemicals are not metabolised in mammals and are excreted unchanged (but chelated to metals such as calcium) in the urine. Deposition of NTA in bone and kidney has been reported (IARC, 1995; WHO, 1996). In male Wistar rats, about 50 % of the applied trisodium NTA dose was rapidly excreted in urine, and the half-life was calculated to be 5-6 hours (REACHb).

After oral administration of 10 mg radiolabelled NTA in gelatin capsules in eight human volunteers, blood concentrations peaked around one to two hours after ingestion. Excretion of the administered dose was mainly in the faeces (77 %); in urine

(approximately 12 %) as unchanged chemical and in exhaled air (< 0.1 %).

Around 87 % of the absorbed quantity of NTA was excreted within 24 hours in the urine (Health Canada, 2010).

After oral intubation of 20 mg/kg bw NTA in dogs, 2 to 3 μg/g of NTA were found in bone and 0.43 μg/g were found in kidney after 72 hours (EU RAR, 2008; Health Canada, 2010).

Acute Toxicity

Oral

Trisodium NTA is classified as hazardous with hazard category 'Acute Toxicity – category 4' and hazard statement 'Harmful if swallowed' (H302) in the HCIS (Safe Work Australia). The available data (median lethal dose—LD50 of 1470 mg/kg bw in female rats and 750 mg/kg bw in monkeys) support this classification. Reported signs of toxicity include ataxia, tremors, hypopnoea, hypothermia, hypoactivity, prostration, staggering, twitching, opisthotonus, tonic convulsion, apathy, salivation and dyspnoea. Available data for NTA indicate an LD50 >6400 mg/kg in rats.

In a acute oral toxicity study conducted similarly to OECD Test Guideline (TG) 401, trisodium NTA was administered to Wistar rats (five animals/sex/dose) at 1000, 1470, 2150 or 2610 mg/kg bw by gavage. Eight animals in the 2610 mg/kg bw dose group, 7 animals in the 2150 mg/kg bw dose group, and 5 animals in the 1470 mg/kg bw dose group died after 14 days of exposure. Clinical signs in all treated animals included abnormal positioning, staggering, twitching, opisthotonus, tonic convulsions, piloerection and salivation for up to 15 mins post exposure and dyspnoea, apathy and poor general health state for up to four hours. Gross pathological examination showed hyperaemic glandular stomach and mucosa with multiple haemorrhagic erosions. The reported oral LD50s were 1470 mg/kg bw for females (EU RAR, 2008; REACHb).

In another study, NTA was administered in rats (strain not specified) (20 animals/sex/dose) at 200, 1600, 3200 or 6400 mg/kg bw/day by gavage and observed for 14 days. Animals in the 200 and 1600 mg/kg bw/day groups showed reversible accelerated breathing and high-stepping gait immediately after exposure. Clinical signs observed in 3200 and 6400 mg/kg bw/day dose groups showed accelerated breathing, high-stepping gait and disturbed behaviour followed by deterioration of health, crusty eyes and noses, intermittent breathing and intensively ruffled fur. An LD50 >6400 mg/kg bw was reported (REACHa).

In two different studies in mongrel dogs, dogs (groups of four/dose) were administered trisodium NTA (80 % aqueous suspension) by stomach tube at 1000, 2500 or 5000 mg/kg bw. Potent emetic activity of the chemical was observed in both studies. An LD50 >5000 mg/kg bw was reported (EU RAR, 2008).

In an acute oral toxicity study, rhesus monkeys (2 animals/dose) were orally administered aqueous solution of trisodium NTA at 500, 1000 or 2000 mg/kg bw. One animal in the 500 mg/kg bw dose group and one animal in the 1000 mg/kg bw dose group vomited immediately after treatment. One animal in the 1000 mg/kg bw dose group and two animals in the 2000 mg/kg bw dose group showed decrease in motor activity post treatment followed by paralysis and death. Mild irritation and haemorrhagic lesions in the stomach were seen in the gross pathological examination. An LD50 of 750 mg/kg was reported (EU RAR, 2008).

