FOREWORD INTRODUCTION

CITRIC ACID

CAS N°:77–92–9

SIDS Initial Assessment Report

for

11th SIAM

(Orlando, Fla., January 2001)

Chemical Name:	Citric acid
CAS No.:	77–92–9
Sponsor Country:	Switzerland
National SIDS Contact Point in Sponsor Country:	Dr Georg Karlaganis Swiss Agency for the Environment, Forests and Landscape CH–3003 Berne, Switzerland georg.karlaganis@buwal.admin.ch

HISTORY:

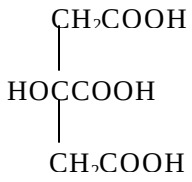
The chemical was chosen by the Sponsor Company and the Swiss authorities in the frame of the ICCA Initiative.

no testing (X)
testing ( )

COMMENTS:

Deadline for Circulation:	10 November 2000
Date of Circulation:	10 November 2000

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	77-92-9
Chemical Name	Citric acid
Structural Formula	

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Based on many experimental data in animals and on human experience, citric acid is of low acute toxicity. The NOAEL for repeated dose toxicity for rats is 1200 mg/kg/d. The major, reversible (sub)chronic toxic effects seem to be limited to changes in blood chemistry and metal absorption/excretion kinetics. Citric acid is not suspected of being a carcinogen nor a reprotoxic or teratogenic agent. The NOAEL for reproductive toxicity for rats is 2500 mg/kg/d. Further, it is not mutagenic *in vitro* and *in vivo*. Also, the sensitising potential is seen as low. In contrast, irritation, in particular of the eyes but also of the respiratory pathways and the skin, is the major toxicological hazard presented by citric acid; this conclusion is confirmed by a series of reports relating to eye and skin irritation.

Environment

Due to its physico-chemical characteristics citric acid is highly mobile in the environment and will partition to the aquatic compartment. Citric acid is rapidly degraded in both sewage works and surface waters and in soil. Citric acid is of low acute toxicity to freshwater fish, daphnia and algae and also to the few marine species tested; longer-term tests show comparable effect values. Similarly, citric acid has no obvious toxic potential against protozoans and many species or strains of bacteria including activated sludge micro-organisms. Based on the available data, citric acid is not judged to be a substance that presents a hazard to the environment.

Exposure

Citric acid is a water soluble organic solid. It is a natural substance that appears as an intermediate in the basic physiological citric acid or Krebs cycle in every eukaryote cell. Citric acid has been produced for many years in high volumes, current global production is estimated to approach 1,000,000 t/a. It has wide dispersive use, being added to processed food and beverages, used in pharmaceutical preparations and in household cleaners as well as in special technical applications.

A large body of physico-chemical, toxicological and environmentally relevant data exists for citric acid, many of which are relatively old and some located only in standard reference works and reviews. While the quality of a single result often may be hard or even impossible to assess, the sheer volume and high congruence of the data result in a uniform picture all the same.

NATURE OF FURTHER WORK RECOMMENDED

No further work recommended.

Full SIDS Summary

CAS No. 77–92–9		Species	Protocol	Results
Physical-Chemical				
2.1	Melting Point		NA	152–159 °C
			NA	~153 °C
2.2	Boiling Point			none; decomposition > 175 °C
2.3	Relative Density		NA	1.665 at 20 °C
2.4	Vapour Pressure			no studies located
			calculated	7.3×10^{-7} Pa (25 °C)
2.5	Partition Coefficient		NA	logPow = –1.72 at 20 °C
2.6	Water solubility		NA	576–771 g/l at 20 °C/room temperature, data from 4 sources
			NA	1330 g/l, "cold water"
	*p*H Value		NA	2.2 at 0.1 *N*
			NA	~1.8 at 50 g/l and 25 °C
	Dissociation Constants		NA	$pKa_1 = 3.13$, $pKa_2 = 4.76$, $pKa_3 = 6.4$
2.11	Oxidation/Reduction Potential			no studies located
2.12	Additional Data: Henry's Law Constant		calculated	$K_H = 2.3 \times 10^{-7}$ Pam^3/mol
Environmental Fate and				
3.1.1	Photodegradation			no studies located
			calculated	$t_{½}$ = 2.3 days in the atmosphere
3.1.2	Stability in Water		calculated	$t_{½}$ = 72.9 years at *p*H 1, stable
3.1.3	Stability in Soil		NA	"substantial disappearance of citrate from soil within 7 days"
3.2	Monitoring Data		background concentration measurement	<0.04–0.2 mg/l, river surface water 0.025–0.145 mg/l, Atlantic coast seawater
3.3.1	Transport			no studies located
3.3.2	Distribution		calculated: fugacity level III (dynamic)	emission 33% each to water, soil and air: 55.76% to water, 44.2% to soil, 0.02% to sediment, 0.02% to air
			calculated: fugacity level I (static)	static equilibrium concentrations: 99.99% to water, <0.01% to soil, <0.01% to sediment, <0.01% to air
3.4	Mode of Degradation in Actual Use		NA	synthesised and metabolised by all eukaryote cells in the Krebs cycle; easily oxidised by common oxidising agents
3.5	Biodegradation		Modified Sturm test	97% (CO_2 evolution), readily biodegradable
			Closed Bottle test	BOD_{30}/COD = 90%, readily biodegradable
			Closed Bottle test	BOD_5 = 526 mg, COD = 728 mg, BOD_5/COD = 0.72, readily
			Closed Bottle test	BOD_5/ThOD = 58%–61% (3 publications), readily
			Closed Bottle test	BOD_1/ThOD = 13%
			Closed Bottle test	BOD_{20}/ThOD = 98%, readily biodegradable

CAS No. 77–92–9		Species	Protocol	Results
			Zahn-Wellens test	85%, 1 day 98%, 7 days; inherently biodegradable
			Coupled Units test	93% (COD removal), ultimately biodegradable
Ecotoxicology				
4.1	Acute/Prolonged Toxicity to Fish	*Carassius auratus*	NA	LC_0 = 625 mg/l, LC_{100} = 894 mg/l, "long-time exposure in hard water"
		Lepomis macrochirus	NA	LC_{50} = 1516 mg/l, 96 h
		Leuciscus idus	NA	LC_{50} = 440–760 mg/l, 96 h, "solution was not neutralised"
4.2	Acute Toxicity to Aquatic Invertebrates	*Daphnia magna*	NA	EC_0 = 80 mg/l, EC_{100} = 120 mg/l, "long-time exposure in soft water"
		Daphnia magna	NA	EC_0 = 1206 mg/l, EC_{50} = 1535 mg/l, EC_{100} = 2083 mg/l (neutralised) EC_0 = 73 mg/l, EC_{50} = 85 mg/l, EC_{100} = 98 mg/l (not neutralised)
		Carcinus maenas (crab)	NA	LC_{50} = 160 mg/l, 48 h
4.3	Toxicity to Aquatic Plants, eg Algae	*Scenedesmus quadricauda*	NA	EC_0 = 640 mg/l, 7 days
		Pavlova lutheri (saltwater	NA	TLC (7d) = 1 – 300 mg/l
		Chaetoceros gracilis	NA	TLC (7d) = 1 – 300 mg/l
4.4	Toxicity to Micro-organisms, eg Bacteria	*Microcystis aeruginosa*	NA	EC_0 = 80 mg/l, 8 days
		Nitrosomonas sp.	NA	no inhibition on NH_3 oxidation at 100 mg/l
		Pseudomonas putida	NA	EC_0 > 10,000 mg/l, 16 h
		37 strains of acidophilic bacteria	NA	positive growth on all strains with 500 mg citric acid/l as sole C source for 30 days at *p*H 3
		Arthrobacter globiformis, 10 strains	NA	good degradation of citric acid as sole C source over 5 days
		Entosiphon sulcatum	NA	EC_0 = 485 mg/l, 72 h
		Tetraselmis tetrathele (saltwater)	NA	TLC (7d) = 1 – 300 mg/l
		Tetramitus rostratus (freshwater)	NA	TLC (35hrs) ≤ 108 mg/l
		Uronema parduzci	NA	TLC = 622 mg/l
4.5.1	Chronic Toxicity to Fish	*Carassius auratus*	NA	LC_0 = 625 mg/l, LC_{100} = 894 mg/l, "long-time exposure in hard water"
4.5.2	Chronic Toxicity to Aquatic Invertebrates	*Daphnia magna*	NA	EC_0 = 80 mg/l, EC_{100} = 120 mg/l, "long-time exposure in soft water"

CAS No. 77–92–9		Species	Protocol	Results
4.6.1	Toxicity to Soil-Dwelling Organisms			no studies located
4.6.2	Toxicity to Terrestrial Plants			all plants produce citric acid
4.6.3	Toxicity to Other Non-Mamm. Terrestrial			no studies located
4.8	Biotransformation and Kinetics			citric acid is an intermediate in the Krebs cycle which takes place in every eukaryote cell
4.9	Additional Remarks			citric acid is “extremely widespread in nature”
				citric acid is “widely distributed in plants and animal tissues and fluids”
				in man, during 24 h approximately 2000 g of citric acid are formed and further metabolised as intermediates of the Krebs cycle in adults
Toxicity				
5.1.1	Acute Oral Toxicity	rat	NA	LD_{50} = 3,000 mg/kg
		rat	NA	LD_{50} = 5,000 mg/kg
		rat	NA	$LD_{50} \geq$ 6,730 mg/kg
		rat	NA	LD_{50} = 12,000 mg/kg
		mouse	NA	LD_{50} = 5,400 mg/kg for males and females; 5 males, 5 females, gavage, 5 concentrations in water, controls
		rabbit	NA	lethal dose = 7,000 mg/kg (probably lowest lethal dose)
5.1.2	Acute Inhalation Toxicity			no studies located
5.1.3	Acute Dermal Toxicity			no studies located
5.1.4	Acute Toxicity, Other Routes	rat	NA	LD_{50} = 5,500 mg/kg by s.c. application
		mouse	NA	LD_{50} = 2,700 mg/kg by s.c. application
5.2.1	Skin Irritation	rabbit	NA	dose = 500 mg/24 h; slightly irritating, effects reported as “mild”
		rabbit	OECD 404	according to guideline; slightly irritating, avg. erythema score = 0.33, oedema = 0
		rabbit	Draize test	0.5 ml of 30% aq. solution for 4 h under occlusive patch produced no effect in intact skin, slight to well defined effect in abraded skin; prim. irritation index = 0.84
		man	clinical report	irritant skin dermatitis in waiters and bakers attributed to citric acid
		man	clinical report	in solution the acid may produce pain if applied to abraded skin
		man	clinical report	a 0.3 *N* solution (~2%) can “sting” intact skin
		man	clinical report	patch testing of 60 eczema patients with 2.5% citric acid in petrolatum (probably 24-h covered contact) did not produce any irritant reactions

CAS No. 77–92–9		Species	Protocol	Results
5.2.2	Eye Irritation	rabbit	NA	irrigation for 30 min with 0.5% or 2% aq. solution caused permanent cloudiness resp. severe dense opacification
		rabbit	NA	750 µg for 24 h caused “severe” effects
		rabbit	OECD 405	according to guideline; avg. cornea score = 2.8; iris = 0.0; conjunctiva = 1.7
CAS No. 77–92–9		**Species**	**Protocol**	**Results**
		rabbit	Draize test	0.1 ml of 10% or 30% aq. solution placed in lower conjunctival sac of 3 animals for 1 s; 10% sol. caused moderate to weak conjunctival irritation for 1 week, avg. Draize score = 9.3; 30% sol. caused well-defined to moderate conjunctival irritation in 2/3 animals for 14 d plus short-lasting superficial lesion of conjunct. epithelium, avg. Draize score =16.0
		man	clinical report	severe eye damage in a man splashed in the eye with saturated aq. solution
5.3	Sensitization	man	clinical report	mouth sores, headache, asthma, nasal blockage, general tiredness. itchiness were reported after the ingestion of foods containinng citric acid
		man	clinical report	citric acid might be a skin sensitizer
5.4	Repeated Dose Toxicity	rat	internal test F. Hoffmann-La Roche Ltd	NOEL = 4,000 mg/kg/d, LD_{50} = 5,600 ± 440mg/kg/d; oral, gavage, once daily for 5 days, post-exposure observation 10 days; 10 males, 10 females, avg. weight = 150 g
		rat	NA	oral, dietary, feed containing 1.2% citric acid, probably ad libitum, for 90 weeks; “...no harmful effects on the growth of two successive generations. No effect on reproduction, blood characteristics, pathology ..., although a slight increase in dental attrition was reported”.
		rat	NA	oral, dietary, feed containing 5% and 3% citric acid for 2 years, slightly decreased growth was observed but no tissue abnormalities were found on examination of the major organs. NOAEL = 1200 mg/kg/d
		rat	NA	oral, dietary, feed containing 1.2, 2.4, 4.8% citric acid for 6 weeks. At the top dose, slight growth reduction, mild blood and urine changes and slight degeneration of the thymus gland and the spleen were observed.

CAS No. 77–92–9		Species	Protocol	Results
		rat	NA	oral, dietary, feed containing 2% citric acid. The absorption and urinary excretion of calcium and magnesium were unaffected, although urinary zinc excretion was temporarily elevated.
		rat	NA	oral, dietary, feed containing 1.2% citric acid for 1 year. No adverse effect were reported (with the possible exception of slight changes in tooth structure) in two successive generations.
		mouse	NA	oral, dietary, feed containing 5% citric acid, probably ad libitum, for unspecified period to male mice; decreased growth and lower survival times in treatment group 11-12 months as opposed to 16-17 months in controls.
		rabbit	NA	oral, dietary, feed containing 7.7% sodium citrate, probably ad libitum, for 150 days to 15 rabbits; no adverse effects were reported
		dog	NA	oral, dietary, fed 1.38 g citric acid/kg bw daily to 3 dogs for up to 120 days; no adverse effects were reported
		guinea pig	NA	oral, dietary supplement with 1–5% citric acid to unknown number of animals for up to 60 days; reduced packed blood cell volume, no histology was performed
		pig	NA	oral, dietary; young pigs fed cadmium-enriched diet containing 5% citric acid; only reported effects were elevated Cd levels in liver and kidneys and decreased zinc level in muscle
		sheep	NA	6 sheep given 795 mg citric acid/kg bw daily via ruminal cannula for uspecified time; no adverse effects were reported
5.5.A	Genetic Toxicity *in vitro*, Bacterial Test	*Salmonella typhimurium*	OECD 471	not mutagenic in 4 defined strains with and without metabolic activation
		Salmonella typhimurium	OECD 471	not mutagenic in 5 defined strains with and without metabolic activation
5.5.B	Genetic Toxicity *in vitro*, Non-Bacterial Test	yeast	"yeast gene mutation assay"	not mutagenic with and without metabolic activation
		Chinese hamster	NA	no clastogenic effects reported in fibroblast culture cells at concentrations up to 1 mg citric acid/ml
5.6	Genetic Toxicity *in vivo*	rat	dominant lethal assay	no mutagenic potential after doses of 3 g/kg (possibly per day) for 5 days
		rat	NA	no chromosomal damage in bone marrow of rats fed up to 3 g/kg/d for 5 days

CAS No. 77–92–9		Species	Protocol	Results
5.8	Toxicity to Reproduction	rat	NA	2-generation study over 90 weeks, oral, dietary, feed containing 1.2% (w/w) citric acid; no harmful effects on growth of two successive generations nor on reproduction parameters, pathology, blood characteristics or calcium levels, only slight dental attrition was reported
		rat	NA	oral, dietary, feed containing 1.2% citric acid plus 0.1% sodium citrate for 29 weeks prior to mating and then for "another few months"; no harmful effects reported
		rat	NA	oral, dietary, feed containing 5% citric acid to female rats prior, during and subsequent to mating; no harmful effects reported NOEL = 2500 mg/kg/d
		rat	NA	oral, 295 mg citric acid/kg/d given to female rats during days 6–15 of pregnancy; no teratogenic or harmful effects reported
		rat	NA	oral, 241 mg citric acid/kg/d given to female rats during days 6–15 of pregnancy; no teratogenic or harmful effects reported
		mouse	NA	oral, dietary, feed containing 5% citric acid to female mice prior, during and subsequent to mating; litter size and survival of offspring were unaffected NOEL = 7500 mg/kg/d
		rabbit	NA	up to 425 mg citric acid/kg given to female rabbits during days 6–18 of pregnancy; no teratogenic or harmful effects reported NOEL = 425 mg/kg/d
		hamster	NA	up to 272 mg citric acid/kg given to female hamsters during days 6–10 of pregnancy; no teratogenic or harmful effects reported
5.9	Developmental Toxicity/ Teratogenicity	rat	NA	oral, > 241 mg citric acid/kg/d given to female rats during days 6–15 of pregnancy; no indication of adverse effects on nidation, foetal survival or abnormalities
		rats and mice	NA	oral, diet, feed contianing 5% citric acid given for unspecified time; no negative effect on litter size or subrvival up to weaning of pups
5.10	Other relevant information	rats, mice, rabbits	NA	citric acid and its salts injected by various routes caused nervous system, lung, spleen and liver effects
		rat	NA	intravenous infusion with sodium citrate solution was shown to increase calcium excretion

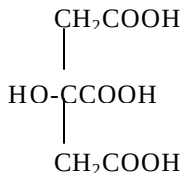
CAS No. 77–92–9		Species	Protocol	Results
		horse	NA	intravenous injection with 0.56 mg sodium citrate/kg bw did not cause any cardiovascular effects or effects on blood composition
		rats, mice, rabbits	NA	Severe damage to the stomach lining and nervous system effects were reported with high doses of citric acid
				citric acid is a powerful chelating agent and there is evidence that dietary citric acid may reduce the biological avilability of iron and calcium
				it has been shown in an in vitro system for the development of artificial caries that the application of citric acid to teeth may make them more susceptible to decay
				citric acid and its salts may increase the absorption and retention of ingested metals such as aluminium, tin, cadmium and lead
		dog	NA	severe ulceration and tissue damage occured in dogs receiving tongue application of 0.1 ml of 50% citric acid solution for 5 minutes
		dog	NA	broncvhoconstriction was induced with citric acid
		guinea-pigs	NA	Coughing was reported when guinea-pigs were exposed for 30 minutes to atmospheric citric acid concentration of 81 mg/m^3
		man		the lowest concentration of inhaled citric acid required to produce involuntary coughing ranged from 0.5 to 32 mg/ml
5.11	Experience with Human Exposure		reference book	total daily consumption of citric acid from natural sources and food additives may exceed 500 mg/kg
			clinical report	after ingesting a single dose of 25 g citric acid (approx. 417 mg/kg) a young woman vomited and almost died
			clinical report, various sources	systemic effects after single exposure through i.v. transfusion of large amounts of citrated blood: depletion of body calcium, effetcs on blood composition, nausea, exacerbation, muscle weakness, breathing difficulties up to cardiac arrest

CAS No. 77–92–9		Species	Protocol	Results
			clinical report, various sources	systemic effects after repeated exposure through oral doses of potassium citrate, either solid or dissolved in water: minor gastrointestinal disturbances, diarrhoea, indigestion, nausea, “burning”
			textbook	potassium and sodium citrate have been used in doses of up to 15 g/d as medications presumably without any marked side effects
			reference book	excretion of citric acid in 82 adults ranges from 1.5 to 3.68 mmol/d (total range 0.4–8.80 mmol/d) respectively from 290 to 707 mg/d (total range 80–1,690 mg/d)

NA = Not available; most of these data are from widely accepted, peer-reviewed secondary sources.

