Citric acid: Human health tier II assessment

28 June 2013

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
1,2,3-Propanetricarboxylic acid, 2-hydroxy-	77-92-9
1,2,3-Propanetricarboxylic acid, 2-hydroxy-, monohydrate	5949-29-1

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

Citric acid and citric acid monohydrate are both listed on AICS under separate CAS numbers. The toxicity of the two substances is expected to be identical.

Import, Manufacture and Use

Australian

Citric acid is listed on the 2006 High Volume Industrial Chemicals List (HVICL) with a total reported volume of 1000–9999 tonnes (NICNAS, 2006).

Citric acid has reported cosmetic use including:

- cleaning and washing agents; and
- additives.

Citric acid and citric acid monohydrate have reported domestic use including:

- cleaning agents.

Citric acid has reported site-limited use including:

- the manufacture of other chemicals.

International

Citric acid is a natural substance that appears as an intermediate in the basic physiological citric acid cycle (Krebs cycle) in every eukaryotic cell (including human cells). It is also naturally occurring at high levels, for example, in citrus juices. It has been produced for many years in high volumes. Current global production is estimated to approach 1000000 tonnes per year.

The following international uses have been identified through the European Union Registration, Evaluation and Authorisation of Chemicals (EU REACH) dossier; the Organisation for Economic Cooperation and Development Screening Information Data Set International Assessment Report (OECD SIAR); Galleria Chemica; Substances and Preparations in the Nordic countries (SPIN) database; the European Commission Cosmetic Ingredients and Substances (CosIng) database; United States (US) Personal Care Product Council International Nomenclature of Cosmetic Ingredients (INCI) Dictionary, and the US National Library of Medicine's Hazardous Substances Data Bank—HSDB.

Citric acid and citric acid monohydrate have reported cosmetic use as:

- perfumes and fragrances;
- makeup such as eye makeup, nail polish, rouges, face powders and lipsticks;
- hair care products such as shampoos, rinses, sprays and straighteners;
- skin care products such as aftershave lotions, cleansers, moisturisers, baby products and sunscreens; and
- oral care products such as mouthwashes and breath fresheners.

Citric acid has reported domestic use including in:

- detergents and cleaning products;
- polishes and wax blends;
- fillers, putties, plasters and modelling clay;
- adhesives and sealants; and
- coatings and paints, thinners and paint removers.

Citric acid monohydrate has reported domestic use including in:

- cleaning and washing agents;
- softeners;
- absorbents/adsorbents;
- anti-freeze agents; and
- anti-static agents.

Citric acid has reported commercial use including:

- as a processing aid;
- in the formulation of corrosion inhibition products, photographic developer products, textile or leather treatment products;
- in heat-transfer fluids, hydraulic fluids, metalworking fluids;
- as a water treatment chemical; and
- in oil extraction processes.

Citric acid monohydrate has reported commercial use including:

- as a mordant to brighten colours;

- in electroplating and surface treatment;
- in surface-active agents, complexing and flocculating agents;
- in construction materials;
- in explosives;
- in fillers, fixing agents, odour agents, oxidising agents; and
- pH-regulators.

Restrictions

Australian

No known restrictions for citric acid or citric acid monohydrate have been identified.

International

Citric acid is listed on (Galleria Chemica):

- the Health Canada List of prohibited and restricted cosmetic ingredients (The Cosmetic Ingredient "Hotlist"). Citric acid is permitted at total concentrations equal to or less than 10%, with a pH equal to or greater than 3.5.

Existing Worker Health and Safety Controls

Hazard Classification

Neither citric acid nor citric acid monohydrate are listed on the Hazardous Substances Information System (HSIS) (Safe Work Australia).

Exposure Standards

Australian

No specific exposure standards are available for citric acid or citric acid monohydrate.

International

No specific exposure standards are available for citric acid or citric acid monohydrate.

Health Hazard Information

This review will largely focus on local effects arising from the acidity of citric acid and citric acid monohydrate. The citrate ion has been determined to pose no systemic hazards to human health [Identification of Chemicals of Low Concern to Human Health, 2013].

