Scientific Literature Review

Citric Acid and Its Inorganic Salts and Alkyl and Glycol Esters as Used in Cosmetics

June 9, 2011

All interested persons are provided 60 days from the above date to comment on this Scientific Literature Review and to identify additional published data that should be included or provide unpublished data which can be made public and included. Information may be submitted without identifying the source or the trade name of the cosmetic product containing the ingredient. All unpublished data submitted to CIR will be discussed in open meetings, will be available at the CIR office for review by any interested party and may be cited in a peer-reviewed scientific journal. Please submit data, comments, or requests to the CIR Director, Dr. F. Alan Andersen.

The 2011 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel Liebler, Ph.D.; James G. Marks, Jr., M.D., Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is F. Alan Andersen, Ph.D. This report was prepared by Monice M. Fiume, Senior Scientific Analyst/Writer and Bart A. Heldreth, Ph.D., Chemist.

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TABLE OF CONTENTS

INTRODUCTION

This report reviews the safety of citric acid, an α-hydroxy tricarboxylic acid, as used in cosmetics. Citric acid may function in cosmetics as a chelating agent, pH adjuster, or fragrance ingredient. This report also addressed the safety of the following 12 inorganic salts, 20 alkyl esters, and 13 glycol esters of citric acid as used in cosmetics:

Inorganic Salts

Aluminum Citrate
Calcium Citrate
Copper Citrate
Diammonium Citrate
Disodium Cupric Citrate
Ferric Citrate
Magnesium Citrate
Manganese Citrate
Monosodium Citrate
Potassium Citrate
Sodium Citrate
Zinc Citrate

Alkyl Mono-, Di-, and Triesters

Isodecyl Citrate
Isopropyl Citrate
Stearyl Citrate
Dilauryl Citrate
Distearyl Citrate
Tributyl Citrate
Tri-C 12-13 Alkyl Citrate
Tri-C14-15 Alkyl Citrate
Tricaprylyl Citrate
Triethyl Citrate
Triethylhexyl Citrate
Trihexyldecyl Citrate
Triisocetyl Citrate
Triisopropyl Citrate
Trilauryl Citrate
Trioctyldodecyl Citrate
Trioleyl Citrate
Triisostearyl Citrate
Tristearyl Citrate
Ethyl Citrates

Glycol Mono-, Di-, and Triesters

Disodium Laureth-7 Citrate
Laureth-6 Citrate
Laureth-7 Citrate
Propylene Glycol Citrate
Dilaureth-7 Citrate
Sodium Dilaureth-7 Citrate
PEG-5 Tricapryl Citrate
PEG-5 Trilauryl Citrate
PEG-5 Trimyristyl Citrate
PEG-5 Tricetyl Citrate
PEG-5 Tristearyl Citrate
Trilaureth-9 Citrate
Tripropylene Glycol Citrate

While some of the inorganic salts of citric acid may function as a pH adjuster or chelating agent, as citric acid does, these salts also have many diverse functions, including skin conditioning agent, buffering agent, cosmetic astringent, oral care agent, cosmetic biocide, or pesticide. The alkyl esters function primarily as skin conditioning agents, but a few have other possible functions, including plasticizer, solvent, and fragrance ingredient. The glycol esters of citric acid are reported to function mostly as skin conditioning agents or surfactants.

Citric acid, calcium citrate, ferric citrate, manganese citrate, potassium citrate, sodium citrate, diammonium citrate, and triethyl citrate are generally recognized as safe (GRAS) direct food additives. Therefore, the oral safety of these ingredients has been well substantiated. Since these ingredients have been shown to be safe for ingestion, this report will focus on the dermal application of these ingredients. For the other ingredients, all available data will be included.

CHEMISTRY

Definition, Structure, Properties, and Production

Citric acid (2-hydroxy-1,2,3-propanetricarboxylic acid), is a common metabolite of plants and animals, and is well known for its part in the Krebs cycle.[1] It precipitates as white, translucent crystals of monoclinic holohedra form. Citric acid

is a polyprotic, α-hydroxy acid (AHA). However, citric acid can also be classified as a β-hydroxy acid, as two of the carboxylic acid functional groups of citric acid are two carbons removed from the hydroxy group. (Figure 1).