Dermal

The chemicals have low acute toxicity based on results from an animal test in rabbits following dermal exposure.

In an acute dermal toxicity study, a 25 % aqueous solution of trisodium NTA monohydrate was applied occlusively to intact skin of rabbits (one animal/sex/dose) at 1000, 1580, 2510, 3980, 6310 or 10000 mg/kg bw. Mild muscle weakness and reduction in activity and appetite were seen in the higher dose groups. No local symptoms or muscular uncoordination were reported. An LD50 of >10,000 mg/kg bw was reported (EU RAR, 2008; REACHa & b).

Inhalation

The chemicals have low acute toxicity based on results from animal tests following inhalation exposure. A median lethal concentration (LC50) in rats of >5.0 mg/L was reported for NTA (EU RAR, 2008; Health Canada, 2010; SCCS, 2010).

In an acute inhalation study, male albino rats were exposed to NTA as an aerosol at 3.3, 3.6 or 5.0 mg/L for four hours and observed for 14 days. Salivation, slow laboured respiration, partially closed eyes and hypoactivity were seen in all treated animals. The effects were fully reversed post-treatment. A LC50 of >5.0 mg/L was reported (EU RAR, 2008; REACHa).

In another acute inhalation toxicity study, mice were exposed to NTA aerosols at concentrations of 0.22, 1.09, 1.41 or 7.6 mg/L for 5 minutes. Animals in the 0.22 mg/L dose group showed slight sensory irritation. Moderate sensory irritation was reported in the 1.09 and 1.41 mg/L dose groups. Animals at the highest dose (7.6 mg/L) showed severe sensory irritation (EU RAR, 2008).

Corrosion / Irritation

Respiratory Irritation

The chemical, NTA is slightly irritating to the respiratory system of animals. The effects were not sufficient to warrant a hazard classification.

The chemical, NTA was tested for respiratory irritation in male rats (10 animals/dose) at 0, 0.002, 0.02, 0.2 or 2 mg/L for 6 hours/day for 4 days. No mortalities were reported. Animals in the high doses showed sensory signs of respiratory irritation, which were reversed after 14 days (EU RAR, 2008).

Skin Irritation

Trisodium NTA is slightly irritating to the animal skin. The effects were not sufficient to warrant a hazard classification.

In a Draize test, a 25 % aqueous solution of trisodium NTA monohydrate was applied to intact skin of three albino rabbits under occlusion. Slight to well-defined erythema and slight oedema was observed 24 hours after application. Mean erythema, oedema and irritation scores at 24, 48 and 72 hours were 2.3, 1.3 and 1.0 respectively. The redness was fully reversed in three days. All signs of irritation were reversed in five days (EU RAR, 2008; SCCS, 2010; REACHb).

In an other study, trisodium NTA (finely ground powder or 10 % aqueous solution) was applied to skin of albino rabbits (1-2/sex) and the animals were observed for five days. No irritation was reported (REACHb).

Eye Irritation

Trisodium NTA is classified as hazardous with hazard category 'Eye Irritation – category 2A' and hazard statement 'Causes serious eye irritation' (H319) in HCIS (Safe Work Australia). The available data support this classification.

In an eye irritation study in rabbits, trisodium NTA was found to be irritating. Conjunctivitis and marked corneal effects were observed at 24, 48 and 72 hours after application (ECHA, 2006). Effects were not reversible within the 7-day period.

In a study, albino rabbits had considerable discomfort immediately after application of 100 mg of trisodium NTA monohydrate. Effects observed one hour after application included copious discharge, oedema with partial eversion of the lids, moderate redness and congestion with obscure iris. Discharge and oedema reduced on washing the eyes with saline solution after 24 hours. Complete reversal oedema occurred but mild redness and slight corneal dullness were observed on days 5 to 7 (EU RAR, 2008; Health Canada, 2010; SCCS, 2010; REACHb).