SIDS Initial Assessment Report

1. IDENTITY

Name	Citric acid
CAS No.	77–92–9
Chemical Name	2-Hydroxy-1,2,3-propanetricarboxylic acid
Synonyms	β-Hydroxytricarballylic acid 2-Hydroxypropanetricarboxylic acid
Structure	
Empirical Formula	$C_6H_8O_7$
Molecular Weight	192.12 g/mol
Purity	> 99 % w/w
Melting Point	~153 °C
Boiling Point	not applicable, decomposition above 175 °C
Water Solubility	≥ 576 g/l (20 °C)
Dissociation constants	pKa_1 = 3.13, pKa_2 = 4.76, pKa_3 = 6.4 (25 °C)
n-Octanol/water partition coefficient	log P_{OW} = –1.72 (20 °C)
Vapour Pressure	known to be nonvolatile; no precise data located QSAR estimation: 7.3 x 10^{-7} Pa at 25 °C
Classification	classified as irritating to eyes

Citric acid is a water soluble organic solid with a melting point of approximately 153 °C. It is an ubiquitous natural substance that appears as an intermediate in the basic physiological citric acid cycle in every eukaryote cell. Citric acid has been produced for many years in high volumes and added to processed food and beverages, used in pharmaceutical preparations and in household cleaners as well as in special technical applications.

2. EXPOSURE

2.1 General Discussion

Between 100,000 and 500,0000 tonnes/annum of citric acid is estimated to have been produced in Europe, including Eastern Europe and Israel, in 1999. Global production is estimated by industry to be approaching 1,000,000 t/a. Worldwide, citric acid production is mainly through microbiological fermentation of molasses and sugar solutions, while extraction from lemon juice or chemical synthesis is negligible. Dilute citric acid from filtered fermentation broths is precipitated with milk of lime (calcium hydroxide) as practically insoluble calcium citrate, which is then reacted with sulfuric acid to form citric acid and calcium sulfate (gypsum) as a recoverable and valorisable by-product.

Approximately 50% of the production is estimated to be used by the beverage and soft drinks industry, another 20% in food processing industry and around 10% in pharmaceutical industry, where citric acid is used as an acidulant, buffering agent, taste enhancer and synergist in antioxidant mixtures. Thus, approximately four fifths are destined for human consumption and have a very wide dispersive use. The remainder is split between technical applications in various industries as a complex-forming agent, cleaning agent, softening agent, decalcifying agent, derusting agent, corrosive agent and synergist in antioxidant mixtures; many of those applications also have wide dispersive use, eg, washing powders and detergents. Last, small fractions are used in special applications such as citrate buffering of whole blood samples for transfusion.

2.2 Environmental Partitioning and Fate

Citric acid is exceedingly soluble in water, has relatively low acid dissociation constants that ensure that the substance is at least partly deprotonated in aqueous solution at all environmentally relevant pH values. Additionally, it has a low *n*-octanol/water partition coefficient; no precise information was found on vapour pressure but the melting point is around 153 °C. The result of a QSAR estimation is 7.3×10^{-7} Pa at 25 °C. These properties of citric acid indicate that it is likely to partition mainly into the water phase, with very little distributing into the atmosphere. In addition, due to the high water solubility the substance is unlikely to adsorb onto soil or sediment. Using a level III generic fugacity model (see Table 1) it is predicted that if citric acid is released to water, it is unlikely to partition into other environmental compartments. Release of citric acid to air is likely to lead to distribution into soil and water through deposition processes, while release or deposition onto soil is predicted to lead to redistribution into the aquatic compartment. In corroboration of this prediction, a pure equilibrium partitioning model reflecting only distribution based on free intermedia exchange (but neglecting emission, advection or reaction; Mackay *et al.:* EQC Model v. 1.0, Level I, Environmental Modelling Centre, Trent University, Canada) results in the partitioning of 99.99% to the aquatic compartment.

Table 1: Environmental distribution of citric acid using a level III generic fugacity model [Mackay *et al.:* Level III, Fugacity-based Environmental Equilibrium Partitioning Model, v. 2.2, Environmental Modelling Centre, Trent University, Canada].

Compartment	**Release:**			
	100 % to air	100 % to water	100 % to soil	33 % each to air, water and soil
Air	0.06 %	< 0.01 %	< 0.01 %	0.02 %
Water	38.41 %	99.96 %	36.28 %	55.76 %
Sediment	0.01 %	0.04 %	0.01 %	0.02 %
Soil	61.51 %	< 0.01 %	63.70 %	44.20 %

In the aquatic compartment, citric acid may be expected to be rapidly degraded as it is known to be well biodegradable from several ready and inherent aerobic biodegradation tests (Table 2).

Table 2: Biodegradation test data for citric acid.

Test system	**Results**	**Notes**
Modified Sturm Test	97% (CO_2 evolution) 100% (DOC removal)	readily biodegradable; exposure period not stated
Closed Bottle Test	BOD_{30}/COD = 90%	readily biodegradable
BOD_5/COD Ratio	BOD_5= 526 mg COD = 728 mg BOD_5/COD = 0.72	readily biodegradable; concentration of test substance and activated sludge not stated
BOD_5/ThOD Ratio	BOD_5/ThOD = 58%–61%	readily biodegradable; data from three publications
BOD_1/ThOD Ratio	BOD_1/ThOD = 13%	
BOD_{20}/ThOD Ratio	BOD_{20}/ThOD = 98%	readily biodegradable; initial test substance concentration 720 mg/l
Zahn-Wellens Test	85%, 1 day (DOC removal)	inherently biodegradable
Zahn-Wellens Test	98%, 7 days (DOC removal)	inherently biodegradable
Coupled Units Test	93% (COD removal)	ultimately biodegradable; exposure period not stated

The prediction of extensive and rapid degradation, both in sewage treatment plants and in natural water bodies, is borne out by experimental data confirming double to three times the degradation of low concentrations of citric acid in lake water at *p*H 8 as compared to in distilled water. Monitoring data show that while raw sewage contains up to 10 mg citrate/l, background concentrations in river water range between < 0.04 and maximally 0.2 mg/l, respectively in Atlantic coast surface seawater between 0.025 and 0.145 mg/l. Regarding these surface water concentrations it should be kept in mind that these citrate concentrations do not only derive from manmade citric acid but that citric acid is extremely widespread in nature respectively widely distributed in plants and animal tissues and fluids and that every single eukaryote organism produces citric acid and excretes part of it to the environment.

Estimation of the indirect photolysis using a photochemical hydroxyl radical reaction constant of 7.02 x 10^{-12} cm^3/mol sec and assuming a hydroxyl radical concentration 0.5 x 10^6 OH/cm^3 would result in an atmospheric half life of 2.3 days (Meylan and Howard, Epiwin, SRC).

2.3 Consumer and Occupational Exposure

Industrial releases of citric acid may occur from the sites of production and through use in industrial processes. Consumers are directly exposed to citric acid or its salts in diluted concentrations in many applications from soft drinks and processed food to common household cleaners, detergents, washing powders etc.; there are no acceptable daily intake levels. Occupational exposure may occur during manufacturing and processing of citric acid; there are no recommended occupational exposure levels.

3. HUMAN HEALTH HAZARDS

In human (as well as in animal and plant) physiology, citric acid is a very common intermediate in one of the central biochemical cycles, the Krebs or tricarboxylic acid cycle, which takes place in every cell. It completes the breakdown of pyruvate formed from glucose through glycolysis, thereby liberating carbon dioxide and a further four hydrogen atoms which are picked up by electron transport molecules. Thus, in man 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.

3.1 Acute toxicity

Citric acid has a low acute toxicity by oral application in both rat (LD_{50} = 3,000–12,000 mg/kg, 3 different values) and mouse (LD_{50} = 5,400 mg/kg). General effects comprised physiological disturbances (acidosis and calcium deficiency), while “high” doses caused nervous system effects as well as severe damage to the stomach mucosa.

By subcutaneous application, LD_{50} values of 5,500 mg/kg in rats and 2,700 mg/kg in mice were reported.

Injection of citric acid by various routes in rats, mice and rabbits (no doses stated) caused nervous system, lung, spleen and liver effects that were in part attributed to acidosis and calcium deficiency.

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

Injection of large volumes of citrated blood during transfusion may lead to hypocalcaemia and changes in blood composition with concomitant nausea, muscle weakness, breathing difficulties and even cardiac arrest.

No animal studies are available for acute dermal and acute inhalation toxicity.

3.2 Irritation and sensitisation

3.2.1 Irritation to the skin

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

The application of a 50% citric acid solution to the tongue of dogs for 5 minutes resulted in severe ulceration and tissue damage.

3.2.2 Irritation to the eye

Two nonstandard studies on eye irritation using presumably neat citric acid applied for 24 hours respectively a 2% aqueous solution for 30 minutes found severe and permanent injury to rabbit eyes. In a recent study the application of 0.1 ml of a 30% solution of citric acid to one eye for one second resulted in a well-defined to 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 no macroscopical alteration of the cornea.

In an acute eye irritation/corrosion test in rabbits according to OECD 405 citric acid was highly irritating.

3.2.3 Irritation to the respiratory tract

Citric acid (concentration and application not stated) caused brochoconstriction in dogs with nonspecific airway hyperreactivity.

Coughing is reported for guinea pigs exposed for 30 minutes to atmospheric citric acid concentrations of 81 mg/m^3 (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.

According to current criteria, pure citric acid and aqueous solutions must be judged as irritant to the eyes but not to the skin.

3.2.4 Experience with human exposure

An 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.

Severe eye damage was described in a patient who was splashed in the eye with a saturated solution of citric acid. Mouth ulcers may be provoked by citric acid and inhalation of citric acid aerosols may induce coughing and bronchoconstriction.

Symptoms of possible sensitisation were described in a man after the ingestion of foods containing citric acid; challenge by direct application of citric acid crystals to inside surface of his mouth produced sores, as did some other organic acids, but potassium citrate crystals and magnesium citrate solution did not. In another case, urticaria and mouth ulcers were reported following exposure to citric acid, with no further details given.

A standard textbook implies that citric acid might be a skin sensitizer by recommending patch tests with aqueous solutions to detect sensitised individuals. However, 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.

3.3 Repeated dose toxicity

3.3.1 Animal data

Groups of 10 male and 10 female rats were given 2 g to 16 g/kg/d orally by gavage during 5 days. A NOEL of 4000 mg/kg/d and an LD_{50} of 5600 mg/kg/d were determined.

Groups of 10 male rats being fed up to 4.8% citric acid in feed (corresponding to approx. 4.67 g/kg/d) for 6 weeks showed slight growth reduction and, in the highest-dose group, mild blood and urine parameter changes and slight degeneration of the thymus gland and spleen.

In 9 rats being fed 2% citric acid (approx. 0.13 g/kg/d) no effect on food consumption or body weight was noted nor were the absorption and urinary excretion of calcium and magnesium affected, however, urinary zinc excretion was found to be temporarily elevated.

In male mice being fed 5% citric acid (approx. 7.5 g/kg/d; in the range of published acute LD_{50}) for an unspecified time, decreased growth and lower survival times (11–13 vs. 16–17 months in controls) were reported.

In guinea pigs fed 1–5% citric acid (approx. 0.4–2 g/kg/d) for 60 days, a reduced packed cell volume in the blood was the only effect noted.

No adverse effects were seen in both rabbits and dogs fed approx. 1.5 resp. 1.4 g/kg/d for 150 resp. 120 days.

Body weight gain was unaffected in young pigs fed a cadmium-enriched diet containing 5% citric acid (approx. 4 g/kg/d), but elevated cadmium in the liver and kidneys and decreased zinc levels in muscle were found.

A 2-year chronic oral study in rats being given 5% or 3% citric acid in feed (approx. 2 resp. 1.2 g/kg/d) found slightly decreased growth in the higher dosage group but no tissue abnormalities in the major organs. From the lower dosage a NOAEL of 1200 mg/kg/d results. Similarly, NOAELs of 1500 mg/kg/d (rabbit) and of 1400 mg/kg/d (dog) have been determined.

No adverse effects, with the possible exception of slight changes of tooth structure, were found when two successive generations of rats were fed 1.2% citric acid (approx. 600 mg/kg/d; duration not stated, probably about one year).

3.3.2 Human data

Repeated exposure of up to 15 g/d of potassium and sodium citrate as medications did not cause any reported marked side effects, but minor gastrointestinal disturbances (diarrhoea, indigestion, nausea, “burning”) were experienced by 22 out of 81 patients taking potassium citrate in water and 7 out of 75 taking solid potassium citrate (doses not stated in both groups) for the treatment of renal calculi.

Ingestion of potassium citrate solutions, an unknown but large volume on possibly more that on occasion in one case and 200–400 ml over 5–7 days in two other cases, caused abnormal heart rhythms, which were assessed as probably due to elevated potassium levels rather than to citrate.

Daily ingestion of 6 g of sodium citrate in 10% aqueous solution over 4 days in 10 men affected the blood acid-base balance, with the urine becoming more alkaline and sodium excretion being increasing while magnesium and potassium excretion was decreased.

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.

The average daily intake of citric acid from natural sources in the diet and food additives was estimated at about 40 mg/kg for women, 130 mg/kg for infants and 400 mg/kg for individuals on slimming diets; maximum daily intake is reported to reach levels of 500 mg/kg. 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.

3.4 Mutagenicity

In several *in vitro* and *in vivo* tests citric acid was not mutagenic. The substance was not mutagenic either in bacterial tests with *Salmonella typhimurium* (Ames test, 2 studies) and *Escherichia coli,* with and without metabolic activation. Citric acid was shown to reduce the activity of a recognised chemical mutagen in *S. typhimurium.* No clear indication of mutagenicity was reported from studies with *S. typhimurium* or the yeast *Saccharomyces cerevisiae* living in the body cavity of an unspecified laboratory animal nor in *S. cerevisiae* cell cultures with or without metabolic activation. Neither was chromosomal damage caused by citric acid in human and hamster cell cultures.

A dominant lethal assay with male rats being treated with up to 3 g/kg/d for 5 days was negative; no chromosomal damage occurred in the bone marrow cell of these male rats.

3.5 Reproduction and developmental toxicity

In a two-generation 90 days study with male and female rats fed 1.2 % citric acid no adverse effect on reproductive parameters nor any teratogenicity of dietary citric acid was seen. There were no indications of teratogenic or other adverse effects in three shorter-term reproductive studies in rats with dietary dosage of either 5% citric acid (approx. 2.5 g/kg/d) previous, during and after mating (NOEL = 2500 mg/kg/d), or 295 mg/kg/d (route unspecified) during days 6–15 of pregnancy.

Similar findings of no effects were reported for two reproductive and teratogenicity studies in mice receiving either 5 % citric acid (approx. 7.5 g/kg/d; in the range of published acute LD_{50}) previous, during and after mating (NOEL = 7500 mg/kg/d) or 241 mg/kg/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 (presumably daily) during days 6–10 of pregnancy nor in female rabbits receiving up to 425 mg/kg/d during days 6–18 (NOEL = 425 mg/kg/d).