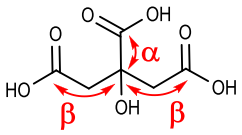


Figure 1. Citric Acid

As an AHA, the US Food and Drug Administration (FDA) recommended *Guidance for Industry: Labeling for Topically Applied Cosmetic Products Containing Alpha Hydroxy Acids as Ingredients*, from 2005,[2] may apply to a cosmetic product containing citric acid, and may warrant the following labeling:

> *Sunburn Alert: This product contains an alpha hydroxy acid (AHA) that may increase your skin's sensitivity to the sun and particularly the possibility of sunburn. Use a sunscreen, wear protective clothing, and limit sun exposure while using this product and for a week afterwards.*

CIR has previously reviewed two AHAs, and the associated salts and esters (i.e., the report on Glycolic Acid, Ammonium, Calcium, Potassium, and Sodium Glycolates, Methyl, Ethyl, Propyl, and Butyl Glycolates, Lactic Acid, Ammonium, Calcium, Potassium, Sodium, and TEA-Lactates, and Lauryl, Myristyl, and Cetyl Lactates[3]). Therein, the Expert Panel concluded that those ingredients "are safe for use in cosmetic products at concentrations ≤10%, at final formulation pH ≥3.5, when formulated to avoid increasing sun sensitivity or when directions for use include the daily use of sun protection. These ingredients are safe for use in salon products at concentrations ≤30%, at final formulation pH ≥3.0, in products designed for brief, discontinuous use followed by thorough rinsing from the skin, when applied by trained professionals, and when application is accompanied by directions for the daily use of sun protection."

Citric acid differs structurally from these AHAs by having three carboxylic functional groups, instead of just one. Due to these three carboxylic acid functional groups, citric acid has three different pK_as, making it a prime buffer component. Even the most acidic of these carboxylates, the center acid functional group, is only a weak acid, with a pKa of 3.1.

Industrial, large scale production of citric acid is accomplished, most commonly, via mycological fermentation of crude sugar stocks (e.g., molasses), historically by strains of *Aspergillus niger*.[4] A common problem associated with these fermentation methods is the co-synthesis of isocitric acid (***1***-hydroxy-1,2,3-propanetricarboxylic acid). However, this can be separated out via variety of crystallization techniques. Careful control of the trace element content is very important for high production.[1,5] While citric acid can also be extracted from citrus fruits, over 99% of the world's citric acid output is produced by microbial fermentation.[5] The citrate salts are produced by the same fermentation process, but are simply crystallized in the presence of appropriate alkaline solutions (e.g., citric acid can be crystallized with sodium hydroxide to produce sodium citrate). Citric acid is soluble in water and soluble in some organic liquids, with an octanol/water partitioning coefficient around -1. Citric acid, and the citrate salts, are solids.

The citrate alkyl esters and citrate glycol esters, however, vary from oily liquids (for shorter chain analogues like ethyl) to powdery solids (for longer chain analogues like stearyl). Directly dependent on chain length and degree of substitution, these esters are less soluble in water and more soluble in organic liquids, with octanol/water partitioning coefficients estimated between 1 and 12. Citrate alkyl esters are typically produced via the condensation of the appropriate alcohol (e.g., utilize butyl alcohol to produce tributyl citrate) with citric acid.[6] Similarly, the citrate glycol esters are

produced via the condensation of the appropriate, previously ethoxylated, alcohol (e.g., utilize laureth-9 to produce trilaureth-9 citrate) with citric acid.

The definitions and structures of the ingredients included in this review are provided in Table 1. The available physical and chemical property information is found in Table 2. Some ingredient specific methods of manufacture are:

Calcium Citrate

Calcium citrate is prepared by neutralizing citric acid with calcium hydroxide or calcium carbonate.[7]

Copper Citrate

Copper citrate is prepared by the interaction of hot aqueous solutions of copper sulfate and sodium citrate.[4]

Ferric Citrate

Ferric citrate is prepared from reaction of citric acid with ferric hydroxide.[8] It is a compound of indefinite ratio of citric acid and iron.

Manganese Citrate

Manganese citrate is obtained by precipitating manganese carbonate from manganese sulfate and sodium carbonate solutions.[9] The filtered and washed precipitate is digested first with sufficient citric acid solution to form manganous citrate and then with sodium citrate to complete the reaction.