In another study conducted according to OECD Test Guideline (TG) 405, trisodium NTA (0.1 mL of 38 % solution) applied to the conjunctival sac of three albino rabbits caused slight eye irritation. The average scores for conjunctival redness and chemosis after 24 hours were 2.0 and 0.7, respectively. The conjunctival redness score was 0.1 after 48 hours and no chemosis was present. The conjunctival redness was reversible within 8 days after application. No effects on the cornea and iris were reported (EU RAR, 2008; Health Canada, 2010; SCCS, 2010; REACHb).

Sensitisation

Skin Sensitisation

Based on the available data, the chemicals are not considered to be skin sensitisers.

In a Buehler test using guinea pigs (20 test animals and 10 controls), 0.5 mL of 50% NTA in distilled water (92.4 % purity) was used for induction treatments on days 0, 7 and 14. No skin reactions were noted at the challenge treatment of 50 % (EU RAR, 2008; Health Canada, 2010; SCCS, 2010; REACHa & b).

The chemical NTA (50 % formulation in distilled water for topical induction and challenge) did not cause responses in a Buehler study in guinea pigs (EU RAR, 2008; SCCS, 2010).

Observation in humans

In a closed patch test conducted on 66 human volunteers, a 1 % aqueous solution of a liquid detergent containing 20 % NTA was applied on the upper arm of human subjects. The patches were removed 24 hours after application and skin reactions were graded after 48 to 96 hours. No sensitisation was observed in the volunteers (Health Canada, 2010; SCCS, 2010).

Repeated Dose Toxicity

Oral

The available data suggest that the chemicals have harmful effects following repeated oral dosing, based on results from animal tests. However, the effects were not sufficient to warrant hazard classification.

In a 4-week study, Charles River and Fischer 344 (F344/N) (five or ten animals/group) rats were fed either 0 % or 1.5 % NTA in the diet. Effects observed included reduced growth, increased relative kidney weight, urinary calcium, haematuria and hydronephrosis. A lowest observed adverse effect level (LOAEL) of 1.5 % NTA (equivalent to 750 mg/kg bw/day) was reported (EU RAR, 2008; Health Canada, 2010).

In a 10-week study in male Sprague Dawley (SD) rats, trisodium NTA was administered to the rats in drinking water at 0 %, 0.01 %, 0.1 % or 1 % (equivalent to 0, 10, 100 or 1000 mg/kg bw/day). Increased kidney weights were observed in the rats treated at 0.1 % (100 mg/kg bw/day) and marked vacuolisation of the renal tubules was observed at 1 % trisodium NTA (1000 mg/kg bw/day dose) group. A LOAEL of 100 mg/kg bw/day (0.1 % trisodium NTA) was reported (EU RAR, 2008; Health Canada, 2010; SCCS, 2010).

Trisodium NTA was administered to male SD rats by gavage at 0, 0.73 or 7.3 mmol/day (equivalent to 0, 187 or 1876 mg/kg bw/day) for 30 days. Cytoplasmic vacuolisation, focal haemorrhage, necrosis, erosion and hyperplasia of the epithelium of the proximal convoluted tubules were observed in all treated animals. An oral LOAEL of 0.73 mmol/day (187 mg/kg bw/day) was reported (EU RAR, 2008; Health Canada, 2010; SCCS, 2010; REACHb).

In a 90-day study in rats (strain not reported), NTA was administered to male rats at 0, 100, 1000 or 5000 mg/L in drinking water. All treated animals showed reduced serum potassium levels (EU RAR, 2008; Health Canada, 2010).

Dermal

In two different studies (28-days and 91-days), New Zealand White (NZW) rabbits (six/group) were treated with either 0 or 2.5 % trisodium NTA on intact or abraded skin. No treatment-related effects were observed with or without abrasion (EU RAR, 2008; Health Canada, 2010; SCCS, 2010; REACHa & b).