3.6 Carcinogenicity

In a study with only 20 male rats receiving op to 5% citric acid in the feed (approx. 2 g/kg/d) for 2 years no evidence of carcinogenicity was reported.

In a further study with rats fed 1.7% sodium citrate (approx. 0.74 g/kg/d) for 8 weeks no increase in DNA synthesis, a measure of cell proliferation, in the bladder epithelium was found.

In contrast, several nonstandard studies report an increased incidence of tumours in rats treated with known carcinogens and receiving citric acid or citrate (between 1.4 and 2.6 g citric acid equivalents/kg/d for 20–45 weeks) at the same time. In at least one of the studies with sodium citrate in feed and the carcinogen given in drinking water the observed tumorigenic effect was not attributed to the citrate anion but to the sodium cation causing increased water (and thereby carcinogen) intake; in this and another study, citric acid was judged not to have a tumour-promoting effect, respectively not to be a potent tumour promoter.

4. HAZARDS TO THE ENVIRONMENT

Citric acid was tested in many, although often nonstandard ecotoxicity tests that are widely cited in standard works of literature and in reviewed databases. Table 3 lists the results of aquatic tests.

Table 3: Ecotoxicity of citric acid.

Species	Results	Notes
Fish:		
Carassius auratus, goldfish (freshwater)	LC_0 = 625 mg/l LC_{100} = 894 mg/l	"long-time exposure in hard water", exposure period and method not stated
Leuciscus idus, golden orfe (freshwater)	96-h LC_{50} = 440–760 mg/l	"solution was not neutralised", method not stated
Lepomis macrochirus, bluegill (freshwater)	96-h LC_{50} = 1,516 mg/l	method not stated
Crustaceans:		
Daphnia magna (freshwater)	24-h EC_0 = 1,206 mg/l 24-h EC_{50} = 1,535 mg/l 24-h EC_{100} = 2,083 mg/l 24-h EC_0 = 73 mg/l 24-h EC_{50} = 85 mg/l 24-h EC_{100} = 98 mg/l	neutralised not neutralised
Daphnia magna (freshwater)	EC_0 = 80 mg/l EC_{100} = 120 mg/l	"long-time exposure in soft water", exposure period and method not stated
Carcinus maenas (saltwater) (crab)	48-h LC_{50} = 160 mg/l	method not stated
Algae:		
Scenedesmus quadricauda (freshwater green algae)	7-day TLC = 640 mg/l	toxic limit concentration, method not stated
Pavlova lutheri (saltwater chrysophytes)	7-day TLC = 1–300 mg/l	toxic limit concentration, method not stated
Chaetoceros gracilis, Navicula ramosissima (saltwater diatoms)	7-day TLC = 1–300 mg/l	toxic limit concentration, method not stated
Protozoa:		
Entosiphon sulcatum (freshwater)	72-h EC_0 = 485 mg/l	method not stated
Tetramitus rostratus (freshwater)	35-h TLC ≤ 108 mg/l	toxic limit concentration, exposure period ambiguous, method not stated
Uronema parduczi (freshwater)	TLC = 622 mg/l	toxic limit concentration, exposure period and method not stated
Tetraselmis tetrathele (saltwater)	7-day TLC = 1–300 mg/l	toxic limit concentration, method not stated

Bacteria (all freshwater):		
Microcystis	8-day EC_0 = 80 mg/l	cyanobacteria, method not stated
***Nitrosomonas* sp.**	EC_0 = 100 mg/l	no inhibition of nitrification, exposure period and method not
"37 Strains of bacteria"	all strains positive growth 30-day EC_0 = 500 mg/l	microbes isolated from acidic mine water, *p*H = 3, citric acid as sole carbon source, method not stated
Pseudomonas putida	16-h EC_0 > 10,000 mg/l	method not stated
Arthrobacter globi-formis, 10 strains	good to excellent degradation	microbes isolated from soil, citric acid as sole C source, mineral salts added, exposure period and method

In freshwater, citric acid appears to be of low toxicity to aquatic acute test standard organisms, fish, daphnia and algae, with consistent LC_{50}/EC_{50} values of several hundred milligrams per litre. Many more results refer to toxic limit concentrations or no effect concentrations, from which no dependable EC_{50} can be derived. In a "long-term" daphnia test in "soft water", which may be assumed not to buffer the acid effect of the test substance, the EC_0 was found to be 80 mg/l and the EC_{100} was 120 mg/l, resulting in a geometric mean EC_{50} of 98 mg/l. Similarly, the lowest reported EC_0 in cyanobacteria was 80 mg/l.

Different strains of bacteria showed positive growth respectively good to excellent degradation with citric acid as the sole carbon source and the same holds for sewage sludge micro-organisms that thrive on citric acid.

The few marine species for which data are available seem to be somewhat more sensitive to citric acid, although at 160 mg/l the only acute LC_{50} reported for a crab is over 100 mg/l, while for two algae and a protozoan the subacute toxic limit concentration is only given as a wide range between 1 and 300 mg/l. Still, at least for the few tested organisms citric acid does not seem to be highly or acutely toxic.

The toxicity of citric acid to other environmentally relevant species has not been determined.

5. CONCLUSIONS AND RECOMMENDATIONS

5.1 Conclusions

A large body of physicochemical, toxicological and environmentally relevant data exists for citric acid, many of which are relatively old. While the quality of a single result often may be hard or even impossible to assess, the sheer volume and high congruence of the data result in a uniform picture all the same.

5.1.1 Human Health

Based on wide spectrum of data relating to experimental animals and on human experience citric acid has a low acute toxicity; only one case of near fatal human intoxication was found. In a repeated dose study with rats a NOAEL of 1200 mg/kg/d and a LOAEL of 2000 mg/kg/d have been determined. The major subchronic and chronic toxic effects seem to be limited to changes in blood chemistry respectively metal absorption and excretion kinetics, even at high doses. Citric acid is a powerful chelating agent and there is evidence that dietary citric acid may reduce the biological avilability of iron and calcium. Tooth erosion through dissolution of the enamel due to the acid effect in aqueous solution as well as exposure to citric acid fumes has been reported as a possible adverse consequence of long-term over-exposure to citric acid.

Based on several studies, citric acid is not suspected of being a carcinogen nor a reprotoxic or teratogenic agent. Further, it is not mutagenic *in vitro* and *in vivo*. Judging from the few reports on intolerance also the sensitising potential of citric acid is seen as low.

Irritation, in particular of the eyes, but also the potential for irritation of the respiratory pathways and the skin is the major, if not the only, genuine toxicological hazard presented by citric acid. This conclusion is borne out by a series of reports relating to eye and skin irritation; further, it is also plausible with regard to the use pattern of citric acid, which must be characterised as ranging from closed to quasi-closed system in manufacturing and processing to wide-dispersive and concerning the whole population in its many final uses.

5.1.2 Environment

Due to its physicochemical characteristics citric acid is highly mobile in the environment and will rapidly partition to the aquatic compartment; distribution to soil is of purely temporary nature, while air or sediment constitute negligible sinks.

Based on several laboratory biodegradation tests (both ready and inherent), one field report in lake water and a few monitoring data, citric acid is rapidly degraded in both sewage works and surface waters. In spite of a genuine high-volume production that has been going on for years, with wide dispersive use pattern, no increase in environmental concentrations has been reported.

Citric acid is of low toxicity to freshwater fish, daphnia and algae; reported EC_{50} values range from just below 100 mg/l to several hundreds of milligrams per litre. LC_{50} values for fish range from 440 to 1516 mg/l. The one marine LC_{50} published for a crab is 160 mg/l. Those tests that may qualify as subacute or possibly long-term show comparable effect values. Similarly, citric acid has no obvious toxic potential against protozoans and many species or strains of bacteria. No toxicity to activated sludge micro-organisms

respectively inhibition of substrate biodegradation was reported in various biodegradability tests.

Based on the available data, citric acid is not judged to be a substance that presents a hazard to the environment.

5.2 Recommendation

The chemical is currently of low priority for further work.

I U C L I D Data Set

Existing Chemical	Substance ID: 77-92-9
CAS No.	77-92-9
EINECS Name	1,2,3-Propanetricarboxylic acid, 2-hydroxy-
EINECS No.	201-069-1
Molecular Weight	192.12
Molecular Formula	C6 H8 O7
Producer Related Part	
Company:	F.Hoffmann-La Roche AG
Creation date:	22-MAY-00
Substance Related Part	
Company:	F.Hoffmann-La Roche AG
Creation date:	22-MAY-00
Printing date:	18-OCT-01
Revision date:	
Date of last Update:	**24-SEP-01**
Number of Pages:	**63**
Chapter (profile):	Chapter: 1, 2, 3, 4, 5, 7
Reliability (profile):	Reliability: without reliability, 1, 2, 3, 4
Flags (profile):	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC

1.0.1 OECD and Company Information

Type: sponsor country
Name: Switzerland

07-MAY-01

Type: lead organisation
Name: Swiss Agency for Environment, Forests and Landscape
Partner: Dr Urs Stämpfli **Date:**
Town: 3003 Bern
Country: Switzerland

08-MAY-01

Type: other: Sponsor Company
Name: F.Hoffmann-La Roche Ltd
Partner: Pascal Iltis **Date:**
Street: Grenzacherstrasse
Town: 4070 Basel
Country: Switzerland
Phone: 061-688'11'11
Telefax: 061-691'93'91
Telex: 962'292

08-MAY-01

Type: other: co-sponsors

Remark: ADM (Republic of Ireland), Jungbunzlauer (Switzerland), Gadot(Israel)
03-NOV-00

1.0.2 Location of Production Site

Name of Plant: European Citric Acid Manufacturers (ECAMA) Companies

Country: Belgium, Republic of Ireland, United Kingdom, Austria, Israel
Remark: Companies: Roche, ADM, T&L/Stately, Jungbunzlauer, Gadot
17-OCT-00

1.0.3 Identity of Recipients

1.1 General Substance Information

Substance type: natural substance
Physical status:
Purity: > 99 % w/w
06-DEC-00 (112)

Substance type: organic
Physical status:
Purity: > 99 % w/w
07-DEC-00 (29)

1.1.1 Spectra

1.2 Synonyms

2-Hydroxypropanetricarboxylic acid
06-DEC-00 (35)

beta-Hydroxytricarballylic acid
06-DEC-00 (22)

1.3 Impurities

CAS-No: 7732-18-5
EINECS-No: 231-791-2
EINECS-Name: water
Contents: < 1 % w/w
07-DEC-00 (29) (30)

CAS-No:
EINECS-No:
EINECS-Name: sulfate
Contents: < .15 % w/w
07-DEC-00 (29) (30)

CAS-No:
EINECS-No:
EINECS-Name: oxalates
Contents: < .035 % w/w
07-DEC-00 (29) (30)

CAS-No: 7440-70-2
EINECS-No: 231-179-5
EINECS-Name: calcium
Contents: < .02 % w/w
07-DEC-00 (29) (30)

CAS-No: 7439-89-6
EINECS-No: 231-096-4
EINECS-Name: iron
Contents: < .005 % w/w
07-DEC-00 (29) (30)

CAS-No:
EINECS-No:
EINECS-Name: chloride
Contents: < .005 % w/w
07-DEC-00 (29) (30)

1.4 Additives

CAS-No:
EINECS-No:
EINECS-Name:

Remark: No additives are being used
06-DEC-00 (30)

1.5 Quantity

Production during the last 12 months: yes
Quantity produced :100 000 - 500 000 tonnes in 2000
Country: European Union, Eastern Europe and Israel
25-JUL-00

Production during the last 12 months: yes
Quantity produced :500 000 - 1 000 000 tonnes in 2000
Country: Worldwide
Remark: industry estimate
20-SEP-00

1.6.1 Labelling

Labelling:
Symbols: Xi
R-Phrases: (36) Irritating to eyes
S-Phrases: (24/25) Avoid contact with skin and eyes
06-DEC-00 (35)

1.6.2 Classification

Classification: as in Directive 67/548/EEC
Class of danger: irritating
R-Phrases: (36) Irritating to eyes
06-DEC-00 (35)

1.7 Use Pattern

Type: industrial
Category: other: wide dispersive use
04-SEP-00

Type: industrial
Category: other: soft drinks and beverage industry, approx. 50%
04-SEP-00

Type: industrial
Category: other: food industry, approx. 20%
04-SEP-00

Type: industrial
Category: other: pharmaceutical industry, approx. 10%
04-SEP-00

Type: industrial
Category: other: various industries (softening agent, cleaning agent,corrosive agent, synergist in antioxidant mixtures)

06-DEC-00 (25) (96)

Type: industrial
Category: other: detergent industry (complex forming agent in washing powders and detergents)
04-SEP-00

1.7.1 Technology Production/Use

Remark: Uses in Consumer Products: Processed food and beverages (solid/liquid); Pharmaceutical preparations, mainly effervescent tablets (solid); Household cleaners (liquid)
22-MAY-00

1.8 Occupational Exposure Limit Values

Type of limit: MAC (NL)
Limit value:
Remark: no data available
06-DEC-00 (48)

Type of limit: MAK (DE)
Limit value:
Remark: no data available
06-DEC-00 (48)

Type of limit: MEL (UK)
Limit value:
Remark: no data available
06-DEC-00 (48)

1.9 Source of Exposure

Memo: Exposure to concentrated solid substance or solutions is most likely during manufacturing, packaging and industrial use.
04-SEP-00

1.10.1 Recommendations/Precautionary Measures

Type: Handling

Remark: For industrial handling use eye protection with tightly fitting goggles, skin protection with acid-proof gloves and full protective working clothes.
03-NOV-00

1.10.2 Emergency Measures

Remark: In case of eye contact, rinse eyes for at least 10 minutes keeping eyelids forcibly open. For skin contact, take off affected clothing and wash skin with water and soap

only. In case of accidental ingestion drink a lot of water. If itching, soreness or irritation develops consult a doctor.

04-SEP-00

1.11 Packaging

Memo: Polyethylene-lined approved strong paper bags or fibre Drum for dry substance; food-approved plastic or stainless steel drums or tanks for aqueous solutions.

20-SEP-00

1.12 Possib. of Rendering Subst. Harmless

Type of destruction: Incineration

04-SEP-00

1.13 Statements Concerning Waste

Memo: Incinerate solids. Biological wastewater treatment for solutions.

04-SEP-00

1.14.1 Water Pollution

1.14.2 Major Accident Hazards

1.14.3 Air Pollution

1.15 Additional Remarks

Memo: The substance can be incinerated in an appropriate installation with flue gas scrubbing

05-DEC-00 (35)

1.16 Last Literature Search

Date of Search: 20-SEP-00

03-NOV-00

1.17 Reviews

Memo: HEDSET Dataset 1993
04-SEP-00 (48)

Memo: Fed. Am. Soc. Exp. Biology (1977): evaluation of the health aspects of citric acid, sodium citrate, ammonium citrate, triethyl citrate, isopropyl citrate and stearyl citrate as food ingredients.
03-NOV-00 (36)

Memo: BIBRA Toxicity profile (1993): Citric acid and its common salts
03-NOV-00 (7)

1.18 Listings e.g. Chemical Inventories

Type: EINECS
Additional Info: 201 069 1

04-SEP-00

Additional Info: RTECS accession no. GE 7350000

21-SEP-00

2.1 Melting Point

Value: = 152 - 159 degree C
Reliability: (4) not assignable
08-MAY-01 (85)

Value: ca. 153 degree C
Decomposition: no
Sublimation: no
Reliability: (4) not assignable
08-MAY-01 (19)

2.2 Boiling Point

Value:
Decomposition: yes
Remark: No boiling point due to substance decomposition above 175 degree C
Reliability: (4) not assignable
08-MAY-01 (96)

Value:
Decomposition: yes
Remark: No boiling point due to substance decomposition
Reliability: (4) not assignable
08-MAY-01 (19)

2.3 Density

Type: relative density
Value: = 1.665 at 20 degree C
Reliability: (4) not assignable
08-MAY-01 (19)

Type: bulk density
Value: ca. 500 - 950 kg/m3 at 20 degree C
Method: other: DIN 53912
Reliability: (2) valid with restrictions
21-SEP-00 (48)

2.3.1 Granulometry

2.4 Vapour Pressure

Value:
Remark: No studies located
24-SEP-01

Value:
Method: QSAR estimation
Result: 7.3 x 10E-7 Pa
24-SEP-01 (94)

2.5 Partition Coefficient

log Pow: = -1.72 at 20 degree C
Method:
Year:
Reliability: (4) not assignable
08-MAY-01 (116)

2.6.1 Water Solubility

Value: ca. 592 g/l at 20 degree C
Reliability: (4) not assignable
08-MAY-01 (77)

Value: ca. 643 g/l at 30 degree C
Reliability: (4) not assignable
08-MAY-01 (77)

Value: ca. 576 g/l at 20 degree C
Reliability: (2) valid with restrictions
05-DEC-00 (48)

Value: ca. 771 g/l
Test condition: Water at room temperature
Reliability: (2) valid with restrictions
08-MAY-01 (28)