Potassium Citrate

Potassium citrate is manufactured by crystallizing and drying a potassium citrate solution that is prepared using a citric acid solution and potassium hydroxide.[10]

Zinc Citrate

Zinc citrate is prepared from zinc carbonate and citric acid.[4]

Diammonium Citrate

Diammonium citrate is prepared by partially neutralizing citric acid with ammonia.[11]

Triethyl Citrate

Triethyl citrate is prepared by esterification of ethyl alcohol with citric acid.[12]

Tributyl Citrate

Tributyl citrate is synthesized from *n*-butyl alcohol and citric acid.[4]

Triisostearyl Citrate

Triisostearyl citrate is manufactured from isostearyl alcohol and citric acid in a proprietary esterification process, without the use of heavy metal catalysts.[13]

Trioctyldodecyl Citrate

Trioctyldodecyl citrate is manufactured from octyldodecyl alcohol and citric acid in a proprietary esterification process, without the use of heavy metal catalysts.[13]

Laureth-7 Citrate

Laureth-7 citrate is produced by the esterification of a fatty alcohol ethoxylate (laureth-7) with citric acid.[14]

Impurities/Composition

Citric Acid

Citric acid anhydrous, USP/FCC (US Pharmacopeia/Food Chemicals Codex), contains a maximum of 0.5% water, 0.015% sulfate, 0.036% w/w oxalic acid, 5.0 ppm heavy metals, and 0.5 ppm lead.[15]

Potassium Citrate

Potassium citrate, USP/FCC, contains a maximum of 10 ppm heavy metals and 2 ppm of lead.[16]

Stearyl Citrate

Commercially available stearyl citrate is composed of 10-15% monostearyl, 70-80% distearyl, and 10-15% tristearyl derivatives.[17]

Isopropyl Citrate

Commercially available isopropyl citrate is composed of 65-80% monoisopropyl, 15-30% diisopropyl, and 5-10% triisopropyl citrate.[17]

Triisostearyl Citrate

According to one supplier, triisostearyl citrate is supplied as >90% triisostearyl citrate.[13] Impurities include residual isostearyl alcohol (<10%) and citric acid (<0.5%).

Trioctyldodecyl Citrate

According to one supplier, trioctyldodecyl citrate is supplied as ~100% trioctyldodecyl citrate.[13] Impurities include [18]residual octyldodecyl alcohol (<5%) and citric acid.

Laureth-7 Citrate

According to one supplier, approximately 0.05% of a mixture of tocopherol and hydrogenated palm glycerides citrate, included as an antioxidant, may be present in laureth-7 citrate.[14] Laureth-7 citrate may also contain 7% (max.) citric acid. No residual preservatives or solvents are reported to be present.

USE

Cosmetic

Citric acid is reported to function in cosmetics as a chelating agent, pH adjuster, or fragrance ingredient.[18] Some of the inorganic salts of citric acid may function as a pH adjuster or chelating agent; these salts also have many diverse functions, including skin conditioning agent, buffering agent, cosmetic astringent, oral care agent, cosmetic biocide, or pesticide. The alkyl esters function primarily as skin conditioning agents, but a few of these have other possible functions, including plasticizer, solvent, and fragrance ingredient. The glycol esters of citric acid are reported to function mostly as skin conditioning agents or surfactants. The various cosmetic functions of these ingredients are provided in Table 3; some ingredients have more than one possible function.

Voluntary Cosmetic Registration Program (VCRP) data obtained from the FDA in 2011,[19] and concentration of use information received in response to a survey conducted by the Personal Care Products Council (Council),[20-22] indicate that 24 of the 46 citrates named in this report are currently used in cosmetic formulations. Citric acid is used in almost every category of cosmetic ingredients, with 6795 reported uses[19] at concentrations up to 39%.[21] Sodium, tributyl, and triethyl citrate are reported to be used in 980, 331, and 244 cosmetic formulations, respectively.[19] All other in-use ingredients have less than 50 uses. The ingredient with the highest concentration of use is triisostearyl citrate; it is used at up to 80% in lipstick formulations.[21] Trioctyldodecyl citrate is used at up to 30% in leave-on formulations; it is used at up to 21% in products applied to the eye area and 19% in lipstick formulations. Tricaprylyl citrate is used at up to 27% in leave-on formulations, and all other in-use ingredients are used at ≤12%.

