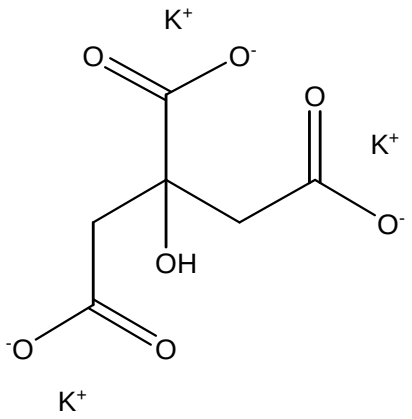
# POTASSIUM CITRATE (TRI)

## SYNONYMS

Citric acid,tripotassium salt
Tripotassium citrate
1,2,3-Propanetricarboxylic acid

## CHEMICAL STRUCTURE




## CHEMICAL FORMULA

$C_6H_5K_3O_7$

## IDENTIFIER DETAILS

| | | |
|---|---|---|
| CAS Number | : | 866-84-2, 6100-05-6 |
| CoE Number | : | - |
| FEMA | : | - |
| EINECS Number | : | 212-755-5 |
| E Number | : | E332 |

## CLP CLASSIFICATION

Ingredient CLP Classification: No

| Endpoint | Classification | Category |
|---|---|---|
| **Acute Oral Toxicity** | - | - |
| **Acute Dermal Toxicity** | - | - |
| **Acute Inhalation Toxicity** | - | - |
| **Skin Corrosive/irritant** | - | - |
| **Eye Damage/Irritation** | - | - |
| **Respiratory Sensitisation** | - | - |
| **Skin Sensitisation** | - | - |
| **Mutagenicity/Genotoxicity** | - | - |
| **Carcinogenicity** | - | - |
| **Reproductive Toxicity** | - | - |
| **Specific Target Organ Toxicity** | - | - |
| **Aspiration Toxicity** | - | - |

## SPECIFICATIONS

Melting Point: -

Boiling point: -

## PURPOSE

Flavouring compound

## STATUS IN FOOD AND DRUG LAWS

**CoE limits:**

| Beverages (mg/kg) | Food (mg/kg) | Exceptions (mg/kg) |
|---|---|---|
| - | - | - |

**Acceptable Daily Intake:**

| ADI (mg/kg) | ADI Set by | Date Set | Comments |
|---|---|---|---|
| Not Limited | JECFA | 1973 | - |

**FDA Status:** [CFR21]

| Section Number | Comments |
|---|---|
| 184.1625 | Potassium citrate - GRAS |

## HUMAN EXPOSURE

***Reported Uses:*** Potassium citrate is an alkaline agent that is prescribed for the prevention of nephrolithiasis in distal renal tubular acidosis [RTA] [Domrongkitchaiporn, *et al*., 2002].

It is used as a buffer to regulate acidity in food, and also in the preservation of cut flowers [HSDB, 2003]

## TOXICITY DATA

### *In Vivo* Toxicity Status

| Species | Test Type | Route | Reported Dosage |
|---|---|---|---|
| Dog | $LD_{50}$ | Intravenous | 167mg/kg |

[Lewis, 2000]

14 volunteers given oral doses of up to 73.5mEq [24.5 mmol] citrate as tripotassium citrate did not report overt gastrointestinal side effects [BIBRA, 1993], however, the i.v. injection of citric acid and it salts into mice, rats and rabbits is reported to produce nervous system, lung, spleen and liver effects. Many of these were changes were thought to be due to physiological disturbances (no further details) [BIBRA, 1993].

Potassium citrate has been used in medications in doses up to 15g/day without reported side effects [BIBRA, 1993].

A study in which 81 patients were administered potassium citrate in water [unknown quantity] revealed minor gastrointestinal disturbances such as diarrhoea, indigestion, nausea and 'burning' in 22 of these patients. These symptoms were also reported in 7 out of 71 people taking an unspecified dose of solid potassium citrate [BIBRA, 1993].

Three patients that had ingested a large volume of potassium citrate solution [One patient took an unknown large volume on more than one occasion, while the other two ingested 200-400 ml over a period of 5-7 days] suffered abnormal heart beat rhythms, which was assumed to be primarily due to the excessive potassium levels rather than due to the presence of the citrate ion [BIBRA, 1993].

### Reproductive and Developmental Toxicity

In a study in which 46 pregnant patients with cystinuria were being treated with high fluid intake alone or in combination with *D*-penicillamine and with most of the patients taking a mixture of sodium bicarbonate and potassium citrate during pregnancy [no number given], revealed that there were no pregnancy related problems in any of these patients [Gregory and Mansell, 1983].

A study in which, 3,200 pregnancies were followed in an investigation into drugs taken in the first trimester of pregnancy during 1953 - 1957 revealed that of these pregnancies, 266 were recorded as resulting in a malformation. The results indicated that maternal potassium citrate intake, may have been

the cause of a single birth resulting in a congenital malformation [Mellin, 1964].