Inhalation

In a 4-week repeated dose inhalation toxicity study, NTA was administered in SD rats, trueblood albino guinea pigs and cynomolgus monkeys at 0, 10, 213 or 343 mg/m^3 concentrations for 6 hours/day by whole body exposure. No respiratory irritation or discomfort was observed at the highest tested concentration. The only treatment-related effects included diarrhoea in monkeys and dyspnoea in rats and guinea pigs. The no observed adverse effect concentration (NOAEC) of 213 mg/m^3 and the lowest observed adverse effect concentration (LOAEC) of 343 mg/m^3 were reported (EU RAR, 2008; Health Canada, 2010; REACHa & b).

In another study, male albino rats were treated with NTA at 0, 2, 20, 200 or 2000 mg/m^3 concentrations for 6 hours/day for four consecutive days by inhalation exposure. All animals in the 2000 mg/m^3 showed signs of nasal, respiratory and eye irritation, which were fully reversed on day 14 (EU RAR, 2008; Health Canada, 2010).

Genotoxicity

Based on the weight of evidence from the available in vitro and in vivo genotoxicity studies, the chemicals are not considered to be genotoxic. Several in vitro and in vivo micronucleus tests for gene mutation and clastogenicity were negative, although several positive results were reported (IARC, 1990; IARC, 1995; EU RAR, 2008; Health Canada, 2010; SCCS, 2010; REACHa & b).

In vitro studies

The chemical NTA was negative for genotoxicity in *Salmonella (S.) typhimurium* strains TA97, TA98, TA100, TA102, TA104, TA1535, TA1537 and TA1538 at concentrations 33–2000 μg/plate and *Escherichia coli* WP2 uvrA at concentrations of 0.01–1000 μg/test without metabolic activation (EU RAR, 2008; Health Canada, 2010; SCCS, 2010).

Trisodium NTA was negative for genotoxicity in *S. typhimurium* strains TA98, TA100, TA102, TA104, TA1535, TA1537 and TA1538 and TK locus assay in mouse L5178Y lymphoma cells, with and without metabolic activation at concentrations of 3–10000 μg/plate (EU RAR, 2008, Health Canada, 2010).

In a chromosome aberration test, NTA was tested for genotoxicity in rat and human kidney cells at concentrations of 1800–5600 μmol. Both the cell types showed positive results with slight toxicity at the highest dose (EU RAR, 2008; Health Canada, 2010; SCCS, 2010; REACHa).

Trisodium NTA was positive without metabolic activation in a cell transformation assay in Syrian hamster embryo (SHE) cells at concentrations up to 3 mg/mL (REACHa).

Trisodium NTA was negative for genotoxicity in two mouse lymphoma assays, with and without metabolic activation at doses of 125–1900 μg/mL. Some cytotoxic effects were observed with the highest dose (EU RAR, 2008; Health Canada, 2010; SCCS, 2010; REACHa).

Trisodium NTA was not genotoxic in a HPRT test without metabolic activation at concentrations of 0.1–15 mmol/L (EU RAR, 2008; Health Canada, 2010; SCCS, 2010; REACHa).

In vivo studies

The chemical NTA gave negative results for genotoxicity in gene mutation and recombination assays, and positive results for DNA damage (doses of 29–87 mg/kg intraperitoneal (i.p.)) and chromosomal damage assay at doses of 87-926 mg/kg (EU RAR, 2008; Health Canada, 2010; SCCS, 2010; REACHa).

Trisodium NTA was negative for genotoxicity in micronuclei formation assays in NMRI mice at doses 500-2000 mg/kg and chromosomal damage assay in spermatocytes of NMRI mice at dose of 275 mg/kg i.p. injection. (EU RAR, 2008; Health Canada, 2010; REACHa & b).

The chemical NTA was positive for genotoxicity in a DNA fragmentation and micronucleus formation assay in kidney cells at 490 mg/kg bw/day for 3 days and in urinary bladder cells at 490 or 735 mg/kg bw in male SD rats (EU RAR, 2008, Health Canada, 2010).

In a dominant lethal assay in Swiss mice, NTA was tested at an oral dose of 1 g/kg bw/day for 5 days or a single i.p. injection of 125 mg/kg bw. The chemical NTA was negative for genotoxicity (Health Canada, 2010; SCCS, 2010, REACHa & b).