Frequency and concentration of use data are provided in Table 4a. The ingredients not in use, according to the VCRP and Council survey, are listed in Table 4b.

Products containing citric acid and some of its salts and esters may be applied to baby skin, used near the eye area or mucous membranes, or could possibly be ingested or inhaled. Since some of these ingredients are reported to be in

products that could be inhaled, effects on the lungs that may be induced by aerosolized products containing these ingredients are of concern. The particle size of aerosol hair sprays and in pump hair sprays is around 38 μm and >80 μm, respectively, and is large compared to respirable particle sizes (≤10 μm). Therefore, because of their size, most aerosol particles are deposited in the nasopharyngeal region and are not respirable.

All of the ingredients included in this review are listed in the European Union inventory of cosmetic ingredients.[23] Zinc citrate has a maximum authorized concentration of use of 1%, calculated as zinc, in finished cosmetic products.[24]

Non-Cosmetic

The following ingredients are direct food additives with GRAS status, restricted only by good manufacturing practices: citric acid; calcium citrate; ferric citrate; manganese citrate; potassium citrate; sodium citrate; diammonium citrate; and triethyl citrate.[25] Additionally, the following are allowed as indirect food additives: citric acid; magnesium citrate; monosodium citrate; potassium citrate; sodium citrate; diammonium citrate; stearyl citrate; isopropyl citrate; distearyl citrate; triethyl citrate; tributyl citrate; tristearyl citrate.[26] Magnesium, potassium, and sodium citrate are used in over-the counter drug products.[18]

Examples of non-cosmetic uses of citric acid and some of the citrates are provided in Table 5.

TOXICOKINETICS

Citric acid is well absorbed and largely metabolized when administered orally; it is an intermediate in the Kreb's cycle. Oral administration of aluminum citrate to male Sprague-Dawley rats, 6 days/wk for 4 wks, resulted in a statistically significant increase in levels of aluminum in the brain in one study. In another study in which Sprague-Dawley rats were given aluminum citrate in the drinking water for 8 mos, aluminum levels were increased in other parts of the body but not in the brain. Distearyl citrate, when added to the diet of rats, was poorly absorbed, while nearly complete absorption was observed when isopropyl citrate was administered in the diet of rats.

Orally administered citric acid is well absorbed and largely metabolized.[17] Exogenous and endogenous citric acid can be completely metabolized and serve as a source of energy. Citric acid is an intermediate in the Krebs (or tricarboxylic acid) cycle.[27] Citric acid completes the breakdown of pyruvate, formed from glucose through glycolysis, and it liberates carbon dioxide. Approximately 2 kg of citric acid are formed and metabolized every day in humans. Citrate is thought to be freely filterable at the glomerulus of the kidney, and 65-90% of filtered citrate is reabsorbed in humans.[28] Ten to 35% of filtered citrate is excreted in the urine. The normal blood citrate level in humans is approximately 25 mg/l.[29]

In Vitro

Trihexyl Citrate

Trihexyl citrate is not a cosmetic ingredient. This information is presented because trihexyl citrate's structural similarity to cosmetic ingredients included in this review may provide read-across data.

Trihexyl citrate was incubated with rat serum, an intestinal cytosolic fraction, and a liver cytosolic fraction obtained from Sprague-Dawley rats to determine the hydrolysis of trihexyl citrate in each of these preparations.[30] Dimethyl sulfoxide (DMSO) was used as the vehicle; the volume of DMSO did not exceed 1% of the total volume of the incubation medium. A concentration of 50 nmol/l was used with all three preparations; a concentration of 1000 nmol/l was also used with rat serum. In rat serum, at concentrations of 50 and 1000 nmol/l, the half -life of trihexyl citrate hydrolysis was 4 and 90 min, respectively. Hexanol was produced as a product of hydrolysis. Dihexyl citrate is formed as an intermediate. Hydrolysis was concentration dependent, being faster at lower concentrations. Hydrolysis did not occur with 5 μmol/ml of serum. Hydrolysis in the rat intestinal and rat liver preparations proceeded much slower that in the serum. The half- life of hydrolysis for 50 nmol/ml trihexyl citrate in the rat liver cytosolic fraction was 1.2 min. (The half-life was not given for the intestinal fraction.)