Toxicokinetics

Toxicokinetics for citric acid and citric acid monohydrate are expected to be the same given that citric acid is present in aqueous solutions in the human body.

In human (as well as in animal and plant) physiology, citric acid is a very common intermediate in one of the central biochemical cycles that takes place in every cell. Thus, in humans approximately 2 kg of citric acid are formed and metabolised every day. This physiological pathway is very well developed and capable of processing very high amounts of citric acid as long as it occurs in low concentrations. Part of the circulating (mainly metabolic but also ingested) citric acid is excreted in urine, with 24-hour urine reference values between 1.5 and 3.68 mmol, corresponding to 0.29–0.71 g citric acid excreted per person per day (OECD, 2001).

Acute Toxicity

Oral

Based on the available information for citric acid, no hazard classification for acute oral toxicity is recommended.

Citric acid was of low acute oral toxicity in animal tests following oral exposure. The median lethal dose (LD50) in rats ranges from 3000 to 12000 mg/kg bw. Observed sub-lethal effects included physiological disturbances (acidosis and calcium deficiency), while high doses caused nervous system effects as well as severe damage to the stomach mucosa (OECD, 2001).

Dermal

Citric acid was of low acute toxicity in rats, with a median lethal dose (LD50) greater than 2000 mg/kg bw, following dermal exposure in tests conducted in accordance with OECD Test Guideline 402 (REACH).

Inhalation

No data on citric acid or citric acid monohydrate are available.

Observation in humans

Ingestion of a single dose of 25 g of citric acid by a woman (corresponding to approximately 417 mg/kg) caused vomiting and nearly led to death in one reported case. Volunteers given oral doses of potassium or magnesium citrate corresponding to approximately 4.7 g of citric acid did not suffer any overt gastrointestinal effects (OECD, 2001).

Corrosion / Irritation

Respiratory Irritation

Neither citric acid nor citric acid monohydrate are classified as hazardous in the HSIS. Human and animal data support classification of citric acid with the risk phrase 'Irritating to respiratory system' (R37). This would also apply to citric acid monohydrate.

Inhalation of citric acid aerosols may induce coughing and bronchoconstriction in humans (OECD, 2001).

Citric acid (concentration and application not stated) caused bronchoconstriction in dogs with nonspecific airway hyperreactivity. Coughing is reported for guinea pigs exposed for 30 minutes to atmospheric citric acid concentrations of 81 mg/m³ (aerosolised 6 % solution). Coughing was also produced in guinea pigs exposed to 75 mg citric acid/mL as an aerosol for 3 minutes. Coughing was also caused by instillation of 1 mL of an approx. 5.2 % solution to the lower trachea in lambs, but not by instillation to the mid-trachea or laryngeal area.

Skin Irritation

Neither citric acid nor citric acid monohydrate are classified as hazardous in the HSIS. Although animal data indicate that citric acid is not irritating, human data support classification of this with the risk phrase 'Irritating to skin' (R38). This would also apply to citric acid monohydrate.

Irritant skin dermatitis attributed to citric acid has been reported amongst waiters and bakers. While presumably aqueous solutions (2 % in one case, not stated in the other) may produce pain or “sting”, patch testing of 60 eczema patients with 2.5 % citric acid in petrolatum did not produce any irritant or allergic reactions; thus, the reaction appears to reflect mainly the acid effect of the substance, which in unbuffered 2 % to 2.5 % aqueous solution results in a pH of approximately 2 (OECD, 2001).

Local effects of citric acid to the skin (rabbit) are reported as slightly irritating in two studies and as not irritating in a third study using a 30 % aqueous solution (OECD, 2001).

Eye Irritation

Neither citric acid nor citric acid monohydrate are classified as hazardous in the HSIS. Human and animal data support classification of citric acid with the risk phrase 'Irritating to eyes' (R36). This would also apply to citric acid monohydrate. Although there is some evidence of severe and permanent damage to eyes arising from non-standard tests or tests conducted with little reported information on the study, this is not sufficient to warrant a higher classification.