Carcinogenicity

Trisodium NTA is classified as hazardous with hazard catergory 'Carcinogenicity – Category 2' and hazard statement ‘Suspected of causing cancer’ (H351) in the HCIS (Safe Work Australia). The available data support the classification for trisodium NTA. Additionally, the classification for carcinogenicity is considered appropriate for NTA.

The International Agency for Research on Cancer (IARC) has classified NTA and its salts as ‘Possibly carcinogenic to humans’ (Group 2B), based on inadequate evidence for carcinogenicity in humans, but sufficient evidence for carcinogenicity in animal tests (IARC, 1990; IARC, 1995).

In two-year carcinogenicity studies in Charles River (CD) rats and B6C3F1 mice, oral administration of Na_3NTA induced benign and malignant tumours of the urinary system in both male and female rats at 80–100 mg/kg bw/day and haematopoietic tumours in male mice at 500–600 mg/kg bw. Trisodium NTA was reported to induce renal tubular adenomas and adenocarcinomas in male rats when administered orally (IARC, 1990; IARC, 1995; EU RAR, 2008; Health Canada, 2010; SCCS, 2010; REACHa & b).

In a carcinogenicity study in B6C3F1 mice and F344/N rats, NTA induced renal cell adenocarcinomas in both male and female mice at a dose range of 1400–1800 mg/kg bw, renal cell tumours in male rats and transitional, squamous cell carcinomas of the urinary bladder, hepatocellular adenomas and adrenal phaeochromocytomas in female rats at doses of 800–1100 mg/kg bw (IARC, 1990; IARC, 1995; EU RAR, 2008; Health Canada, 2010; SCCS, 2010; REACHa & b).

The chemicals, NTA and trisodium NTA increased the incidences of urinary-tract tumours in male Wistar rats in other two-stage studies and accelerated urinary system tumour development was seen in animals pre-treated with nitrosamines in 28–30 weeks studies at 10000 ppm (EU RAR, 2008; Health Canada, 2010; SCCS, 2010; REACHa & b).

The chemical NTA is a chelating agent causing alterations in zinc and calcium cation distribution in the urinary tract at higher doses. Available data suggest that dose-dependent changes in the Zn++ homeostasis secondary to the chelating properies of NTA is responsible for accentuating the nephrotoxicity of NTA. However, the cellular toxicity and regenerative hyperplasia associated with urothelial effects of NTA are seen only at high doses and are related to depletion of cellular calcium and formation of NTA-containing microcrystals (Health Canada, 2010; IARC, 1990; IARC, 1995; SCCS, 2010).

Reproductive and Developmental Toxicity

Based on the available information, the chemicals do not cause specific reproductive or developmental toxicity.

In different two-generation reproductive and developmental toxicity studies, oral administration of up to 0.5 % trisodium NTA (equivalent to 450 mg/kg bw/day) in the diet of Charles River rats, up to 250 mg/kg bw/day trisodium NTA by gavage in pregnant NZW rabbits, and up to 0.2 % NTA (equivalent to 570 mg/kg bw/day) in drinking water in Naval Medical Research Institute (NMRI) mice, caused no significant maternal, embryonic or foetal effects. No effect on neonatal development was seen in any of the above studies (NTP, 1977; IARC, 1995; EU RAR, 2008; Health Canada, 2010; SCCS, 2010; HSDB; REACHa & b).

In a developmental study, female NZW rabbits (groups of 20) were treated by gavage with trisodium NTA in drinking water at 0, 2.5, 25, 100 or 250 mg/kg bw/day during gestation days 7–16. All animals were sacrificed on day 28 of gestation. No treatment-related effects were observed (EU RAR, 2008; Health Canada, 2010; SCCS, 2010; REACHa & b).