Oral

Aluminum Citrate

Male Sprague-Dawley rats were gavaged with 100 mg aluminum/kg bw, as aluminum citrate, 6 days/wk for 4 wks.[31] A control group was given tap water. Half of the animals were killed at the termination of dosing; the remaining animals were killed after a 5-wk non-treatment period. The levels of aluminum in the brain were statistically significantly increased after 4 wks of dosing with aluminum citrate, and there was no major difference between the animals killed at the termination of dosing or 5 wks later.

Ten female Sprague-Dawley rats were given drinking water with 80 mmol/l aluminum citrate for 8 mos; a control group of 8 rats was given untreated water.[32] After 8 mos of dosing, aluminum concentrations were statistically significantly increased in bone, the spleen, liver, and kidneys, but not the brains, of treated animals.

Distearyl Citrate

Stearyl citrate is hydrolyzed readily to stearyl alcohol and citric acid in dogs, and to a lesser extent, in rats.[33] Stearyl citrate, predominantly as distearyl citrate, was added to the feed of rats at a concentration of 2.5-10%.[17] Stearyl citrate was poorly absorbed. (Additional details were not provided.)

Isopropyl Citrate

Isopropyl citrate, mostly as the monoisopropyl ester, was administered in the diet of 6 rats in a mono- and diglycerides vehicle at concentrations of ≤10%.[17] Isopropyl citrate was nearly completely absorbed. (Additional details were not provided.)

Effect on Transdermal Absorption

Triethyl Citrate

Triethyl citrate inhibited the transdermal absorption of viprostol, a synthetic prostaglandin E_2, through the skin of male hypertensive rats.[34] This effect was demonstrated by the statistically significant decrease in blood radioactivity levels following the topical application of [^{14}C]viprostol in triethyl citrate compared to those found with the use of petrolatum or silicone as the vehicle. Comparison of metabolic profiles also demonstrated slower hydrolysis of viprostol to free acid with the use of triethyl citrate as the vehicle.

TOXICOLOGICAL STUDIES

The dermal LD_{50} values for citric acid and triethyl citrate were >5 g/kg in rabbits. Results of oral, inhalation, and other parenteral single-dose studies with various citrates did not indicate any notable toxic effects in mice, rats, rabbits, or dogs. Oral dosing with aluminum citrate for 6 wks did not affect the body weights of rats. Repeated oral dosing with an isostearyl citrate ester mixture or a distearyl citrate ester mixture did not have adverse effects on rats, rabbits, or dogs. Repeated oral dosing with tributyl citrate did not have an adverse effect on rats or cats.

Single Dose (Acute) Toxicity

Acute toxicity studies are summarized in Table 6. Acute toxicity testing did not raise any toxicological concerns.

Repeated Dose Toxicity

Oral

Aluminum Citrate

In a toxicokinetics study described previously in this report, a group of 10 female Sprague-Dawley rats were given aluminum citrate in the drinking water at a concentration of 80 mmol/l for 8 mos.[32] Final body weights of animals of the test group were statistically significantly decreased compared to the controls. Kidney function was not affected by dosing.

Isostearyl Citrate

A 6-wk feeding study of an isopropyl citrate ester mixture, consisting of 27% isostearyl citrate, 9% diisopropyl citrate, and 2% triisostearyl citrate, in a vehicle consisting of mono- and diglycerides (1:1) of vegetable oil was performed using rats.[35] Male rats had an average daily intake of 0.78 g and females 0.54 g, and no adverse effects were observed. (Additional details were not provided).

Groups of 10 rats were fed diets containing 0, 0.28, 0.56, or 2.8% of the above isopropyl citrate ester mixture in the same vehicle (corresponding to 0, 0.11, 0.21, and 1.06% isopropyl citrate ester, respectively) for 2 yrs.[35] Again, no signs of toxicity were observed. Microscopic examination of select tissues did not reveal any test-article related changes.