In a recent study, the application of 0.1 mL of a 30 % solution of citric acid to one eye resulted in well-defined moderate conjunctival irritation which disappeared in two of the three treated rabbits within 14 days; additionally, a short-lasting superficial lesion of the conjunctival epithelium was noted, but macroscopical alteration of the cornea was not observed. When tested with a 10 % solution of citric acid, the chemical was found to be minimally irritating (OECD, 2001).

These results were supported by another study in rabbits tested in accordance with OECD TG 405 which found citric acid to be highly irritating. In this study, average results at 24, 48 and 72 hours after exposure gave scores of 2.8 for the cornea, 0.0 for the iris and 1.7 for the conjunctiva (OECD, 2001).

One nonstandard study using a 2 % aqueous solution of citric acid applied continuously for 30 minutes found severe and permanent injury to rabbit eyes including severe dense opacification (OECD, 2001). However, this nonstandard study was not considered for hazard evaluation.

Severe eye damage was described in a patient who was splashed in the eye with a saturated solution of citric acid (OECD, 2001).

Sensitisation

Skin Sensitisation

Based on the available information on citric acid, no hazard classification for sensitisation is recommended.

Patch testing of 60 eczema patients with 2.5 % citric acid in petrolatum did not produce any irritant or allergic reactions. Genuine sensitisation to citric acid seems to be a rare phenomenon (OECD, 2001).

Repeated Dose Toxicity

Oral

Considering the no observed adverse effect levels (NOAELs) available from 2-year rat studies (1200–2000 mg/kg bw/d), and based on the treatment-related effects reported in various repeat dose toxicity studies using relatively high doses in mice, guinea pigs, rabbits, dogs and pigs, citric acid is not considered to cause serious damage to health from repeated oral exposure.

A 2-year chronic oral study in rats being given 5 % (approximately 2000 mg/kg bw/d) or 3 % citric acid in feed (approximately 1200 mg/kg bw/d) found slightly decreased growth in the higher dosage group but no tissue abnormalities in the major organs. A NOAEL of 1200 mg/kg bw/d was determined. Similarly, NOAELs of 1500 mg/kg bw/d (rabbit) and of 1400 mg/kg bw/d (dog) have been determined for citric acid (OECD, 2001).

Dermal

No data are available.

Inhalation

No data are available.

Observation in humans

The main effects relating to consuming large and/or frequent doses of citric acid in humans relate to its acidity and strong chelating properties potentially leading to dental erosion or effects on how the body handles metals. However, these effects are only seen at relatively large doses.

In general, citric acid is a strong chelating agent, the dietary uptake of which may interfere with biological availability, absorption and excretion of metals. Further, loss of superficial enamel and erosion of teeth as well as local irritation result from frequent ingestion of citric acid in beverages including natural fruit juices; citric acid fumes were reported to apparently affect the teeth of exposed workers (OECD, 2001).

The average daily intake of citric acid from natural sources in the diet and food additives was estimated at about 40 mg/kg bw for women, 130 mg/kg bw for infants and 400 mg/kg bw for individuals on slimming diets; maximum daily intake is reported to reach levels of 500 mg/kg bw. No formal ADI (acceptable daily intake) level has been specified for citric acid and its common salts by the Joint FAO/WHO Expert Committee on Food Additives nor by the EC Scientific Committee for Food (OECD, 2001).

Genotoxicity

Based on the available information, no hazard classification for mutagenicity is recommended.

Citric acid was not found to be mutagenic or genotoxic in several in vitro and in vivo tests including bacterial mutation assays with and without metabolic activation, in vitro chromosomal aberration assays and a dominant lethal assay with male rats being treated up to 3000 mg/kg/d for 5 days (OECD, 2001).

Carcinogenicity

Based on the available information no hazard, classification for carcinogenicity is recommended.

In a study with only 20 male rats receiving up to 5 % citric acid in the feed (approximately 2000 mg/kg bw/d) for 2 years no evidence of carcinogenicity was reported. In a further study with rats fed 1.7 % sodium citrate (approximately 740 mg/kg bw/d) for 8 weeks no increase in DNA synthesis, a measure of cell proliferation, in the bladder epithelium was found. Various studies concluded that citric acid does not act as a tumour promoter (OECD, 2001).