A study was conducted in pregnant NMRI albino mice (10 animals/group) treated with 0 or 0.2 % trisodium NTA (equivalent to 0 or 570 mg/kg bw/day) in drinking water on 6–18 days of gestation. No significant differences in maternal weight gains and no developmental effects were observed (EU RAR, 2008; Health Canada, 2010; SCCS, 2010; REACHa & b).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation include systemic long-term effects (carcinogenicity) for all three chemicals, and systemic acute effects (acute toxicity from oral exposure) and local effects (eye irritation) for trisodium NTA and tripotassium NTA only.

Public Risk Characterisation

Although use in cosmetic and domestic products in Australia is not known, the chemicals are reported to be used in cosmetic and domestic products overseas (see **Import, manufacture and use**). Considering the range of domestic and cosmetic products that could contain these chemicals, the main route of public exposure is expected to be through the skin and eyes, inhalation from products applied as cosmetics, and from using domestic products.

While the chemicals have various uses, the chemicals are not expected to be present in sufficiently high concentrations in these products to lead to toxic effects. The known uses of the chemicals overseas are stated to be up to 5 % concentration in cosmetic and domestic products (SCCS, 2010).

Therefore, the risk to public health is not considered to be unreasonable and further risk management is not considered necessary for public safety.

Occupational Risk Characterisation

Given the critical systemic long-term health effects, the chemicals could pose an unreasonable risk to workers unless adequate control measures to minimise dermal, ocular and inhalation exposure are implemented. The chemicals should be appropriately classified and labelled to ensure that a person conducting a business or undertaking (PCBU) at a workplace (such as an employer) has adequate information to determine the appropriate controls.

Based on the available data, the hazard classification in the HCIS (Safe Work Australia) is considered appropriate.

NICNAS Recommendation

Assessment of these chemicals are considered to be sufficient, provided that the recommended amendment to the classification is adopted, and labelling and all other requirements are met under workplace health and safety and poisons legislation as adopted by the relevant state or territory.

Regulatory Control

Work Health and Safety

The chemicals are recommended for classification and labelling aligned with the Globally Harmonised System of Classification and Labelling of Chemicals (GHS) as below. This does not consider classification of physical hazards and environmental hazards.

This is the existing classification for Trisodium NTA (CAS No. 5064-31-3). The classification for carcinogenicity applies to all three chemicals in this group. However, the hazardous category 'acute toxicity – category 4 (H302)' and 'Eye irritation – category 2A (H319)' only applies to trisodium NTA and tripotassium NTA and should not be applied to NTA as the local effects of trisodium and tripotassium NTA are due to their alkalinity.

From 1 January 2017, under the model Work Health and Safety Regulations, chemicals are no longer to be classified under the Approved Criteria for Classifying Hazardous Substances system.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Acute Toxicity	Not Applicable	Harmful if swallowed - Cat. 4 (H302)
Irritation / Corrosivity	Not Applicable	Causes serious eye irritation - Cat. 2A (H319)

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Carcinogenicity	Not Applicable	Suspected of causing cancer - Cat. 2 (H351)

[a] Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)].

[b] Globally Harmonized System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third Edition.

[*] Existing Hazard Classification. No change recommended to this classification

Advice for consumers

Products containing the chemicals should be used according to the instructions on the label.

Advice for industry

Control measures

Control measures to minimise the risk from oral exposure to the chemicals should be implemented in accordance with the hierarchy of controls. Approaches to minimise risk include substitution, isolation and engineering controls. Measures required to eliminate, or minimise risk arising from storing, handling and using a hazardous chemical depend on the physical form and the manner in which the chemicals are used. Examples of control measures that could minimise the risk include, but are not limited to:

- using closed systems or isolating operations;
- health monitoring for any worker who is at risk of exposure to the chemicals, if valid techniques are available to monitor the effect on the worker's health;
- air monitoring to ensure control measures in place are working effectively and continue to do so;
- minimising manual processes and work tasks through automating processes;
- work procedures that minimise splashes and spills;
- regularly cleaning equipment and work areas; and
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemicals.

Guidance on managing risks from hazardous chemicals are provided in the *Managing risks of hazardous chemicals in the workplace—Code of practice* available on the Safe Work Australia website.