Value: = 1330 g/l
Test condition: "cold" water
Reliability: (4) not assignable
21-SEP-00 (116)

pH: = 2.2 at .1 other: N (normal)
Test substance: Citric acid monohydrate
Reliability: (4) not assignable
08-MAY-01 (85)

pH: ca. 1.8 at 5 other: w% and 25 degree C
Test substance: Citric acid
Reliability: (2) valid with restrictions
21-SEP-00 (48)

pKa: 3.13 at 25 degree C
Remark: pKa(1)
Reliability: (4) not assignable
08-MAY-01 (77)
pKa: 4.76 at 25 degree C
Remark: pKa(2)
Reliability: (4) not assignable
08-MAY-01 (77)

pKa: 6.4 at 25 degree C
Remark: pKa(3)
Reliability: (4) not assignable
08-MAY-01 (77)

2.6.2 Surface Tension

2.7 Flash Point

2.8 Auto Flammability

Value: = 1010 degree C
Test substance: Citric acid powder
Reliability: (4) not assignable
08-MAY-01 (113)

2.9 Flammability

Result: non flammable
GLP: no
Remark: "Fire potential slight when heated"
Reliability: (4) not assignable
08-MAY-01 (99)

2.10 Explosive Properties

Result: other: dust explosion
Method: other: Modified Hartmann Tube
GLP: no
Remark: Dust explosible at a concentration of 500 mg/l air, substance swirled up using a defined jet of pressurised air, ignition source electrical spark. In same test series dust ignition (but not explosion, based on the energy liberated) was found starting at concentrations of 200 mg/l air.
Reliability: (1) valid without restriction
06-DEC-00 (98)

Result: not explosive
Remark: Minimum ignition energy of citric acid (particle size range 3 to 150 mcm) was between 1300 mJ (no ignition) and 4000 mJ (ignition)
Reliability: (2) valid with restrictions
06-DEC-00 (48)

2.11 Oxidizing Properties

Result: no oxidizing properties
Remark: No studies located, but not expected from structure to have oxidizing properties
08-MAY-01

2.12 Additional Remarks

Memo: Henry's Law Constant: KH<=2.3*10E-7 Pa*m3/mol
Method: QSAR estimation assuming a water solubility of >= 600 mg/l
08-MAY-01 (95)

Memo: Viscosity = 6.5 cP (50% aqueous solution) at 25 degree C
Reliability: (4) not assignable
08-MAY-01 (20)

3.1.1 Photodegradation

Type:
Method:
Year: **GLP:**
Test substance:
Remark: no data available
25-MAY-00

3.1.2 Stability in Water

Type: abiotic
t1/2 pH 1 **:** = 72.9 year
Method: other: chemical analysis, half-life calculated
Year: **GLP:** no
Test substance:
Remark: abiotic degradation due to the reaction with OH radicals, based on literature value for OH radical concentration in water of 1*10E-17 mol/l
Result: degradation rate constant: 0.30*10E8 l/mol*s
Test condition: room temperature
Test substance: aqueous solution
Reliability: (4) not assignable
21-MAY-01 (4)

3.1.3 Stability in Soil

Type: other: biotic degradation in soil Radiolabel: no data
Concentration:
Cation exch. capac. other: not stated
Microbial biomass: other: not stated
Method: other: not stated
Year: 1977 **GLP:** no
Test substance: other TS: "citrate"
Result: "Substantial disappearance of citrate from soil is reported to occur in seven days"
Reliability: (4) not assignable
08-MAY-01 (80)

3.2 Monitoring Data (Environment)

Type of measurement: background concentration
Medium: surface water
Result: 0.025-0.145 mg/l, Atlantic coast seawater
Reliability: (4) not assignable
24-SEP-01 (89)

Type of measurement:
Medium: surface water
Result: < 0.04-0.2 mg/l, river water
Reliability: (4) not assignable

24-SEP-01 (1) (23)

Type of measurement:
Medium: other: raw sewage
Result: Raw sewage contains up to 10 mg/l of citrate
Reliability: (4) not assignable
24-SEP-01 (80)

3.3.1 Transport between Environmental Compartments

Type:
Media:
Method:
Year:
Remark: No studies located
25-MAY-00

3.3.2 Distribution

Media: other: air-sediment-soil-water
Method:
Year:
Method: Level III, Fugacity-based Environmental Equilibrum Partitioning Model v.2.20
Remark: System default values for the environmental parameters were not changed. Water solubility 576,000 mg/l, vapour pressure 1Pa and logPow -1.72 were used for the calculation; 33% emission each to air, soil and water.
Result: 55.76% to water, 44.20% to soil, 0.02% to sediment and 0.02% to air
21-MAY-01 (72)

Media: other: air-sediment-soil-water
Method:
Year:
Method: Level I, EQC Model v.1.0
Remark: System default values for the environmental parameters were not changed. Water solubility 576,000 mg/l, vapour pressure 1 Pa and logPow -1.72 were used for the calculation.
Result: 99.99% to water, <0.01% to soil, <0.01% to sediment and <0.01% to air
21-MAY-01 (72)

3.4 Mode of Degradation in Actual Use

Result: Citric acid is found in all eukaryote cells, forming an intermediate in the Krebs cycle. It is synthesised but subsequently broken down in the course of this very basic biochemical cycle.
Citric acid is easily biodegradable by sewage treatment bacteria. It is expected to be biodegradable by common soil and sediment bacteria.
Citric acid is easily oxidised by a variety of oxidising

agents, eg, peroxides or hypochlorites. The usual oxidation products are acetonedicarboxylic acid (CAS 542-05-2), oxalic acid (CAS 6153-56-6), carbon dioxide (CAS 124-38-9) and water (CAS 7732-18-5)

24-SEP-01 (17) (48) (116)

3.5 Biodegradation

Type: aerobic
Inoculum: other: non-adapted
Result: readily biodegradable
Method: Directive 84/449/EEC, C.5 "Biotic degradation - modified Sturm test"
Year: **GLP:** no
Test substance: other TS: Not stated
Remark: Medium: sewage treatment
Result: Readily biodegradable.
97% (duration not stated), based on CO2 evolution
100% (duration not stated), based on DOC removal
Reliability: (2) valid with restrictions
21-MAY-01 (41)

Type: aerobic
Inoculum: activated sludge, non-adapted
Degradation: = 85 % after 1 day
Kinetic: 1 day = 85 %
Method: Directive 87/302/EEC, part C, p. 99 "Biodegradation: Zahn-Wellens test"
Year: **GLP:** no
Test substance: other TS: Not stated
Remark: Medium: sewage treatment
Result: inherently biodegradable, related to DOC (Dissolved Organic
Carbon)
Reliability: (2) valid with restrictions
21-MAY-01 (41)

Type: aerobic
Inoculum: activated sludge, non-adapted
Degradation: = 98 % after 7 day
Kinetic: 7 day = 98 %
Method: Directive 87/302/EEC, part C, p. 99 "Biodegradation: Zahn-Wellens test"
Year: **GLP:** no
Test substance: other TS: purity > 99%
Remark: Medium: sewage treatment
Result: inherently biodegradable, related to DOC (Dissolved Organic
Carbon)
Reliability: (2) valid with restrictions
08-MAY-01 (28)

3.6 BOD5, COD or BOD5/COD Ratio

B O D 5

Method: Directive 84/449/EEC, C.8 "Biodegradation: Biochemical Oxygen Demand"
BOD5: = 526 mgO2/l

C O D

COD: = 728 mg/g substance

R A T I O B O D 5 / C O D

BOD5/COD: = .72

Reliability: (2) valid with restrictions
21-SEP-00 (48)

Method: other: Coupled Units Test

Result: 93% of COD removed
Reliability: (2) valid with restrictions
21-MAY-01 (41)

Method: Closed Bottle Test
Result: Ratio BOD30/COD = 90% of COD
Reliability: (2) valid with restrictions
21-MAY-01 (41)

Remark: Data collated from three publications
Result: Ratio BOD5/ThOD = 58% to 61%
Reliability: (4) not assignable
08-MAY-01 (116)

Remark: Sewage treatment, initial concentration 720 mg/l, BOD determination
Result: Activated sludge after 20d: 98% of ThOD
Reliability: (2) valid with restrictions
06-DEC-00 (71)
Remark: Sewage treatment, BOD determination
Result: Activated sludge after 24h: 13% of ThOD
Reliability: (2) valid with restrictions
06-DEC-00 (74)

3.7 Bioaccumulation

Species: other: Fish
Exposure period:
Concentration:
BCF: = .01
Elimination: no
Method: other
Year: **GLP:** no
Test substance:
Remark: Estimate: logBCF (wet wt, fish)=0.85*logPow - 0.70

[for logPow < 6.0] = -2.16
Type of test: calculated
Reliability: (2) valid with restrictions
07-DEC-00 (115)

3.8 Additional Remarks

Memo: Indirect photolysis
Remark: Estimation of the indirect photolysis using a photochemical hydroxyl radical reaction constant of 7.02*10E-12 cm3/mol.sec and assuming a hydroxyl radical concentration 0.5*10E6 OH/cm3 would result in an atmospheric half life of 2.3 days (Meylan and Howard, Epiwin, SRC).
08-MAY-01 (79)

Memo: Other Information
Remark: Initial concentrations 6.5*10E-7 M citric acid, 0.01 M FeCl3
Result: In a parallel citric acid recovery tests by iron coprecipitation, only half to one third of citric acid recovered from distilled water was recovered from Lake Mendota water at pH values above 8.5, showing appreciable abiotic or biotic degradation under natural conditions
Reliability: (2) valid with restrictions
21-MAY-01 (109)

AQUATIC ORGANISMS

4.1 Acute/Prolonged Toxicity to Fish

Type: static
Species: Leuciscus idus (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l **Analytical monitoring:**
LC50: 440 - 760
Method: other: not stated
Year: **GLP:** no
Test substance:
Remark: "Solution was not neutralised"
Reliability: (2) valid with restrictions
05-DEC-00 (58)

Type: static
Species: Lepomis macrochirus (Fish, fresh water)
Exposure period: 96 hour(s)
Unit: mg/l **Analytical monitoring:**
LC50: = 1516
Method: other: not stated
Year: **GLP:** no
Test substance:
Reliability: (2) valid with restrictions
05-DEC-00 (104)

Type: other: not stated
Species: Carassius auratus (Fish, fresh water)
Exposure period:
Unit: mg/l **Analytical monitoring:**
LC0: = 625
LC100: = 894
Method: other: not stated
Year: **GLP:** no
Test substance:
Remark: Exposure period: "Long-time exposure in hard water". "Hard water" buffers the acidity respectively the acid effect.
Reliability: (2) valid with restrictions
21-MAY-01 (27)

4.2 Acute Toxicity to Aquatic Invertebrates

Species: Daphnia magna (Crustacea)
Exposure period:
Unit: mg/l **Analytical monitoring:**
EC0: = 80
EC100: = 120
Method: other: not stated
Year: **GLP:** no
Test substance:
Remark: Exposure period: "Long-time exposure in soft water". "Soft water", does not buffer the acidity respectively the acid effect.
Reliability: (2) valid with restrictions

08-MAY-01 (1)

Species: Daphnia magna (Crustacea)
Exposure period: 24 hour(s)
Unit: mg/l **Analytical monitoring:**
EC0: = 1206
EC50: = 1535
EC100: = 2083
Method: other: not stated
Year: 1982 **GLP:** no data
Test substance:
Test condition: neutralised
Reliability: (4) not assignable
21-MAY-01 (13)

Species: Daphnia magna (Crustacea)
Exposure period: 24 hour(s)
Unit: mg/l **Analytical monitoring:**
EC0: = 73
EC50: = 85
EC100: = 98
Method: other: not stated
Year: 1982 **GLP:** no data
Test substance:
Test condition: not neutralised
Reliability: (4) not assignable
21-MAY-01 (13)

Species: other aquatic crustacea: Carcinus maenas (crab)
Exposure period: 48 hour(s)
Unit: mg/l **Analytical monitoring:**
LC50 : = 160
Method: other: not stated
Year: **GLP:** no
Test substance:
Reliability: (2) valid with restrictions
21-MAY-01 (93)

4.3 Toxicity to Aquatic Plants e.g. Algae

Species: Scenedesmus quadricauda (Algae)
Endpoint:
Exposure period: 7 day
Unit: mg/l **Analytical monitoring:**
EC0: = 640
Method: other: not stated
Year: **GLP:** no
Test substance:
Reliability: (2) valid with restrictions
21-MAY-01 (12)

Species: other algae: Pavlova lutheri (saltwater chrysophytes)
Endpoint:
Exposure period: 7 day
Unit: mg/l **Analytical monitoring:**
TLC: = 1 - 300

Method: other: not stated
Year: **GLP:** no data
Test substance:
Reliability: (4) not assignable
24-SEP-01 (84)

Species: other algae: Chaetoceros gracilis, Navicula ramosissima (saltwater diatoms)
Endpoint:
Exposure period: 7 day
Unit: mg/l **Analytical monitoring:**
TLC : = 1 - 300
Method: other: not stated
Year: **GLP:** no data
Test substance:
Reliability: (4) not assignable
24-SEP-01 (84)

4.4 Toxicity to Microorganisms e.g. Bacteria

Type: aquatic
Species: Microcystis aeruginosa (Bacteria)
Exposure period: 8 day
Unit: mg/l **Analytical monitoring:**
EC0: = 80
Method: other: not stated
Year: **GLP:** no
Test substance:
Reliability: (2) valid with restrictions
08-MAY-01 (10)

Type: aquatic
Species: Nitrosomonas sp. (Bacteria)
Exposure period:
Unit: mg/l **Analytical monitoring:**
NOEC : = 100
Method: other: not stated
Year: **GLP:** no
Test substance:
Remark: No inhibition on NH3 oxidation
Reliability: (2) valid with restrictions
08-MAY-01 (49)

Type: aquatic
Species: Pseudomonas putida (Bacteria)
Exposure period: 16 hour(s)
Unit: mg/l **Analytical monitoring:**
EC0: > 10000
Method: other: not stated
Year: **GLP:** no
Test substance:
Reliability: (2) valid with restrictions
21-MAY-01 (12)

Type: aquatic
Species: other bacteria: 37 strains of bacteria

Exposure period: 30 day
Unit: mg/l **Analytical monitoring:**
EC0: = 500
Method: other: not stated
Year: **GLP:** no
Test substance:
Remark: Concentration: 500 mg/l, pH=3.0; Microbes from acidic mine water (Central Pennsylvania), isolated from enrichment cultures, test substance as C source in static culture
Result: positive growth on all strains
Reliability: (2) valid with restrictions
08-MAY-01 (121)

Type: other: not stated
Species: Entosiphon sulcatum (Protozoa)
Exposure period: 72 hour(s)
Unit: mg/l **Analytical monitoring:**
EC0: = 485
Method: other: not stated
Year: **GLP:** no
Test substance:
Reliability: (2) valid with restrictions
21-MAY-01 (12)

Type: other: not stated
Species: other bacteria: Arthrobacter globiformis, 10 strains
Exposure period: 5 day
Unit: **Analytical monitoring:**
Method: other: not stated
Year: **GLP:** no
Test substance:
Remark: Microbes isolated from soil, test substance as sole C source, mineral salts added
Result: good to excellent degradation with all strains
Reliability: (2) valid with restrictions
21-MAY-01 (56)

Type: other: not stated
Species: other protozoa: Tetraselmis tetrathele (saltwater)
Exposure period: 7 day
Unit: mg/l **Analytical monitoring:**
TLC : = 1 - 300
Method: other: not stated
Year: **GLP:** no data
Test substance:
Reliability: (4) not assignable
24-SEP-01 (84)

Type: other: not stated
Species: other protozoa: Tetramitus rostratus (freshwater)
Exposure period: 35 hour(s)
Unit: mg/l **Analytical monitoring:**
TLC : <= 108
Method: other: not stated
Year: **GLP:** no data
Test substance:

Reliability: (4) not assignable
24-SEP-01 (55)

Type: other: not stated
Species: Uronema parduzci (Protozoa)
Exposure period:
Unit: mg/l **Analytical monitoring:**
TLC : = 622
Method: other: not stated
Year: **GLP:** no data
Test substance:
Reliability: (4) not assignable
21-MAY-01 (11)

4.5 Chronic Toxicity to Aquatic Organisms

4.5.1 Chronic Toxicity to Fish

Species:
Endpoint:
Exposure period:
Unit: **Analytical monitoring:**
Method:
Year: **GLP:**
Test substance:
Remark: No studies located, with the possible exception of the one recorded under 4.1
14-JUL-00

4.5.2 Chronic Toxicity to Aquatic Invertebrates

Species:
Endpoint:
Exposure period:
Unit: **Analytical monitoring:**
Method:
Year: **GLP:**
Test substance:
Remark: No studies located with the possible exception of the one recorded chapter 4.2
21-SEP-00

TERRESTRIAL ORGANISMS

4.6.1 Toxicity to Soil Dwelling Organisms

Type:
Species:
Endpoint:
Exposure period:
Unit:
Method:
Year: **GLP:**
Test substance:
Remark: No studies located
14-JUL-00