It is documented that potassium citrate may be administered to pregnant women when maternal serum potassium levels are low [as in the case of a patient on a diuretic]. As high or low potassium levels are detrimental to maternal and foetal cardiac function, serum levels should be closely monitored if potassium citrate is administered. It should also be noted that human breast milk is naturally low in potassium, so no threat should come to a nursing infant as long as maternal potassium is kept within physiological ranges [Briggs *et al*., 1984].

Potassium citrate administered to Wistar rats at 5 % of the basal diet [for a 2 week period] was observed to reduce the promoting effect of Potassium dibasic phosphate [10 %] on *N*-ethyl-*N*-hydroxyethyl-nitrosamine [1000ppm] induced renal epithelial tumours [Konishi *et al*., 1993].

**Inhalation Toxicity**

The addition of potassium citrate at 12 ppm to reference cigarettes, used in a 90 day-sub-chronic inhalation exposure in rats, led to a series of pathological changes to smoke exposure that were indistinguishable from those changes caused by the control cigarettes. This indicated that addition of potassium citrate to a reference cigarette had no discernable effect upon the type or severity of the treatment related pathological changes associated with tobacco smoke exposure [Baker *et al.,* 2004]

**Other Relevant Studies**

The effect of potassium citrate (K-cit) as a dietary supplement on blood pressure in young healthy predominantly normotensive volunteers was assessed in a double blinded randomized placebo controlled trial. After 6 weeks supplementation compared with a placebo group (n=31) of 30mmol K-cit/day (n=28) resulted in a change in mean arterial pressure -5.22mmHg (95% CI-8.85, -4.43). Similar results were also observed with potassium chloride (KCl). For K-cit changes in systolic and diastolic BP were -6.69 (95% CI -8.85, -4.43) and -4.26 (95% CI -6.31, -2.21mmHg). A greater treatment related effect was observed in those with higher systolic BP. In summary increasing dietary potassium (K-cit and KCl) could have a substantial effect on the populations increasing BP levels [Braschi & Naismith, 2008].

A randomized cross-over trial compared the effects of potassium chloride, previously shown to lower blood pressure, with potassium citrate treatment in 14 hypertensives. Each treatment was given for 1 week with a 1 week washout between treatments. Blood pressure was significantly reduced for both treatments compared with baseline measurements. There was no significant difference between the treatments. It was concluded that foods high in potassium may have the same effect on blood pressure as potassium chloride [He *et al.,* 2005].

Direct application of potassium citrate crystals to the inside surface of the mouth did not produce sores, [this is in contrast to that reported for citric acid crystals] [BIBRA, 1993].

It has been reported that potassium supplements may cause mucosal damage of the gastrointestinal tract, therefore a study in which 36 healthy adults were given potassium-magnesium citrate, potassium citrate [70 mmol/day potassium and 23.4 mmol/day citrate], or placebo for seven days and examination of stools on day eight of the treatment, [stools were examined for traces of blood] and an oesophagogastroduodenoscopy, was also carried out [any mucosal lesions were scored at 5 sites] revealed that short-term use of potassium-magnesium citrate or potassium citrate did not induce mucosal lesions in the upper gastrointestinal tract [Gonzalez *et al*., 1998].

Vormann *et al*., (2001) reported that a study in which a lactose based alkaline multimineral supplement was administered for a 4 week period to patients with lower back pain, [received 30 g of the supplement which provided a 219 mg/daily dose of potassium citrate along with calcium, sodium and magnesium citrate with various other trace elements as lactates]. Was able to reduce the pain symptoms [possibly indicates that an acid-base disturbance contributes to lower back pain] [Vormann *et al*., 2001]

Renal stone patients (n=30) were given potassium citrate as a supplement for 1 month and evaluated for oxidative stress and renal tubular cell damage. Potassium citrate supplementation improved urinary citrate levels and oxidative stress, but there was no reduction in urinary lipid peroxidation products and the treatment provided no remedy to the renal tubular cell damage [Tungsanga K *et al.,* 2005].

A study on the blood pressure lowering effect of potassium citrate [administered as 120 mmol potassium and citrate], revealed that treatment for an 8 week period, in 25 patients [18 men, 7 women; mean age 48 [24-70] years] all with a history of essential hypertension lead to a significant reduction in both systolic and diastolic pressures by a mean of 6.2/3.8 mm Hg [$P < 0.05$] [Overlack *et al*., 1995].

Potassium citrate is an alkaline agent that is prescribed for the prevention of nephrolithiasis in distal renal tubular acidosis [RTA]. A recent study was conducted in order to determine the optimal dosage for correction of urinary abnormalities and the prevention of nephrolithiasis in eight children with distal RTA. The mean age of children in the study was $9.7 \pm 1.2$ years [mean body weight $29.1 \pm 4.7$ kg]. Children were treated in a stepwise fashion starting with an initial dose of 2 mEq/kg/d potassium citrate for 2 months this dose was then increased to 3 mEq/kg/d [2 months] and finally 4 mEq/kg/d [2 months]. Samples [blood and urine] were collected at the beginning of the study and every 2 months before an increase in the dose. Only at a dose of 4 mEq/kg/d was there a correction of urinary abnormalities and elevated urinary saturation for calcium oxalate but not for calcium phosphate in children with distal RTA [Domrongkitchaiporn *et al*., 2002].