Reproductive and Developmental Toxicity

Based on the available information, no hazard classification for reproductive or developmental toxicity is recommended.

Four tests on rats using doses up to 2500 mg/kg bw/day, including a two-generation 90 days study with male and female rats, showed no adverse effects on reproductive parameters or teratogenicity. Similar findings of no effects were reported for two reproductive and teratogenicity studies in mice receiving either 5 % citric acid (approx. 7500 mg/kg bw/d; in the range of published acute LD50) previous, during and after mating (NOEL = 7500 mg/kg bw/d) or 241 mg/kg bw/d during days 6–15 of pregnancy. Further, there were no indications of teratogenicity or other adverse effects in female hamsters receiving 272 mg citric acid/kg bw (presumably daily) during days 6–10 of pregnancy nor in female rabbits receiving up to 425 mg/kg bw/d during days 6–18 (NOEL = 425 mg/kg bw/d) (OECD, 2001).

Risk Characterisation

Critical Health Effects

The critical health effects for risk characterisation of citric acid citric acid monohydrate are local effects (skin, eye and inhalation irritation).

Public Risk Characterisation

The public may be exposed to citric acid and citric acid monohydrate through cosmetic use. In cosmetic products, the pH is expected to be much lower than that of simple solutions of these chemicals. In domestic uses, given the low hazard of these chemicals, they are not considered to pose an unreasonable risk to public health.

Occupational Risk Characterisation

The data available for citric acid and citric acid monohydrate support an amendment to the hazard classification in HSIS (refer to **Recommendation section**).

NICNAS Recommendation

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

Regulatory Control

Work Health and Safety

Citric acid and citric acid monohydrate are recommended for classification and labelling under the current approved criteria and adopted GHS as below. This assessment does not consider classification of physical hazards and environmental hazards.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Irritation / Corrosivity	Irritating to eyes (Xi; R36) Irritating to skin (Xi; R38) Irritating to respiratory system (Xi; R37)	Causes serious eye irritation - Cat. 2A (H319) Causes skin irritation - Cat. 2 (H315) May cause respiratory irritation - Specific target organ tox, single exp Cat. 3 (H335)

[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 industry

Control measures

Control measures to minimise the risk from dermal, inhalation or ocular exposure to citric acid and citric acid monohydrate 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 which may minimise the risk include, but are not limited to:

- using local exhaust ventilation to prevent either chemical from entering the breathing zone of any worker;
- 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 either chemical.

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 assist with meeting 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 chemical 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 either chemical has not been undertaken as part of this assessment.

References

ChemIDPlus Advanced. Accessed June 2013 at http://chem.sis.nlm.nih.gov/chemidplus/

Cosmetics Directive (CosIng). Accessed June 2013 at http://ec.europa.eu/consumers/cosmetics/cosing

eChemPortal. Accessed June 2013 at http://www.echemportal.org/echemportal/substancesearch/substancesearchlink.action.

Galleria Chemica. Accessed June 2013 at http://jr.chemwatch.net/galleria/

Hazardous Substances Data Bank (HSDB). US National Library of Medicine. Accessed June 2013 at http://toxnet.nlm.nih.gov.

Health Canada List of Prohibited and Restricted Cosmetic Ingredients (Hotlist). Accessed June 2013 at http://www.hc-sc.gc.ca/cps-spc/cosmet-person/indust/hot-list-critique/index-eng.php

Human & Environmental Risk Assessment on Ingredients of Household Cleaning Products 2003. Citric acid and salts. Accessed June 2013 at http://www.heraproject.com/files/37-F-05-HERA_citricacid_version1_April05.pdf

NICNAS 2006. Australian High Volume Industrial Chemicals List (AHVICL). Accessed June 2013 at http://www.nicnas.gov.au/Industry/Australian_High_Volume_Industrial_Chemicals/NICNAS_AHVICL_2006_PDF.pdf

OECD 2001. SIAR on Citric acid (77-92-9). Accessed June 2013 at http://www.inchem.org/documents/sids/sids/77929.pdf.