4.6.2 Toxicity to Terrestrial Plants

Species:
Endpoint:
Expos. period:
Unit:
Method:
Year: **GLP:**
Test substance:
Remark: All plants produce citric acid as an intermediate of the Krebs cycle.
No studies located.
08-MAY-01 (24) (96)

4.6.3 Toxicity to other Non-Mamm. Terrestrial Species

Species:
Endpoint:
Expos. period:
Unit:
Method:
Year: **GLP:**
Test substance:
Remark: No studies located
03-NOV-00

4.7 Biological Effects Monitoring

Remark: Based on the low n-octanol/water partition coefficient on one hand and based on the fact that citric acid as an intermediate in the Krebs cycle (see 4.8) is transformed into other substances in every body cell of eukaryotes on a daily basis, no biomagnification is given.
No studies located.
05-DEC-00

4.8 Biotransformation and Kinetics

Type:
Result: Citric acid is an intermediate in the citric acid or Krebs cycle, also known as the tricarboxylic acid cycle, which takes place in every eukaryote cell and which breaks down glucose through glycolysis
08-MAY-01 (17)

4.9 Additional Remarks

Memo: (a)
Result: Citric acid is "extremely widesprad in nature"
21-MAY-01 (37)

Memo: (b)
Result: Citric acid is "widely distributed in plants and animal tissues and fluids"
08-MAY-01 (77)

Memo: (c)
Result: In man, during 24h approxymately 2000 g of citric acid are formed and further metabolised as intermediates in the citric acid cycle in adults
08-MAY-01 (96)

5.1 Acute Toxicity

5.1.1 Acute Oral Toxicity

Type: LD50
Species: mouse
Sex: male/female
Number of Animals: 10
Vehicle:
Value: = 5400 mg/kg bw
Method:
Year: 1981 **GLP:** no
Test substance:
Remark: 5 male and 5 female mice in each treatment group were administered 3000 mg/kg, 4243 mg/kg, 6000 mg/kg, 8485 mg/kg or 12000 mg/kg of citric acid by gavage. The test substance was dissolved in pure water at such concentrations that in every group 20 ml/kg were given. Controls were administered 0.4 ml tap water by gavage.
Reliability: (2) valid with restrictions
08-MAY-01 (32)

Type: other: lethal dose
Species: rabbit
Sex:
Number of Animals:
Vehicle:
Value: = 7000 mg/kg bw
Method:
Year: **GLP:** no
Test substance:
Remark: Probably lowest Lethal dose
Reliability: (4) not assignable
21-MAY-01 (119)

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Value: = 3000 mg/kg bw
Method: other: not stated
Year: **GLP:** no
Test substance:
Reliability: (2) valid with restrictions
06-DEC-00 (88)

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Value: = 12000 mg/kg bw

Method: other: not stated
Year: **GLP:** no
Test substance:
Reliability: (2) valid with restrictions
16-MAY-01 (125)

Type: LD50
Species: rat
Sex:
Number of Animals:
Vehicle:
Value: = 5000 mg/kg bw
Method: other: not stated
Year: **GLP:** no
Test substance:
Reliability: (2) valid with restrictions
16-MAY-01 (125)

5.1.2 Acute Inhalation Toxicity

Type:
Species:
Sex:
Number of Animals:
Vehicle:
Exposure time:
Value:
Method:
Year: **GLP:**
Test substance:
Remark: No studies located
17-JUL-00

5.1.3 Acute Dermal Toxicity

Type:
Species:
Sex:
Number of Animals:
Vehicle:
Value:
Method:
Year: **GLP:**
Test substance:
Remark: No studies located
17-JUL-00

5.1.4 Acute Toxicity, other Routes

Type: LD50
Species: rat
Sex:

Number of Animals:
Vehicle:
Route of admin.: s.c.
Value: = 5500 mg/kg bw
Method: Other
Year: **GLP:** no
Test substance:
Reliability: (2) valid with restrictions
16-MAY-01 (125)

Type: LD50
Species: mouse
Sex:
Number of Animals:
Vehicle:
Route of admin.: s.c.
Value: = 2700 mg/kg bw
Method: Other
Year: **GLP:** no
Test substance:
Reliability: (2) valid with restrictions
16-MAY-01 (125)

5.2 Corrosiveness and Irritation

5.2.1 Skin Irritation

Species: human
Concentration:

Exposure:
Exposure Time:
Number of Animals:
PDII:
Result:
EC classificat.:
Method:
Year: **GLP:**
Test substance:
Remark: An irritant skin dermatitis attributed to citric acid has been reported amongst waiters and bakers.
16-MAY-01 (38)

Species: human
Concentration:

Exposure:
Exposure Time:
Number of Animals:
PDII:
Result:
EC classificat.:

Method:
Year: **GLP:**
Test substance:
Remark: In solution, the acid may produce pain if applied to abraded skin.
08-MAY-01 (46)

Species: human
Concentration:

Exposure:
Exposure Time:
Number of Animals:
PDII:
Result:
EC classificat.:
Method:
Year: **GLP:**
Test substance:
Remark: A 0.3 N solution (approximatively 2%) can "sting" intact skin, this appears unrelated to irritant potential.
08-MAY-01 (65)

Species: human
Concentration:

Exposure:
Exposure Time:
Number of Animals:
PDII:
Result:
EC classificat.:
Method:
Year: **GLP:**
Test substance:
Remark: Patch testing of 60 eczema patients with 2.5 % citric acid in petrolatum (probably 24 h covered contact) did not produce any irritant reactions.
Reliability: (4) not assignable
08-MAY-01 (83)

Species: other: rabbit, New Zealand White, > 3 kg bw
Concentration: other: 30% aqueous solution

Exposure: Occlusive
Exposure Time:
Number of Animals: 3
PDII:
Result: not irritating
EC classificat.: not irritating
Method: Draize Test
Year: **GLP:** no
Test substance:

Remark: Dose=0.5ml (corresponding to 0.15 g in aqueous solution) during 4 h under occlusive patch; subsequent observations at 4 h, 24 h and 48 h. Effects reported as nil (no erythema/eschar, no oedema) for intact skin, effects reported as "slight to well defined" in one instance for abraded skin. Overall Primary Irritation Index (average of all observations) = 0.84, hence in this test the substance is not a primary skiirritant.
Reliability: (1) valid without restriction
08-MAY-01 (33)

Species: rabbit
Concentration:

Exposure:
Exposure Time: 24 hour(s)
Number of Animals:
PDII:
Result: slightly irritating
EC classificat.: irritating
Method: other: not stated
Year: **GLP:** no data
Test substance:
Remark: Dose=500 mg/24 h; Effects reported as "mild"
Reliability: (4) not assignable
21-MAY-01 (75)

Species: rabbit
Concentration:

Exposure:
Exposure Time:
Number of Animals:
PDII:
Result: slightly irritating
EC classificat.: not irritating
Method: OECD Guide-line 404 "Acute Dermal Irritation/Corrosion"
Year: **GLP:** no data
Test substance:
Remark: "Average result of 24, 48 and 72 hours: erythema score=0.33, oedema score=0"
Reliability: (4) not assignable
21-MAY-01 (63)

5.2.2 Eye Irritation

Species: other: rabbit, New Zealand White, > 2 kg bw
Concentration: other: 10% and 30% aqueous solution
Dose:
Exposure Time:
Comment:
Number of Animals: 3
Result: not irritating

EC classificat.: not irritating
Method: Draize Test
Year: **GLP:** no
Test substance:
Remark: Dose=0.1 ml (corresponding to 0.01 g resp. 0.03 g in aqueous solution) is placed into the lower conjunctival sac of one eye held closed for one second; subsequent observation period was14 days. Effects of the 10% solution reported as moderate to weak conjunctival irritation disappearing within one week, without further effects on the cornea. Overall Primary Eye Irritation Index (Draize score, average of all observations) = 9.3 for the 10% solution, resulting in a classification of "minimally irritating". Effects of the 30% solution reported as well-defined to moderate conjunctival irritation which disappeard in two of the three rabbits within 14 days; additionally, a short-lasting superficial lesion of the conjunctival epithelium was noted; no macroscopical alteration of the cornea was observed. Overall Primary Eye Irritation Index (Draize score, average of all observations)=16.0 for the 30% solution, resulting in a classification of "mildly to moderately irritating"
Reliability: (1) valid without restriction
07-DEC-00 (34)

Species: human
Concentration:
Dose:
Exposure Time:
Comment:
Number of Animals:
Result:
EC classificat.:
Method:
Year: **GLP:**
Test substance:
Remark: Severe damage was reported in a patient who was splashed in the eye with a saturated solution of citric acid.
Reliability: (4) not assignable
21-MAY-01 (118)

Species: rabbit
Concentration:
Dose:
Exposure Time:
Comment:
Number of Animals:
Result: irritating
EC classificat.: irritating
Method: other: not stated
Year: **GLP:** no data
Test substance: other TS: 0.5% aq. solution, 2% solution aq.
Remark: "Irrigation for 30 min with 0.5% to 2% solution causes severe injury; the 0.5% solution causes permanent

cloudiness of the cornea and the 2% solution causes severe dense opacification"
Reliability: (4) not assignable
16-MAY-01 (43)

Species: rabbit
Concentration:
Dose: 750 other: ug/24 h
Exposure Time:
Comment:
Number of Animals:
Result: highly irritating
EC classificat.: irritating
Method: other: not stated
Year: **GLP:** no data
Test substance:
Remark: Effect reported as "severe"
Reliability: (4) not assignable
16-MAY-01 (75)

Species: rabbit
Concentration:
Dose:
Exposure Time:
Comment:
Number of Animals:
Result: highly irritating
EC classificat.: irritating
Method: OECD Guide-line 405 "Acute Eye Irritation/Corrosion"
Year: **GLP:** no data
Test substance:
Remark: "Average results of 24, 48 and 72 hours: cornea score = 2.8, iris score = 0.0, conjunctiva score = 1.7"
Reliability: (4) not assignable
16-MAY-01 (63)

5.3 Sensitization

Type:
Species: human
Number of Animals:
Vehicle:
Result:
Classification:
Method:
Year: **GLP:**
Test substance:
Remark: Mouth sores (canker sores), headache, asthma, nasal blockage, general tiredness and itchiness were some of the symptoms reported by a man after the ingestion of foods containing citric acid. Application of crystals to the inside surface of the mouth produced sores (as did some other organic acids) but potassium citrate crystals

and magnesium citrate solution did not. Control subjects did not react to mouth application of citric acid.

16-MAY-01 (111)

Type:
Species: human
Number of Animals:
Vehicle:
Result:
Classification:
Method:
Year: **GLP:**
Test substance:
Remark: A standard text implies that citric acid might be a skin sensitizer by recommending 1% aqueous solutions for (24/48-hr covered) patch-tests to detect the sensitized state.

16-MAY-01 (38)

Type:
Species: human
Number of Animals:
Vehicle:
Result:
Classification:
Method:
Year: **GLP:**
Test substance:
Remark: No allergic reactions were seen when 60 patients with hand eczema, all of whom were involved in handling food, were patch tested (covered contact, probably 24 hr) with 2.5% citric acid in petrolatum.

16-MAY-01 (83)

Type:
Species: human
Number of Animals:
Vehicle:
Result:
Classification:
Method:
Year: **GLP:**
Test substance:
Remark: Urticaria (a skin complaint) and mouth ulcers have been noted following exposure to citric acid [no other details were given].

21-MAY-01 (110)

5.4 Repeated Dose Toxicity

Species: rat **Sex:** male/female
Strain:

Route of admin.: other: oral, gavage
Exposure period: 5 days
Frequency of treatment: Once daily
Post. obs. period: 10 days
Doses: 2000 mg/kg/day, 4000 mg/kg/day, 8000 mg/kg/day, 16000 mg/kg/day
Control Group: no data specified
Method: other: not stated
Year: **GLP:** no
Test substance:
Remark: 10 males and 10 females, avg weight = 150 g
Result: NOEL = 4000 mg/kg
LD50 = 5600 +- 440 mg/kg/d, identical for males and females
Reliability: (1) valid without restriction
16-MAY-01 (31)

Species: mouse **Sex:** male
Strain:
Route of admin.: oral feed
Exposure period:
Frequency of treatment:
Post. obs. period:
Doses:
Control Group:
Method:
Year: **GLP:** no data
Test substance:
Remark: Decreased growth and lower survival times (11-13 months as opposed to 16-17 months in the untreated controls) were reported in male mice receiving 5% citric acid in the diet (about 7.5 g/kg bw/day) for an unspecified period.
Reliability: (4) not assignable
16-MAY-01 (124)

Species: rabbit **Sex:**
Strain:
Route of admin.: oral feed
Exposure period:
Frequency of treatment:
Post. obs. period:
Doses:
Control Group:
Method:
Year: **GLP:** no data
Test substance:
Remark: No adverse effects were seen in limited studies in 15 rabbits receiving 7.7% sodium citrate (equivalent to 5% free citric acid) in the diet (about 1.5 g citric acid/kg bw/day) for 150 days.

Result: NOAEL = 1500 mg/kg/d
Reliability: (4) not assignable
16-MAY-01 (90)

Species: dog **Sex:**
Strain:
Route of admin.: oral feed
Exposure period:
Frequency of treatment:
Post. obs. period:
Doses:
Control Group:
Method:
Year: **GLP:** no data
Test substance:
Remark: No adverse effects were seen in three dogs fed daily doses of 1.38 g citric acid/kg bw for up to 120 days.
Result: NOAEL = 1400 mg/kg/d
Reliability: (4) not assignable
21-MAY-01 (64)

Species: guinea pig **Sex:**
Strain:
Route of admin.: oral feed
Exposure period:
Frequency of treatment:
Post. obs. period:
Doses:
Control Group:
Method:
Year: **GLP:** no data
Test substance:
Remark: A reduced packed cell volume in the blood was the only effect noted in guinea-pigs receiving diets supplements with 1-5% citric acid (about 0.4-2 g/kg bw/day) for a maximum of 60 days. No tissue examinations were undertaken. (The unsupplemented diets contained around 1.2% citric acid, so actual citric acid intakes were greater than the quoted values).
Reliability: (4) not assignable
16-MAY-01 (123)

Species: pig **Sex:**
Strain:
Route of admin.: oral feed
Exposure period:
Frequency of treatment:
Post. obs. period:
Doses:
Control Group:
Method:

Year: **GLP:** no data
Test substance:
Remark: Body weight gain was unaffected in young pigs fed a cadmium-enriched diet containing 5% citric acid (corresponding to about 4 kg/kg bw/day). Cadmium levels were, however, elevated in the liver and kidneys and the zinc level was decreased in muscle in citric acid/cadmium treated pigs compared with pigs treated with cadmium only.
Reliability: (4) not assignable
21-MAY-01 (100)

Species: sheep **Sex:**
Strain:
Route of admin.: other: ruminal cannula
Exposure period:
Frequency of treatment:
Post. obs. period:
Doses:
Control Group:
Method:
Year: **GLP:** no data
Test substance:
Remark: When six sheep were given 795 mg citric acid/kg bw/day for 60 days via a ruminal cannula, no effects were seen on feed intake, weight gain or mineral metabolism.
Reliability: (4) not assignable
16-MAY-01 (3)

Species: rat **Sex:** male/female
Strain:
Route of admin.: other: oral, dietary
Exposure period: 90 weeks
Frequency of treatment: Daily (feed)
Post. obs. period: Not stated
Doses: Feed containing 1.2% citric acid
Control Group: no data specified
Method: other: not stated
Year: **GLP:** no
Test substance:
Remark: Cited as "... no harmful effects on the growth of two successive generations of rats over a 90-week period. No effect on reproduction, blood characteristics, pathology or calcium was observed. Although a slight increase in dental attrition was reported."
Reliability: (2) valid with restrictions
21-MAY-01 (8)

Species: rat **Sex:** male
Strain:
Route of admin.: other: oral, dietary
Exposure period: 6 weeks
Frequency of

treatment:
Post. obs. period:
Doses: Feed containing 1.2, 2.4, 4.8% citric acid
Control Group:
Method:
Year: **GLP:** no
Test substance:
Remark: Japanese investigators have recorded slight growth reduction in groups of 10 male rats fed 1.2, 2.4 or 4.8% citric acid (apparently 1.15, 2.26 or 4.67 g/kg bw/d) for 6 weeks and, at the top dose, mild blood and urine changes and slight degeneration of the thymus gland and the spleen.
Reliability: (4) not assignable
21-MAY-01 (125)

Species: rat **Sex:**
Strain:
Route of admin.: other: oral dietary
Exposure period:
Frequency of treatment:
Post. obs. period:
Doses: Feed containing 2% citric acid
Control Group:
Method:
Year: **GLP:** no data
Test substance:
Remark: Citric acid had no effects on food consumption or body weight when fed at a dietary level of 2% (about 0.13 g/kg bw/d) to nine rats. The absorption and urinary excretion of calcium and magnesium were unaffected, although urinary zinc excretion was temporarily elevated.
Reliability: (4) not assignable
21-MAY-01 (103)