Potassium citrate is used to treat recurrent hypercalciuric nephrolithiasis in combination with a thiazide diuretic. A recent study was conducted to determine if administration of a nonchloride potassium alkali with a kaliuretic and natriuretic agent (thiazide) may not be suitable to correct/prevent hypokalemia consequently resulting in hypochloremic metabolic alkalosis. Serum K+ and Cl- was measured in 95 patients (receiving combined therapy for 4 months). Serum K+ did not vary compared to controls. However, serum Cl- levels were found to be significantly lower (only by 1mEq/L) from pre-treatment but remained within the normal limits during treatment. The author concluded that co-administration of potassium citrate did not induce hypokalemia or hypochloremic metabolic alkalosis in patients treated with thiazide [Odvina *et al.,* 2003].

A group of 120 patients with calcium oxalate stones (idiopathic calcium stone formers) were treated with potassium citrate for 2 years. A metabolic study and distal radius bone mineral density (BMD) measurements were conducted. Potassium citrate treatment significantly increased forearm BMD, net gastrointestinal alkali absorption, urinary citrate and potassium excretion. Potassium citrate treatment was proposed as another therapeutic option for osteoporosis among calcium stone formers [Vescini *et al*., 2005].

A study in which researchers wanted to assess if long-term potassium citrate treatment enhanced aluminium absorption, in 10 patients with functioning kidneys who had calcium nephrolithiasis and were subsequently taking potassium citrate [40 mEq/day or more] for a period of 2-8 years revealed that 'there was no abnormal total body retention of aluminium following this long-term treatment' [Sakhaee *et al*., 1996].

Potassium citrate is thought to improve the heat stability of cow's milk in infant formulae which usually undergoes denaturation and aggregation of proteins on heating. Potassium citrate was permitted in follow-on-formula [both for infants and young children in good health] and foods for special medical purposes up to a maximum use level of 2g/kg. The opinion for foods, for infants and young children in good health and for special medical purposes indicated that the inclusion of potassium citrate is acceptable from birth onwards for the requested conditions of use [SCF, 1997].

The charts of 215 adult patients were retrospectively reviewed with recurrent renal stones whose only urinary metabolic risk factors were either hypocitraturia (HCit) or unduly acidic urine pH (UAUpH). In patients with HCit (n=55) potassium citrate therapy (average dose 48 +/- 14.7 mEq/d) caused a sustained increase in urinary citrate to normal levels, in urinary potassium and pH and in serum potassium. In patients with UAUpH (n=120) potassium citrate therapy (average dose 42.8 +/- 15.5 mEq/d) produced a significant increase in urinary pH, potassium, and uric acid. Remission rate was studied in 35 of these patients, whose median follow-up was 31.6 +/- 14.3 months. All of these patients received a mean dose of potassium citrate of 45.4 +/- 15.2 mEq/d. In 91% of these patients, there was no stone recurrence, similar for HCit and UAUpH patients. The authors concluded treatment with potassium

citrate corrects the metabolic abnormalities seen in patients with HCit and UAUpH [Spivacow et al., 2010]

**Behavioural data**

No data identified

***In Vitro* Toxicity Status**

**Carcinogenicity and Mutagenicity**

Potassium citrate gave a negative Ames mutation assay with *S. typhimurium* strains TA97 and TA102 [0.1-10 mg/plate] [test material solvent: distilled water]. A negative Ames mutation assay was also observed with metabolic activation [rat, liver, S-9, Aroclor 1254] for the above strains at 0.1-10 mg/plate [Fujita, 1992]. A negative Ames mutation assay with also observed with *Escherichia coli* [no strain given] in the absence and presence of liver enzymes, [no concentrations given] [BIBRA, 1993].

No clear evidence of mutagenicity was noted in assays using *S. cerevisiae* cells [in culture] with / without metabolic activation [BIBRA, 1993].

Baker *et al.,* [2004]; examined the effects of the addition of 482 tobacco ingredients upon the biological activity and chemistry of mainstream smoke. The ingredients, essentially different groups of flavourings and casings, were added in different combinations to reference cigarettes. The addition of potassium citrate at 12 ppm was determined not to have affected the mutagenicity of the total particulate matter (TPM) of the smoke in either the Ames, *in vitro* micronucleus assay or the neutral red assay when compared with that of the control cigarettes [Baker *et al.,* 2004].

Additional information concerning the *in vitro* mutagenicity of this material may be found in “An Interim report on data originating from Imperial Tobacco Limited’s Genotoxicity testing programme September 2003” or “An updated report on data originating from Imperial Tobacco Limited’s external Genotoxicity testing programme – Round 2 August 2007”.

## REACH Statement

This ingredient has been registered under REACH. Under REACH, registrants have an obligation to provide information on substances they manufacture or import. This information includes data on hazardous properties (covering various toxicological endpoints), guidance on safe use and classification and labelling. The European Chemicals Agency (ECHA) makes this information publicly available on its website: http://echa.europa.eu/.

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