Personal Care Products Council (INCI Dictionary). Accessed June 2013 at http://www.ctfa-gov.org/jsp/gov/GovHomePage.jsp

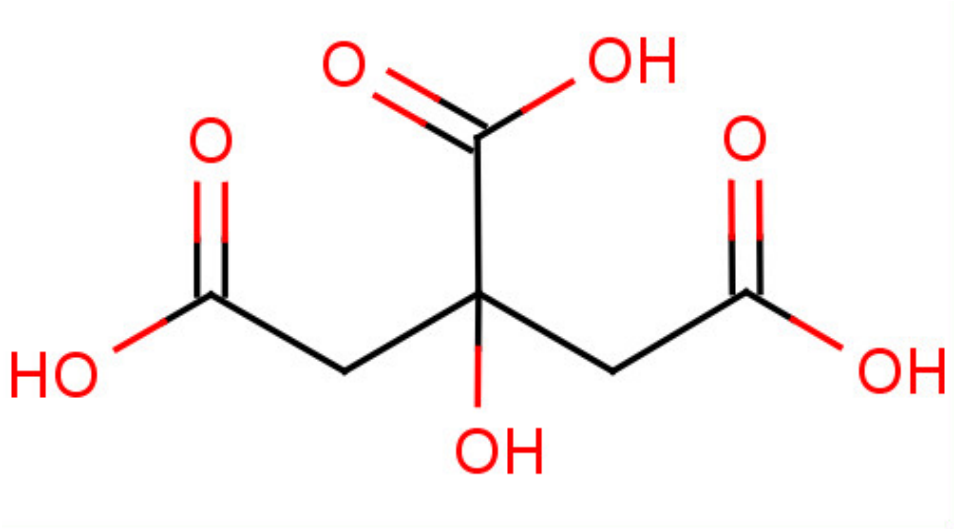
REACH Dossier. Citric acid (77-92-9). Accessed June 2013 at http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances (REACH)

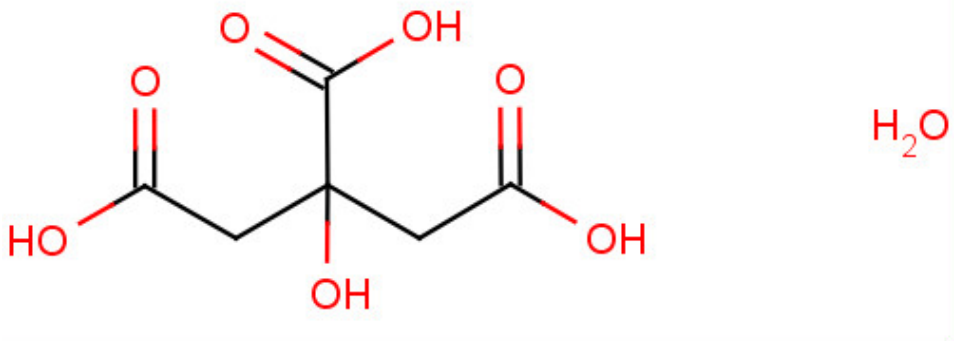
Substances in Preparations in Nordic Countries (SPIN). Accessed June 2013 at http://188.183.47.4/dotnetnuke/Home/tabid/58/Default.aspx

US Department of Health and Human Services, Household Products Database (HHPD), Health and safety information on household products. Accessed June 2013 at http://householdproducts.nlm.nih.gov/.
Last Update 28 June 2013

Chemical Identities

Chemical Name in the Inventory and Synonyms	**1,2,3-Propanetricarboxylic acid, 2-hydroxy-** 2-Hydroxy-1,2,3-propanetricarboxylic acid 2-Hydroxypropane-1,2,3-tricarboxylic acid CITRIC ACID
CAS Number	77-92-9
Structural Formula	

	
Molecular Formula	C6H8O7
Molecular Weight	192.12

Chemical Name in the Inventory and Synonyms	**1,2,3-Propanetricarboxylic acid, 2-hydroxy-, monohydrate** Citric acid monohydrate 1,2,3-Propanetricarboxylic acid, 2-hydroxy-, monohydrate
CAS Number	5949-29-1
Structural Formula	
Molecular Formula	C6H8O7.H2O
Molecular Weight	210.14

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