Species: rat **Sex:** male
Strain:
Route of admin.: other: oral dietary
Exposure period: 2 years
Frequency of treatment:
Post. obs. period:
Doses: Feed containing 5% and 3% citric acid
Control Group:
Method:
Year: **GLP:** no
Test substance:
Remark: In 2 year studies with groups of 20 male rats, dietary levels of 5% citric acid (about 2g/kg bw/d) or 3% slightly decreased growth (food consumption was also lower in the top-dose group), but no tissue

abnormalities were found on examination of the major organs.
Result: NOAEL = 1200 mg/kg/d
Reliability: (4) not assignable
21-MAY-01 (50)

Species: rat **Sex:**
Strain:
Route of admin.: other: oral dietary
Exposure period: 1 year
Frequency of treatment:
Post. obs. period:
Doses: Feed containing 1.2% citric acid
Control Group:
Method:
Year: **GLP:** no
Test substance:
Remark: No adverse effects were reported (with the possible exception of slight changes in tooth structure) when two successive generations of rats were fed 1.2% citric acid (about 600 mg/kg bw/d) and 0.1% sodium citrate in the diet for apparently up to about 1 year (only a limited range of tissues was examined microspically).
Reliability: (4) not assignable
21-MAY-01 (8)

5.5 Genetic Toxicity 'in Vitro'

Type: Bacterial reverse mutation assay
System of testing: Species/strain: Salmonella typhimurium TA 97, TA 98, TA 100, TA 104
Concentration: Not stated
Metabolic activation: with and without
Result: negative
Method: OECD Guide-line 471 "Genetic Toxicology: Salmonella thyphimurium Reverse Mutation Assay"
Year: **GLP:** no data
Test substance:
Remark: Activation system: Liver homogenate from rats pretreated with phenobarbital
Reliability: (2) valid with restrictions
16-MAY-01 (2)

Type: Bacterial reverse mutation assay
System of testing: Species/strain: Salmonella typhimurium TA 94, TA 98, TA 100, TA 1535, TA 1537
Concentration: Up to 5 mg/plate
Metabolic activation: with and without
Result: negative

Method: OECD Guide-line 471 "Genetic Toxicology: Salmonella thyphimurium Reverse Mutation Assay"
Year: **GLP:** no data
Test substance:
Remark: Activation system: Liver homogenate from rats preteated with polychlorinated biphenyl KC-400
Reliability: (2) valid with restrictions
21-MAY-01 (54)

Type: Bacterial reverse mutation assay
System of testing: Escheria coli
Concentration:
Metabolic activation:
Result: negative
Method:
Year: **GLP:** no data
Test substance:
Reliability: (4) not assignable
16-MAY-01 (47)

Type: Yeast gene mutation assay
System of testing: Not stated
Concentration: > 3.5 g/kg
Metabolic activation: with and without
Result: negative
Method: other
Year: **GLP:** no
Test substance:
Reliability: (4) not assignable
21-MAY-01 (70)

Type: Yeast gene mutation assay
System of testing: Saccharomyces cerevisiae

Concentration:
Metabolic activation: with and without
Result: negative
Method:
Year: **GLP:** no
Test substance:
Reliability: (4) not assignable
21-MAY-01 (69)

Type: other: clastogenic assay
System of testing: Fibroblast culture from chinese hamster (Cricetulus griseus)
Concentration: Up to 1mg/ml
Metabolic activation:
Result:

Method: other: not stated
Year: **GLP:** no data
Test substance:
Remark: No clastogenic effects reported
Result: Genotoxic effects: negative
Reliability: (2) valid with restrictions
21-MAY-01 (54)

5.6 Genetic Toxicity 'in Vivo'

Type: Dominant lethal assay
Species: rat **Sex:** no data
Strain:
Route of admin.: unspecified
Exposure period:
Doses:
Result:
Method:
Year: **GLP:** no
Test substance:
Remark: No mutagenic potential was detected in a dominant lethal assay in rats in which doses of up to 3 g citric acid/kg bw/day were administrated for 5 days. (A dominant lethal effect is normally reflected by increased early foetal death when treated males are mated with untreated females).
Reliability: (4) not assignable
21-MAY-01 (69)

Type:
Species: rat **Sex:** no data
Strain:
Route of admin.: unspecified
Exposure period:
Doses:

Result:
Method:
Year: **GLP:** no
Test substance:
Remark: No chromosomal damage occurred in the bone marrow of rats ingesting up to 3 g citric acid/kg bw/day for 5 days.
Reliability: (4) not assignable
21-MAY-01 (69)

5.7 Carcinogenicity

Species: rat **Sex:** male
Strain:
Route of admin.: oral feed
Exposure period:
Frequency of treatment:
Post. obs.

period:
Doses:
Result:
Control Group:
Method:
Year: **GLP:** no
Test substance:
Remark: In a limited study, no evidence of carcinogenicity was reported in 20 male rats receiving up to 5% citric acid in the diet (about 2g/kg bw/day) for 2 years. (Modern regulatory guidelines recommend that groups of 50 rodents of each sex are exposed to one of several doses and that a comprehensive range of tissues is examined microscopically).
Reliability: (4) not assignable
21-MAY-01 (50)

Species: rat **Sex:** male
Strain:
Route of admin.: oral feed
Exposure period:
Frequency of treatment:
Post. obs. period:
Doses:
Result:
Control Group:
Method:
Year: **GLP:** no data
Test substance:
Remark: Male rats were fed citric acid or sodium citrate at dietary levels providing about 2.6 g/kg bw/day (based on their final body weights) for 20 weeks and were simultaneously given a known bladder carcinogen in their drinking water.
More carcinomas (malignant tumours) were induced in rats treated with carcinogen and sodium citrate than in those treated with carcinogen alone, however, this was attributed to the increased water intake (and hence carcinogen intake) in this group. Citric acid did not have a tumour promoting effect.
Reliability: (2) valid with restrictions
24-SEP-01 (53)

Species: rat **Sex:**
Strain:
Route of admin.: oral feed
Exposure period:
Frequency of treatment:
Post. obs. period:
Doses:
Result:
Control Group:
Method:

Year: **GLP:** no data
Test substance:
Remark: No increase in DNA synthesis (a measure of cell proliferation) in the bladder epithelium was found in rats fed 1.7% sodium citrate (about 0.74 g/kg bw/day) in the diet for 8 weeks.
Reliability: (4) not assignable
16-MAY-01 (86)

Species: rat **Sex:** male
Strain:
Route of admin.: other: oral, stomach tube
Exposure period:
Frequency of treatment:
Post. obs. period:
Doses:
Result:
Control Group:
Method:
Year: **GLP:** no
Test substance:
Remark: Three liver tumours developed in a group of 80 male rats treated with a known carcinogen and receiving 470 mg citric acid/kg bw three times daily by stomach tube for up to 45 weeks. (No control animals were apparently used in this study, but clearly citric acid did not act as a potent tumour promoter).
Reliability: (4) not assignable
21-MAY-01 (6)

Species: rat **Sex:** male
Strain: other: Albino Carworth
Route of admin.: oral feed
Exposure period: 24 months
Frequency of treatment: Daily
Post. obs. period: Not stated
Doses: 2g/kg body weight/day
Result:
Control Group: yes, concurrent no treatment
Method: other
Year: **GLP:** no
Test substance:
Result: No differences between controls and experimental group
Reliability: (2) valid with restrictions
16-MAY-01 (50)

Species: rat **Sex:** male
Strain:
Route of admin.: oral feed
Exposure period:
Frequency of treatment:
Post. obs.

period:
Doses:
Result:
Control Group:
Method:
Year: **GLP:** no data
Test substance:
Remark: Tumour yield increased when groups of 20 to 25 male rats who had been treated with a known bladder carcinogen were then given 5% sodium citrate in the diet (about 2.5 g/kg bw/day) for 32 weeks, then 5% sodium citrate in the diet for 4 weeks (actual intake about 1.9 g/kg bw/day), followed by a 3-week period of treatment with uracil (to accelerate tumour promotion), and then the sodium citrate for a further 9 weeks.
The incidence of bladder papillomas (benign tumours) was increased in rats treated with sodium citrate (and carcinogen/uracil) compared with those treated with only the carcinogen uracil. One of fifteen rats in the sodium citrat-treated group developed a bladder carcinoma. No papillomas or carcinomas developed in rats treated with sodium citrate and uracil but not carcinogen.
Reliability: (4) not assignable
16-MAY-01 (117)

Species: rat **Sex:**
Strain:
Route of admin.: oral feed
Exposure period:
Frequency of treatment:
Post. obs. period:
Doses:
Result:
Control Group:
Method:
Year: **GLP:** no data
Test substance:
Remark: When the sodium citrate level was only 1.7% (actual intake about 0.74 g/kg bw/day) no effects were seen on the bladder tumour incidence in rats treated with citrate (and carcinogen/uracil) compared with those treated with carcinogen and uracil only. However, if the 1.7% sodium citrate treatment was combined with the administration of two other sodium salts (the ascorbate and bicarbonate), the yield of papillomas and carcinomas was increased in a synergist fashion.
Reliability: (4) not assignable
16-MAY-01 (86)

5.8 Toxicity to Reproduction

Type:
Species: rat **Sex:**
Strain:

Route of admin.: oral feed
Exposure Period:
Frequency of treatment:
Duration of test:
Doses:
Control Group:
Method:
Year: **GLP:** no
Test substance:
Remark: No effects on reproduction were reported in limited studies in which rats were fed diets containing 1.2% citric acid (about 600 mg/kg bw/day) and 0.1% sodium citrate for 29 weeks prior to mating and then for another few months.
Reliability: (4) not assignable
21-MAY-01 (8)

Type:
Species: rat **Sex:**
Strain:
Route of admin.: unspecified
Exposure Period:
Frequency of treatment:
Duration of test:
Doses:
Control Group:
Method:
Year: **GLP:** no
Test substance:
Remark: There were no indications of teratogenicity (malformations in the offspring) or other adverse effects when female rats received up to 295 mg citric acid/kg bw/day on days 6 to 15 of pregnancy.
Reliability: (4) not assignable
21-MAY-01
(39)

Type:
Species: rat **Sex:** female
Strain:
Route of admin.: unspecified
Exposure Period:
Frequency of treatment:
Duration of test:
Doses:
Control Group:
Method:
Year: **GLP:** no
Test substance:
Remark: No teratogenicity or other adverse effects were reported when females received up to 241 mg citric acid/kg bw on days 6 to 15 of pregnancy.
Reliability: (4) not assignable
21-MAY-01 (39)

Type:
Species: mouse **Sex:** female
Strain:
Route of admin.: oral feed
Exposure Period:
Frequency of treatment:
Duration of test:
Doses:
Control Group:
Method:
Year: **GLP:** no data
Test substance:
Remark: Litter size and survival of offspring up to weaning were unaffected when female mice consumed 5% citric acid in the diet (about 7.5 g/kg bw/day) previous to, during, and subsequent to mating.
Result: NOEL = 7500 mg/kg/d
Reliability: (4) not assignable
16-MAY-01
(124)

Type:
Species: rabbit **Sex:** female
Strain:
Route of admin.: unspecified
Exposure Period:
Frequency of treatment:
Duration of test:
Doses:
Control Group:
Method:
Year: **GLP:** no
Test substance:
Remark: There were no indications of teratogenicity or other adverse effects when female rabbits were given up to 425 mg/kg bw on days 6 to 18 of pregnancy.
Reliability: (4) not assignable
21-MAY-01 (39)

Type:
Species: hamster **Sex:** female
Strain:
Route of admin.: unspecified
Exposure Period:
Frequency of treatment:
Duration of test:
Doses:
Control Group:
Method:
Year: **GLP:** no
Test substance:
Remark: There were no indications of teratogenicity or other adverse effects when female hamsters received up to 272 mg citric acid/kg (presumably daily) on days 6 to 10 of

pregnancy.
Reliability: (4) not assignable
21-MAY-01 (39)

Type: Two generation study
Species: rat **Sex:** male/female
Strain:
Route of admin.: other: oral, dietary
Exposure Period: 90 weeks
Frequency of treatment: Daily (feed)
Duration of test:
Doses: Feed containing 1.2 w/w % citric acid
Control Group: no data specified
Method: other: not stated
Year: **GLP:** no
Test substance:
Remark: Cited as "... no harmful effects on the growth of two successive generations of rats over a 90-week period. No effect on reproduction, blood characteristics, pathology or calcium was observed, although a slight increase in dental attrition was reported."
Reliability: (2) valid with restrictions
07-DEC-00 (8)

Type:
Species: rat **Sex:** female
Strain:
Route of admin.: oral feed
Exposure Period:
Frequency of treatment:
Duration of test:
Doses:
Control Group:
Method:
Year: **GLP:** no data
Test substance:
Remark: No effects on reproduction were reported in a study in which female rats ingested 5% citric acid (about 2.5 g/kg bw/day) previous to, during and subsequent to mating.
Result: NOEL = 2500 mg/kg/d
Reliability: (4) not assignable
21-MAY-01
(124)

5.9 Developmental Toxicity/Teratogenicity

Species: rat **Sex:** female
Strain:
Route of admin.: other: not stated
Exposure period: Not stated
Frequency of treatment: Daily
Duration of test: Days 6 to 15 of gestation

Doses: > 241 mg/kg body weights per day
Control Group: no data specified
Method: other
Year: **GLP:** no data
Test substance:
Result: "No indication of adverse effects on nidation, maternal or foetal survival. The number of abnormalities did not differ from control group."
Reliability: (4) not assignable
16-MAY-01 (39)

Species: other: rats and mice **Sex:** male/female
Strain:
Route of admin.: other: oral, diet
Exposure period: Not stated
Frequency of treatment: Not stated
Duration of test: Not stated
Doses: Feed containing 5% citric acid
Control Group: no data specified
Method: other: not stated
Year: **GLP:** no data
Test substance:
Remark: "5% Citric acid did not depress food intake but caused a loss in body weight gain and reduced survival time in mice, with a slightly greater influence on mature animals." ... "No effect was detected on the litter size or survival up to weaning of young in mice or rats."
Reliability: (4) not assignable
16-MAY-01 (124)

5.10 Other Relevant Information

Type: other: General systemic effects, single exposure (non-human,injection)
Remark: Citric acid and its salts injected by various routes into rats, mice and rabbits caused nervous system, lung, spleen and liver effects, some of which were attributed to physiological disturbances (acidosis and calcium deficiency).
Reliability: (4) not assignable
21-MAY-01 (44) (50) (125)

Type: other: General systemic effects, single exposure (non-human,injection)
Remark: Intravenous infusion of rats with sodium citrate solution (25 mM) was shown to increase calcium excretion.
Reliability: (4) not assignable
21-MAY-01 (9)

Type: other: General systemic effects, single exposure (non-human,injection)
Remark: No significant cardiovascular effects or effects on blood composition were seen in six horses injected intravenously with 0.56 mg sodium citrate/kg bw.