Personal protective equipment should not solely be relied upon to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk. Guidance in selecting personal protective equipment can be obtained from Australian, Australian/New Zealand or other approved standards.

Obligations under workplace health and safety legislation

Information in this report should be taken into account to help meet obligations under workplace health and safety legislation as adopted by the relevant state or territory. This includes, but is not limited to:

- ensuring that hazardous chemicals are correctly classified and labelled;
- ensuring that (material) safety data sheets ((M)SDS) containing accurate information about the hazards (relating to both health hazards and physicochemical (physical) hazards) of the chemicals are prepared; and
- managing risks arising from storing, handling and using a hazardous chemical.

Your work health and safety regulator should be contacted for information on the work health and safety laws in your jurisdiction.

Information on how to prepare an (M)SDS and how to label containers of hazardous chemicals are provided in relevant codes of practice such as the *Preparation of safety data sheets for hazardous chemicals—Code of practice* and *Labelling of workplace hazardous chemicals—Code of practice*, respectively. These codes of practice are available from the Safe Work Australia website.

A review of the physical hazards of these chemicals has not been undertaken as part of this assessment.

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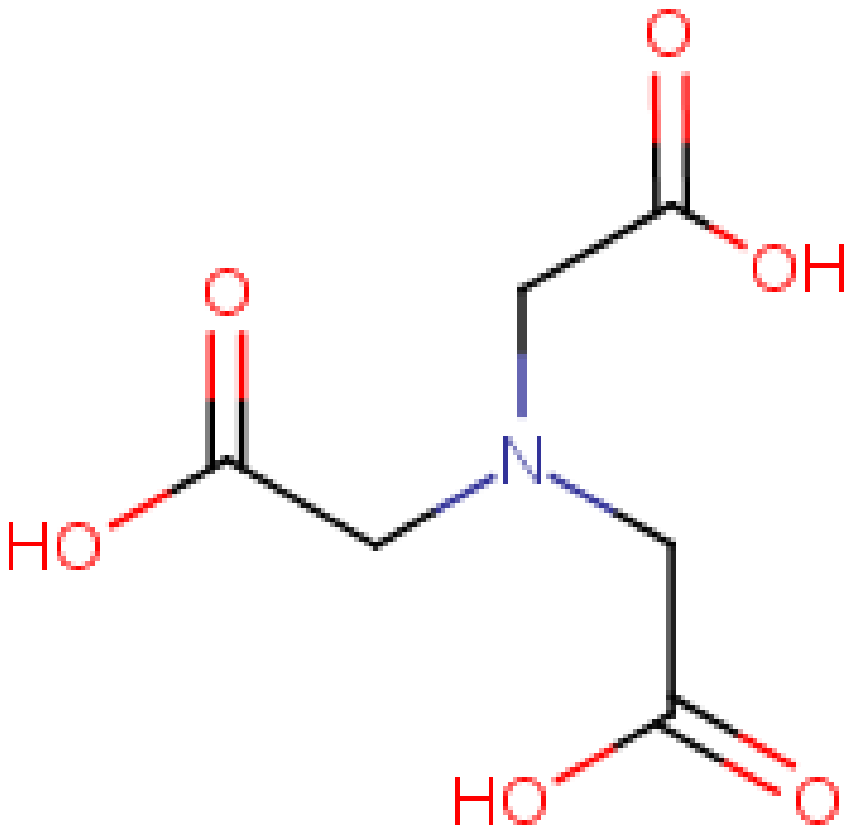
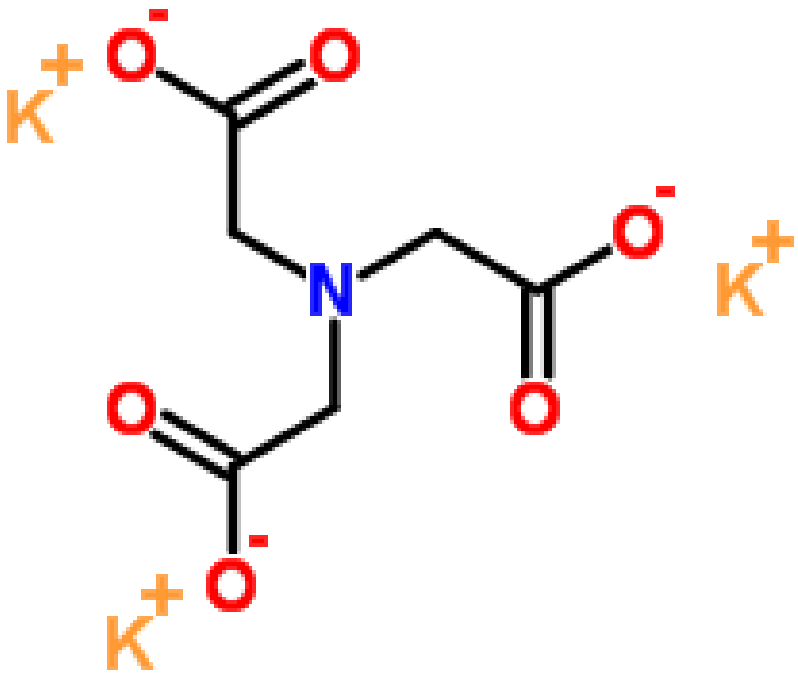
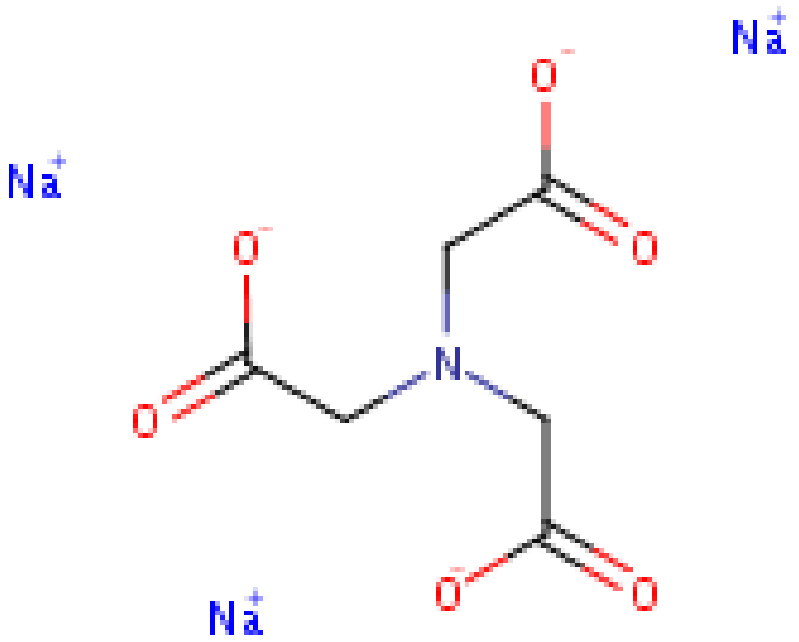
Last Update 10 March 2017

Chemical Identities

Chemical Name in the Inventory and Synonyms	**Glycine, N,N-bis(carboxymethyl)-** NTA triglycollamic acid triglycine nitrilotriacetic acid
CAS Number	139-13-9
Structural Formula	
Molecular Formula	C6H9NO6
Molecular Weight	191.1

Chemical Name in the Inventory and Synonyms	**Glycine, N,N-bis(carboxymethyl)-, tripotassium salt** NTA, K3 tripotassium NTA
CAS Number	2399-85-1
Structural Formula	
Molecular Formula	C6H9NO6.3K
Molecular Weight	304.5

Chemical Name in the Inventory and Synonyms	**Glycine, N,N-bis(carboxymethyl)-, trisodium salt** trisodium NTA trisodium nitrilotriacetate nitrilotriacetic acid, trisodium salt sodium nitriloacetate
CAS Number	5064-31-3
Structural Formula	

	
Molecular Formula	C6H9NO6.3Na
Molecular Weight	257.0

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