Reliability: (4) not assignable
21-MAY-01 (51)

Type: other: General systemic effects, single exposure (non-human, oral)
Remark: The effects of citric acid in mice and rats include physiological disturbances (acidosis and calcium deficiency).
16-MAY-01 (36)

Type: other: General systemic effects, single exposure (non-human, oral)
Remark: Severe damage to the stomach lining and nervous system effects were reported in rats, mice and rabbits receiving high doses of citric acid.
Reliability: (4) not assignable
21-MAY-01 (119) (125)

Type: other: General systemic effects, single exposure (non-human, oral)
Remark: The administration of 2ml/kg of a 500 mN citric acid solution (64 mg/kg bw) to rats by stomach tube decreased the volume of gastric juice secreted and the pepsin activity, but increased the total gastric acid content of the stomach.
Reliability: (4) not assignable
16-MAY-01 (81)

Type: other: Toxicity consideration
Remark: Citric acid is a powerful chelating agent and there is evidence that dietary citric acid may reduce the biological availabilty of iron and calcium.
16-MAY-01 (97) (124)

Type: other: Toxicity consideration
Remark: Other studies suggest that dietary citric acid and its salts may enhance calcium absorption and excretion and the absorption of sodium.
21-MAY-01 (18) (21) (92) (102)

Type: other: Toxicity consideration
Remark: It has been shown in an in vitro system for the development of artificial caries, that the application of citric acid to teeth may make them more susceptible to decay.
16-MAY-01 (73)

Type: other: Toxicity consideration
Remark: No formal acceptable daily intake level has been specified by the joint FAO/WHO Expert Committee on Food Additives since it was felt that citric acid and its calcium, potassium and sodium salts did not constitute a significant toxicological hazard to man when used according to good manufacturing practice.
A similar view was expressed by the EC's Scientific Committee for Food when it evaluated citrate.
16-MAY-01 (105) (120)

Type: other: Toxicity consideration
Remark: Citric acid and its salts may increase the absorption and retention of ingested metals such as aluminium, tin, cadmium and lead.
21-MAY-01 (42) (57) (60) (62) (100) (107) (108) (114)

Type: other: Toxicity consideration
Remark: Bovine teeth immersed in a soft drink containing 2.6 g citric acid/l were eroded within 2 hours.
21-MAY-01 (78)

Type: other: Toxicity consideration
Remark: Severe ulceration and tissue damage occured in dogs receiving tongue applications of 0.1ml of 50% citric acid solution (presumably aqueous) for 5 minutes.
21-MAY-01 (67)

Type: other: Toxicity consideration
Remark: Bronchoconstriction was induced with citric acid (of unspecified concentration) in dogs, which have non-specific airway hyperactivity.
21-MAY-01 (68)

Type: other: Toxicity consideration
Remark: When 14 guinea-pigs were exposed for 30 minutes to atmospheric citric acid concentrations of 31.1 or 81 mg/m3 (obtained by aerosolizing 4 or 6% solutions respectively), only one cough was recorded at the lower concentration, but significant coughing occured in the top group.
16-MAY-01 (126)

Type: other: Toxicity consideration
Remark: Coughing was produced in guinea-pigs exposed to 75 mg citric acid/ml as an aerosol for 3 minutes. Bronchoconstriction occured after 3-4 minutes.
16-MAY-01 (40)

Type: other: Toxicity consideration
Remark: Coughing occured frequently when 1 ml of an aqueous 0.27 M (about 52 g/l; 5.2%) solution of citric acid was instilled into the lower drachea (windpipe) of lambs, an effect which was not apparently seen when the acid was instilled into the mid-drachea or laryngeal area.
21-MAY-01 (52)

Type: other: Toxicity consideration
Remark: Mouth ulcers may be provoked by citric acid (human).
21-MAY-01 (38)

Type: other: Toxicity consideration
Remark: The lowest concentration of inhaled citric acid required to produce involuntary coughing in 23 men ranged from 0.5 to 32 mg/ml.
16-MAY-01 (101)

Type: other: Toxicity consideration

Remark: Citric acid (of unspecified concentration) induced bronchoconstriction) in human asthmatics.
16-MAY-01 (68)

Type: other: Toxicodynamics, Toxicokinetics
Remark: No studies located
16-MAY-01

5.11 Experience with Human Exposure

Remark: Systemic effects, single exposure (human, oral): a young woman vomited and almost died after ingesting a single dose of 25g citric acid [about 417 mg/kg bw].
21-MAY-01 (82)

Remark: Systemic effects, single exposure (human, injection): transfusions of large volumes of citrated blood may cause depletion of body calcium (hypocalcaemia) and effects on blood composition which may be accompanied by nausea, exacerbation of muscle weakness, breathing difficulties and even cardiac arrest.
21-MAY-01 (15) (16) (59) (106) (122)

Remark: General systemic effects, repeated exposure (human): minor gastrointestinal disturbances (diarrhoea, indigestion, nausea and "burning") were experienced by 22 out of 81 patients taking potassium citrate in water and seven out of 75 taking solid potassium citrate (dose unspecified in both cases) for the treatment of kidney stones.
21-MAY-01 (91)

Remark: Literature review: excretion of citric acid in 82 male and female adults ranges from 1.5 to 3.68 mmol/d (total range 0.4-8.80 mmol/d) respectively from 290 to 707 mg/d (total range 80-1,690 mg/d).
21-MAY-01 (66)

Result: Man's total daily consumption of citric acid from natural sources and from food additive sources may exceed 500 mg/kg
17-MAY-01 (124)

Remark: Citric acid ingested frequently or in large quantities may cause tooth erosion and local irritation.
17-MAY-01 (76)

Remark: Fourteen volunteers given oral doses of up to 73.5 m Eq (24.5 mmol) citrate as potassium-magnesium citrate, tripotassium citrate or trimagnesium citrate during the course of a bioavailability study did not suffer any overt gastrointestinal side effects.
17-MAY-01 (61)

Remark: General systemic effects, repeated exposure (human): potassium and sodium citrate (as the monohydrate and

dihydrate respectively) have been used presumably without marked side effects as medications in dose of up to 15 g/day.

21-MAY-01 (76) (120)

Remark: Three patients who ingested potassium citrate solution (one took an unknown large volume, probably on more than one occasion, two ingested 200-400 ml over 5-7 days) suffered abnormal heart rhythms, probably due to excessive potassium levels rather than to the citrate ion.

21-MAY-01 (14) (26)

Remark: The acid-base balance of the blood was affected in 10 men who ingested 60 ml of a solution containing 100 mg sodium citrate/ml daily (i.e. about 0.86 mg/kg bw/d) for 4 days. Their urine became more alkaline and the amount of sodium excreted was increased while that of magnesium and potassium was decreased.

21-MAY-01 (87)

Remark: Tooth erosion through dissolution of the enamel due to the acid effect in aqueous solution has been reported

21-MAY-01 (5)

Remark: Citric acid fumes apparently affected the teeth of exposed workers.

21-MAY-01 (45)

(1) A.N. Khomenco et al: Gidrokhim. Mater. 50: 96-101, 1969

(2) Al-Ani, Al-Lamy: Mutat. Res. 206: 467, 1988

(3) Allen et al.: J. Anim. Sci. 68: 2496, 1990 (BIBRA toxicity profile)

(4) Anbar, Neta: A compilation of specific biomolecular rate constant for the reactions of hydrated electrons, hydrogen atoms and hydroxyl radical with inorganic and organic compounds in aqueous solution. Int. J. Appl. Radiat. Isotopes 18: 493-523, 1967

(5) Asher & Read: Br. dent. J. 162: 384, 1987 (BIBRA toxicity profile)

(6) Behnke et al.: Ernährungsforschung 9 (2): 129, 1964 (BIBRA toxicity profile)

(7) BIBRA Toxicity profile: Citric acid and its common salts (TNO BIBRA Ltd., Carshalton, Surrey SM5 4DS, UK, 1993)

(8) Bonting, Jansen: Voeding 17: 137, 1956

(9) Borensztein et al.: Miner. Electrolyte Metab. 15: 353, 1989 (BIBRA toxicity profile)

(10) Bringmann, Kühn: Gwf Wasser/Abwasser 117(9), 1976

(11) Bringmann, Kühn: Gwf Wasser/Abwasser 122 (7): 308, 1981

(12) Bringmann, Kühn: Water Res. 14:231-241, 1980

(13) Bringmann, Kühn: Z.Wasser Abwasser Forsch. 15: 1-6, 1982

(14) Browning & Channer: Br. med. J. 283: 1366, 1981 (BIBRA toxicity profile)

(15) Bunker et al.: J. Am. med. Ass. 157: 1361, 1955 (BIBRA toxicity profile)

(16) Charney & Salmond: ASAIO Trans. 36: M217, 1990 (BIBRA toxicity profile)

(17) Coleman, Dewar: Addison-Wesley Science Handbook. Addison-Wesley, Don Mills (Ontario), 1997

(18) Cowley et al.: Clin. Chem. 35: 23, 1988 (BIBRA toxicity profile)

(19) CRC Handbook of Chemistry and Physics, 73 rd ed. CRC Press, Boca Raton, FL, 1992-1993

(20) CRC Handbook of Food Additives, 2nd ed. Chemical Rubber Company, Cleveland OH, 1972

(21) de Leacy et al.: Clin. Chem. 35: 1541, 1989 (BIBRA toxicity profile)

(22) DIMDI (Deutsches Institut für Medizinische Dokumentation und Information), Chemline-Database, 1993

(23) E.E. Shannon et al: Res. Rep. no. 61, Project 73-3-7, Canada, 1977

(24) E.Strassburger: Lehrbuch der Botanik, 1975

(25) ECAMA (European Citric Acid Manufacturers Association)

(26) Elizabeth & Carter: Br. med. J. 295: 993, 1987 (BIBRA toxicity profile)

(27) Ellis: US Fisheries Bull. 22 (XLVIII): 365-437, 1937

(28) F. Hoffmann-La Roche Environmental Laboratories, unpublished data, 1983

(29) F. Hoffmann-La Roche Ltd, specifications of Citric Acid, 1987

(30) F. Hoffmann-La Roche Ltd, unpublished Product Data Sheet, 1999

(31) F. Hoffmann-La Roche Ltd, unpublished report, 1976

(32) F. Hoffmann-La Roche Ltd, unpublished report, 1981

(33) F. Hoffmann-La Roche Ltd, unpublished report, 1984(a)

(34) F. Hoffmann-La Roche Ltd, unpublished report, 1984(b)

(35) F. Hoffmann-La Roche Safety Data Sheet, 25.02.2000

(36) Fed. Am. Soc. Exp. Biology, Bethesda, MD, for FDA, Bureau of Foods, 1977

(37) Fenaroli's Handbook of Flavour Ingredients, vol. 2, 2nd ed. Chemical Rubber Company, Cleveland OH, 1975

(38) Fisher: Contact Dermatitis, 3rd edition, Lea & Febiger, Philadelphia, p.420 (BIBRA toxicity profile)

(39) Food & Drug Research Laboratories, Inc.: Teratologic Evaluation of FDA 71-54 Contract no. 71-260, 1973 (BIBRA toxicity profile)

(40) Forsberg & Karlsson: Bull. Eur. Physiopathol. Respir. 23 (Suppl. 10): 71S, 1986 (BIBRA toxicity profile)

(41) Gericke, Fischer: A correlation study of biodegradability determinations with various chemicals in various tests. Ecotox. Environm. Safety 3: 159-173, 1979

(42) Gomez et al.: Toxicologist 11: 45, 1991 (BIBRA toxicity profile)

(43) Grant: Toxicology of the Eye, 3rd ed. Charles C.Thomas, Springfield IL, 1986

(44) Gruber & Halbeisen: J. Pharm. exp. Ther. 94: 65, 1948

(45) Gupta: J. Soc. Occup. Med. 40: 149, 1990 (BIBRA toxicity profile)

(46) Harry: The Principles and Practice of Modern Cosmetics, Vol. 2 Leonard Hill (Books) Ltd, London (BIBRA toxicity profile)

(47) Hayes et al.: Mutation Res. 130: 97, 1984 (BIBRA toxicity profile)

(48) HEDSET, Jungbunzlauer (for ECAMA), 1993

(49) Hockenbury, Grady: JWPCF (Journal of the Water Pollution Control Federation), May 1977

(50) Horn et al.: J. agric. Fd Chem. 5(10): 759, 1957

(51) Hubbell et al.: Vet. Surg. 16: 245, 1987 (BIBRA toxicity profile)

(52) Hutchinson et al.: Pediat. Pulmonol. 3: 45, 1987 (BIBRA toxicity profile)

(53) Inoue et al.: Cancer Lett. 40: 265, 1988 (BIBRA toxicity profile)

(54) Ishidate et al.: Food Chem. Toxicol. 22: 623, 1984

(55) Jaffe Toxicol. Ind. Health 11(5): 543, 1995

(56) Jensen: Studies on soil bacteria (Arthrobacter globiformis) capable of decomposing the herbicide endothal. Acta Agric. Scand. 14: 193-207

(57) Jugo et al.: Toxic. Appl. Pharmac. 34: 259, 1975 (BIBRA toxicity profile)

(58) Juhnke, Lüdemann: Z Wasser Abwasserforsch. 11:161, 1978

(59) Kelleher & Schulman: Am. J. Kidney Dis 9: 235, 1987 (BIBRA toxicity profile)

(60) Kirschbaum & Schoolwerth: Hum. Toxicol. 8: 45, 1989 (BIBRA toxicity profile)

(61) Koenig et al.: J. Urol. 145: 330, 1991 (BIBRA toxicity profile)

(62) Kojima et al.: Yakugaku Zasshi 98(4): 495, 1978 (BIBRA toxicity profile)

(63) Kowalski, RL; Hartnagel, RE: Toxicological Department, Miles Inc., unpubl. report, 1991

(64) Krop & Gold: J. Am. pharm. Ass. Sci. Ed. 34: 86, 1946 (BIBRA toxicity profile)

(65) Laden: J. Soc. cosmet. Chem. 24: 385, 1973 (BIBRA toxicity profile)

(66) Lentner et al.: Ciba-Geigy Tables. Basel 1975

(67) Lilly & Cutcher: J. biomed. Mater. Res. 6: 545, 1972 (BIBRA toxicity profile)

(68) Lindemann et al.: Fed. Amer. Soc. Exp. Biology J. 3: A 1227, 1989 (BIBRA toxicity profile)

(69) Litton Bionetics Inc. Summary of mutagenicity screening studies: host-mediated assay, cytogenetics, dominant lethal assay, compound FDA 71-54, citric acid (BIBRA toxicity profile)

(70) Litton Bionetics Inc; Contract no. FDA 71-268, 1975

(71) Ludzack, Ettinger: JWPCF (Journal of the Water Pollution Control Federation), 32(12): 1173, 1960

(72) Mackay D, Di Guardo A, Paterson S, Cowan CE: Evaluating the environmental fate of a variety of chemicals using the EQC model. Environ Toxicol Chem 15: 1627-1637, 1996. EQC and level III software is available free at http://www.trentu.ca/academic/aminss/envmodel/models.html

(73) Makris & Kotsanos: Odontostomat. Proodos. 42: 53, 1988 (BIBRA toxicity profile)

(74) Malaney, Gerhold: JWPCF (Journal of the Water Pollution Control Federation), 41(2, part 2): R18-R33, 1969

(75) Marhold: Preheld Prumyslove Toxikologie; Organicky Latky. Avicenum, Prague (CZ), p.658 (1986)

(76) Martindale, 1989

(77) Merck Index, 11 th edition, 1989

(78) Meurman et al.: Scand. J. Dent. Res. 98: 120, 1990 (BIBRA toxicity profile)

(79) Meylan, Howard, Epiwin, SRC

(80) Miles Laboratories, Inc., Pfizer, Inc., and Proctor and Gamble Co., 1977: The environmental safety of citrate. Presentation to the IJC task force on the ecological effects of non-phosphate detergent builders.

(81) Mochizucki et al.: Nut. Rep. Int. 40: 585, 1989

(82) Nazario: Ref. Inst. Adolfo Lutz 2: 141, 1952 (BIBRA toxicity profile)

(83) Niinimäki: Contact Dermatitis, 16: 11, 1987 (BIBRA toxicity profile)

(84) Ohgai, Matsui, Tsujinaka & Odanaka: Bull. Jpn. Soc. Sci. Fish 59(4): 647, 1993

(85) OHS Material Safety Data Sheet (10 September 1998), MDL Information Systems, Nashville, Tenn., USA

(86) Ono et al: Jap. J. Cancer Res. 83: 995, 1992 (BIBRA toxicity profile)

(87) Oster et al.: Clin. Chem. 35: 23, 1988 (BIBRA toxicity profile)

(88) Oyo Yakuri: Pharmacometrics 43: 561 (1992)

(89) P. Creach: C.R. Acad. Sci. (Paris) 240: 2551-2553, 1995

(90) Packman et al.: Toxic. appl. Pharmaz. 5: 163, 1963 (BIBRA toxicity profile)

(91) Pak: Miner. Elect. Metab. 13: 257, 1987 (BIBRA toxicity profile)

(92) Patra et al.: J. Pediatr. Gastroenterol Nutr. 11: 385, 1990 (BIBRA toxicity profile)

(93) Portmann & Wilson, Shellfish Information Leaflet No.22 (2nd ed), 1971

(94) QSAR, Epiwin 3.05 Syracuse Research Co.

(95) QSAR, modified Grain method, Epiwin

(96) Römpp Chemie-Lexikon, 9th ed. Georg Thieme, Stuttgart, 1989

(97) Rümenapf & Schwille Calcif. Tissue Int. 42: 326, 1988 (BIBRA toxicity profile)

(98) Safety Laboratory Test Report BS-2699, F. Hoffmann-La Roche Ltd, Basel

(99) Sax: Dangerous Properties of Industrial Materials. Van Nostrand Reinhold, New York NY, 1975

(100) Schenkel & Matthes In: Trace element analytical chemistry in medicine and biology. Proceedings Int. Workshop, Vol. 5. Edited by P. Braetter & P. Schramel, p.587, Walter de Gruyter & Co. Berlin, 1988 (BIBRA toxicity profile).

(101) Schreiber et al.: Am. Rev. Resp. Dis. 133: A216, 1986 (BIBRA toxicity profile)

(102) Schuette & Knowles Am. J. Clin. Nutr. 47: 884, 1988 (BIBRA toxicity profile)

(103) Schwartz et al.: J. Nutr. 118: 183, 1988 (BIBRA toxicity profile)

(104) Schwartz, Davis: EPA-600/2-74-003, US EPA, Washington, 1973

(105) Scientific Committee for Food. 25th Series. EUR 13416 EN, 1991 (BIBRA toxicity profile)

(106) Silverstein et al.: Trans. Am. Soc. Artif. Int. Organs 35: 22, 1989 (BIBRA toxicity profile)

(107) Slanina et al.: Clin. Chem. 32/3: 39, 1986 (BIBRA toxicity profile)

(108) Spickett et al.: Agents and actions 15: 3/4, 1984 (BIBRA toxicity profile)

(109) Sridharan, Lee: Environ. Sci. Technol. 6(12): 1031-1033, 1972

(110) Temime et al.: Revue fr. Diet. 69: 41, 1974 (BIBRA toxicity profile)

(111) Tuft & Ettelson: J.Allergy 27: 536, 1956 (BIBRA toxicity profile)

(112) Ullmann, Encyclopaedia of Technical Chemistry, 4th ed., 1975

(113) US Coast Guard, Dept of Transportation: Hazardous Chemical Data, vol II. US Government Printing Office, Washington DC, 1984-1985

(114) Van der Voet et al.: Toxic. Appl. Pharmac. 99: 90, 1989 (BIBRA toxicity profile)

(115) Veith et al: J Fish Res Bd Can 26: 1040-1048, 1976

(116) Verschueren: Handbook of Environmental Data on Organic Chemicals; 3rd ed. Van Nostrand Reinhold, 1996

(117) Viana de Camargo et al.: Jap. J. Cancer Res. 83: 1220, 1991 (BIBRA toxicity profile)

(118) Villard: Archs. Ophtal. 44: 21, 93, 167, 222 (BIBRA toxicity profile)

(119) Weiss et al.: Ind. Engng. Chem. 15: 6, 1923 (BIBRA toxicity profile)

(120) WHO Food Additives Series No.5 and 733, 1974 and 1986 (BIBRA toxicity profile)

(121) Wichlacz, Unz: Acidophilic, heterotrophic bacteria of acid mine waters. Appl. Environm. Microbiol. 41: 1254-1261, 1981

(122) Wirguin et al.: Ann. Neurol. 27: 328, 1990 (BIBRA toxicity profile)

(123) Wright, Hughes: Fd Cosmet. Toxicol. 14: 561, 1976 (BIBRA toxicity profile)

(124) Wright, Hughes: Nutr. Rep. Int. 13: 563, 1976 (BIBRA toxicity profile)

(125) Yokotani et al.: J.Takeda Res. Lab. 30(1): 25, 1971 (BIBRA toxicity profile)

(126) Zelenak et al.: Fund. Appl. Toxic. 2: 177, 1982 (BIBRA toxicity profile)

Robust Study Summaries

Citric Acid (CAS No. 77–92–9)

PHYSICAL/CHEMICAL ELEMENTS

1) Melting Point

Test Substance
- Citric Acid (CAS: 77–92–9)
- Purity: not stated

Method
- Method: not stated
- GLP: no
- Year: 1969

Results
- Melting Point Value: 152–159 ^{o}C

Conclusions

Data Quality
- Reliabilities: not assignable

References (Free Text)
- OHS Material Safety Data Sheet (10 September 1998), MDL Information Systems, Nashville, Tennessee, USA

Other
-

2) Boiling Point

Test Substance
- Citric Acid (CAS: 77–92–9)
- Purity: not stated

Method
- Method: not stated
- GLP: no
- Year: 1989

Results
- Value: –
- Decomposition: yes
- Remark: no boiling point due to substance decomposition above 175 ^{o}C

Conclusions
- The boiling point could not be determined due to substance decomposition

Data Quality
- Reliabilities: not assignable

References (Free Text)
- Römpps Chemie-Lexikon, 9th ed. Georg Thieme, Stuttgart, 1989

Other

3) Vapour Pressure

Test Substance
- Citric Acid (CAS: 77–92–9)

Method
- Method: QSAR estimation

Results
- Value: 7.3 x 10^{-7} Pa at 25 °C

Conclusions

Data Quality
- –

References (Free Text)
- QSAR, Epiwin 3.05 Syracuse Research Co.

Other
- –

4) Partition Coefficient

Test Substance
- Citric Acid (CAS: 77–92–9)
- Purity: not stated

Method
- Method: not stated
- GLP: no
- Year: 1983

Results
- Log Pow: –1.72
- Temperature: 20 °C

Conclusions
- –

Data Quality
- Reliabilities: not assignable

References (Free Text)
- Verschueren: Handbook of Environmental Data of Organic Chemicals, 3rd ed. Van Nostrand Reinold, New York, 1996

Other
- –

5) Water Solubility: Solubilities and *p*Ka Values

Test Substance
- Citric Acid (CAS: 77–92–9)
- Purity: not stated

Method
- Method: not stated
- GLP: no
- Year: 1989

Results
- Solubility value: 592,000 mg/l at 20 °C
- Solubility value: 643,000 mg/l at 30 °C
- pKa_1 = 3.13 at 25 °C
- pKa_2 = 4.76 at 25 °C
- pKa_3 = 6.4 at 25 °C

Conclusions
- Freely soluble in water
- Substance is partly present in ionised form at all environmentally relevant *p*H values.

Data Quality
- Reliabilities: not assignable

References (Free Text)
- The Merck Index, 11th edition, 1989

Other
- –

5) Water Solubility: *p*H Value

Test Substance
- Citric Acid (CAS: 77–92–9)
- Purity: not stated

Method
- Method: not stated
- GLP: no
- Year: 1998

Results
- *p*H value: 2.2 at 0.1 *N*

Conclusions
- –

Data Quality
- Reliabilities: not assignable

References (Free Text)
- OHS Material safety Data Sheet (10 September 1998), MDL Information Systems, Nashville, Tennessee, USA

Other
- –

ENVIRONMENTAL FATE AND PATHWAYS ELEMENTS

6) Photodegradation

Test Substance
- Citric Acid (CAS: 77–92–9)

Method
- Method:
- GLP:
- Year:

Results
- No studies located

Conclusions
- –

Data Quality
- –

References (Free Text)
- –

Other
- –

7) Stability in water

Test Substance
- Citric Acid (CAS: 77–92–9)
- Purity: not stated

Method
- Test type: abiotic degradation, no details stated
- Method: chemical analysis, half-life calculated
- GLP: no
- Year: 1967

Results
- $t_{½}$ at *p*H 1 = 72.9 years (calculated)
- Degradation rate constant: 0.30×10^{8} l/mol·s at room temperature in aqueous solution

Conclusions
- Remarks: abiotic degradation due to the reaction with OH radicals, based on literature value for OH radical concentration in water of 1×10^{-17} mol/l

Data Quality
- Reliabilities: not assignable

References (Free Text)
- Anbar, Neta: A compilation of specific biomolecular rate constant for the reactions of hydrated electrons, hydrogen atoms and hydroxyl radical with inorganic and organic compounds in aqueous solution. Int J Appl Radiat Isotopes 18: 493–523, 1967.

Other
- –

8) Transport between Environmental Compartments (Fugacity)

Test Substance

- Citric Acid (CAS: 77–92–9)

Method

- Method: Static environmental distribution model based on physicochemical parameters: Level I, EQC Model v.1.0
- Year: 1996

Results

- Media: air, sediment, soil and water
- Values: 99.99% to water, <0.01% to soil, <0.01% to sediment and <0.01% to air
- Remarks: Default values for the environmental parameters were not changed. Water solubility 592,000 mg/l, vapour pressure arbitrarily assigned 1 Pa and logPow –1.72 were used for the calculation.

Conclusions

- Practically no partitioning to air, soil and sediment, substance distributes heavily to water.

Data Quality

- –

References (Free Text)

- Mackay D, Di Guardo A, Paterson S, Cowan CE: Evaluating the environmental fate of a variety of chemicals using the EQC model. Environ Toxicol Chem 15: 1627–1637, 1996.

Other

- EQC software is available free at http://www.trentu.ca/academic/aminss/envmodel/models.html

9) Biodegradation

Test Substance
- Citric Acid (CAS: 77–92–9)
- Purity: not stated

Method
- Method: Directive 84/449/EEC, C.5 „Biotic degradation – modified Sturm test“
- Duration: not stated, probably 28 days (regular duration of test according to guideline)
- GLP: no
- Year: 1979
- Medium: water with activated sludge

Results
- Values: 97%, based on CO_2 evolution
  100%, based on DOC removal

Conclusions
- Readily biodegradable

Data Quality
- Reliabilities: reliable with restrictions

References (Free Text)
- Gericke, Fischer: A correlation study of biodegradability determinations with various chemicals in various tests. Ecotox Environm Safety 3: 159–173, 1979

Other
- –

ECOTOXICITY ELEMENTS

10) Acute Toxicity to fish

Test Substance
- Citric Acid (CAS: 77–92–9)
- Purity: not stated

Method
- Method: not stated
- Type: static
- GLP: no
- Year: 1978
- Species: *Leuciscus idus* (golden orfe, freshwater)
- Exposure period: 96 hours

Results
- Value: LC_{50} = 440–760 mg/l
- Remarks: solution was not neutralised

Conclusions
- Low toxicity for fish

Data Quality
- Reliabilities: reliable with restrictions

References (Free Text)
- Juhnke, Lüdemann: Z Wasser Abwasserforsch. 11: 161, 1978

Other
- –

11) Toxicity to aquatic plants

Test Substance
- Citric Acid (CAS: 77–92–9)
- Purity: not stated

Method
- Method: not stated
- GLP: no
- Year: 1980
- Species: *Scenedesmus quadricauda* (Algae, freshwater)
- Exposure period: 7 days

Results
- Value: EC_0 = 640 mg/l

Conclusions
- Low toxicity for algae

Data Quality
- Reliabilities: reliable with restrictions

References (Free Text)
- Bringmann, Kühn: Water Res 14: 231–241, 1980

Other
- –

12) Acute toxicity to aquatic invertebrates

Test Substance
- Citric Acid (CAS: 77–92–9)
- Purity: not stated

Method
- Method: not stated
- GLP: no
- Year: 1969
- Species: Daphnia magna (Crustacea)
- Exposure period: “Long-time exposure period in soft water”.

Results
- Values: EC_0 = 80 mg/l
  EC_{100} = 120 mg/l

Conclusions
- Geometric mean EC_{50} = 98 mg/l
- „Soft water“ does not buffer the acidity respectively the acid effect of the test substance.
- Low toxicity for daphnids

Data Quality
- Reliabilities: reliable with restrictions

References (Free Text)
- A.N. Khomenco et al: Gidrokhim. Mater 50: 96–101, 1969

Other
- –

HEALTH ELEMENTS

13) Acute toxicity

Test Substance
- Citric Acid (CAS: 77–92–9)
- Purity: > 99%

Method
- Type: acute oral toxicity study
- GLP: no
- Year: 1981
- Species: mouse, SPF, albino, source on record
- Sex: male + female
- Number of animals: 5 males + 5 females per treatment respectively control group, 60 animals in total in main study.
- Housing: single sex groups in macrolon cages, with ad libitum access to water and NAFAG 850 complete rodent maintenance diet feed, in a climate-controlled room with environmental parameters defined and on record
- Route of administration: oral, gavage
- Range-finding study: Performed with the following doses: 2,000 mg/kg, 2,828 mg/kg, 4,000 mg/kg, 5,657 mg/kg, 8,000 mg/kg and 10,000 mg/kg; 100% mortality after 24 h in highest dose group, 50% at 8,000 mg/kg, 20% at 5,657 mg/kg and 0% in all lower dose groups.
- Description main study: 5 male and 5 female mice in each treatment group were administered 3,000 mg/kg, 4,343 mg/kg, 6,000 mg/kg, 8,485 mg/kg or 12,000 mg/kg of citric acid by gavage. The test substance was dissolved in food grade tap water at such concentrations that in every group 20 ml/kg, corresponding to approx. 0.4 ml per animal, were given. Controls were administered 0.4 ml tap water by gavage. Clinical symptoms were observed 2 h and 24 h after administration. The survivors were followed-up for 10 days after dosing, mortalities were recorded daily, then survivors were sacrificed.
- LD_{50} was calculated using probit analysis and rounded to the nearest 100 mg value.

Results
- Value: LD_{50} = 5400 mg/kg bw, 95% confidence interval = 4,500–6,400 mg/kg.
- All mortalities occurred in the first 24 h after administration.

Conclusions
- Low toxicity to mic e.

Data Quality
- Reliabilities: reliable with restriction

References (Free Text)
- F. Hoffmann-La Roche Ltd, unpublished report, 1981

Other
- –

14) Genetic toxicity *in vivo* (chromosomal aberrations)

Test Substance
- Citric Acid (CAS: 77–92–9)
- Purity: not stated

Method
- Type: Dominant lethal assay
- Species: rat
- Sex: males (treated) and females (untreated)
- Number of animals: not stated
- Route of administration: oral
- Year: 1975
- GLP: no

Results
- No reduced number of foetuses resp. newborn rats in treatment group
- No chromosomal damage occurred in the bone marrow of rats ingesting up to 3 g citric acid/kg bw/day for 5 days.

Conclusions
- Not mutagenic in the reported test
- No mutagenic potential was detected in a dominant lethal assay in rats in which doses of up to 3 g citric acid/kg bw/day were administered for 5 days. A dominant lethal effect is normally reflected by increased early foetal death when treated males are mated with untreated females.

Data Quality
- Reliabilities: not assignable

References (Free Text)
- Litton Bionetics Inc 1975a, cited in: BIBRA Toxicity profile: citric acid and its common salts (TNO BIBRA Ltd., Carshalton, Surrey SM5 4DS, UK, 1993).

Other
- –

15) Genetic toxicity *in vitro* (gene mutations)

Test Substance
- Citric Acid (CAS: 77–92–9)
- Purity: not stated

Method
- Method: OECD Guideline 471, „Genetic Toxicology: *Salmonella thyphimurium* Reverse Mutation Assay“
- Type: bacterial reverse mutation assay
- Species/strains: *Salmonella typhimurium* TA 94, TA 98, TA 100, TA 1535, TA 1537
- Metabolic activation: with and without
- Meatbolic activation system: liver homogenate from rats pretreated with polychlorinated biphenyl KC-400
- Concentration: up to 5 mg/plate
- Year: 1984
- GLP: not stated

Results
- Result: no increased incidence of revertant colonies, both with and without metabolic activation

Conclusions
- Not mutagenic in the reported test

Data Quality
- Reliabilities: reliable with restrictions

References (Free Text)
- Ishidate et al.: Food Chem. Toxicol 22: 623, 1984

Other
- –

16) Repeated dose toxicity

Test Substance
- Citric Acid (CAS: 77–92–9)
- Purity: > 99 %

Method
- Method: not stated
- Year: 1976
- GLP: no
- Species: rat
- Strain: not stated
- Sex: 10 males and 10 females, average weight = 150 g
- Route of administration: oral, gavage
- Doses: 2,000 mg/kg/day, 4,000 mg/kg/day, 8,000 mg/kg/day, 16,000 mg/kg/day, vehicle only (control group)
- Vehicle: water, with test substance dissolved to attain the respective dose in the same volume administered
- Frequency of treatment: once daily
- Exposure period: 5 days
- Post. obs. period: 10 days, animals were observed for clinical signs, after 10 days survivors were sacrificed

Results
- Results: NOEL = 4000 mg/kg
  LD_{50} = 5600 ± 440 mg/kg/d, identical for males and females

Conclusions
- Low toxicity on repeated oral administration

Data Quality
- Reliabilities: reliable with restrictions

References (Free Text)
- F. Hoffmann La Roche Ltd, unpublished report, 1976

Other
- –

17) Reproductive toxicity

Test Substance
- Citric Acid (CAS: 77–92–9)
- Purity: not stated

Method
- Method: not stated
- Species: rat
- Type: two generation study
- Sex: male + female
- Route of administration: oral, dietary
- Frequency of treatment: daily (feed)
- Exposure period: 90 weeks
- Doses: feed containing 1.2% w/w citric acid, probably ad libitum
- Endpoints: reproduction parameters, blood chemistry, gross pathology, no further details given
- Year: 1956
- GLP: no

Results
- Results: cited as „ ... no harmful effects on the growth of two successive generations of rats over a 90-week period. No effect on reproduction, blood characteristics, pathology or calcium was observed, although a slight increase in dental attrition was reported.“

Conclusions
- No indication for reprotoxicity.

Data Quality
- Reliabilities: not assignable

References (Free Text)
- Bonting, Jansen: Voeding 17: 137, 1956; BIBRA Toxicity profile: citric acid and its common salts (TNO BIBRA Ltd., Carshalton, Surrey SM5 4DS, UK, 1993).

Other
- –

17) Reproductive toxicity

Test Substance
- Citric Acid (CAS: 77–92–9)
- Purity: not stated

Method
- Method: not stated
- Species: rat
- Sex: female
- Route of administration: oral, dietary
- Doses: feed containing 5% w/w citric acid (about 2.5 g/ kg bw/day)
- GLP: no

Results
- No effects on reproduction.
- NOEL = 2500 mg/kg/d

Conclusions
- No indication for reprotoxicity.

Data Quality
- Reliabilities: not assignable

References (Free Text)
- Wright, Hughes: Nutr. Rep. Int. 13: 563, 1976; BIBRA Toxicity profile: citric acid and its common salts (TNO BIBRA Ltd., Carshalton, Surrey SM5 4DS, UK, 1993).

Other
- –

18) Developmental Toxicity/Teratogenicity

Test Substance
- Citric Acid (CAS: 77–92–9)
- Purity: not stated

Method
- Method: not stated
- Species: rat
- Sex: males + females, numbers not stated
- Route of administration: not stated, probably oral, feed
- Frequency of treatment: daily
- Exposure period: days 6 to 15 of gestation
- Doses: > 241 mg/kg bw/d
- Year: 1973
- GLP: no

Results
- Results: „No indication of adverse effects on nidation, maternal or fetal survival. The number of abnormalities did not differ from control group.“

Conclusions
- No indication of maternal or foetal toxicity, no teratogenicity reported.

Data Quality
- Reliabilities: not assignable

References (Free Text)
- Food & Drug Research Laboratories, Inc.: Teratologic Evaluation of FDA 71-54 Contract no. 71-260, 1973

Other
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