Six-wk dietary and 6-wk gavage studies were performed in rabbits using the same isopropyl citrate ester mixture in the same vehicle.[35] Signs of toxicity was not observed in groups of 1-8 rabbits given feed containing 1.9-22.5% of the isopropyl citrate ester mixture or in groups of 1-3 rabbits gavaged daily with 0, 2.2, 4.4, or 9.2% of the isopropyl citrate ester mixture. Select tissues of the 8 high-dose males used in the feeding study were examined microscopically, and no abnormalities were found.

Groups of 2 cocker puppies and 2 adult mongrel dogs were also fed a diet containing the isopropyl citrate ester mixture in vehicle.[35] Adverse effects were not observed when dogs were fed a diet containing 0.06% of the test article for 12 wks.

Distearyl Citrate

A 6-wk feeding study of a distearyl citrate ester mixture, consisting of 12.5% stearyl citrate, 75% distearyl citrate, and 12.5% tristearyl citrate, was performed using rats.[35] Male rats had an average daily intake of 1.32 g and females 1.06 g, and no adverse effects were observed. (Additional details were not provided).

Groups of 10 rats were fed diets containing 0, 0.5, 2.0, or 10.0% of the distearyl citrate ester mixture for 2 yrs.[35] No signs of toxicity were observed. Microscopic examination of select tissues did not reveal any test-article related changes.

In a 6-wk dietary study in rabbits with the same distearyl citrate ester mixture, two groups of 8 rabbits were given feed containing 2 or 10 % of the mixture.[35] No signs of toxicity were observed. Select tissues of the rabbits of the 10% group were examined microscopically, and no abnormalities were found.

Groups of 2 cocker puppies and 2 adult mongrel dogs were also fed a diet containing the distearyl citrate ester mixture.[35] Adverse effects were not observed when dogs were fed a diet containing 3.0% of the test article for 12 wks.

Tributyl Citrate

Groups of three or four rats, number per sex not specified, were fed a diet containing 0, 5, or 10% tributyl citrate for 6 wks.[36] No effect on body weight gain was observed in the 5% group. Body weight gains in the 10% group were decreased; the decrease may have been attributable to frequent diarrhea. No effects on blood counts were reported, and no microscopic lesions were observed.

Two cats were dosed daily by gavage with 5 ml/kg tributyl citrate daily for 2 mos, and two cats were used as negative controls.[36] No significant effects were observed.

Intraperitoneal

Tributyl Citrate

A test group of 20 mice (sex not stated) were dosed by intraperitoneal (i.p.) injection with 580 mg/kg tributyl citrate in 3% acacia for 14 days, while a group of 20 control mice were dosed with vehicle only.[37] Two animals per group were killed at the end of the study. Body weight gains were decreased in the test animals, and the decrease was significant after 7 days. No significant changes in blood counts were observed, and no microscopic lesions were observed.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Oral administration of aluminum citrate concurrent with citric acid to rats was not maternally-, embryo-, or fetotoxic; the aluminum concentration was statistically significantly increased in the liver, bone, and placenta of the test animals, but no aluminum was detected in the fetus. Oral administration of an isopropyl citrate or diisostearyl citrate ester mixture did not produce any reproductive or developmental effects in multigeneration studies.

Oral

Aluminum Citrate

A group of 20 presumed pregnant rats were dosed daily by gavage with 1064 mg/kg bw aluminum citrate and 62 mg/kg bw citric acid, concurrently, on days 6-15 of gestation, and a negative control group of 20 gravid rats received distilled water only.[38] All animals were killed on day 20 of gestation. The actual numbers of gravid test and control rats were 15 and 17, respectively. Administration of aluminum citrate with citric acid was not maternally-, embryo-, or fetotoxic. A statistically significant increase in the absence of xiphoides was the only skeletal variation reported. The aluminum concentration in the maternal liver, kidney, brain, bone (femur), and placenta, as well as in the whole fetus, was determined. The aluminum concentration was statistically significantly increased in the liver, bone, and placenta of the test animals compared to controls; however, no aluminum was detected in the whole fetuses of treated animals.

Isopropyl Citrate

A multigeneration study was performed in which 5 generations of rats were fed a diet containing 0 or 2.8% of the isopropyl citrate ester mixture in vehicle (equivalent to 1.1% of isopropyl citrate esters) that was described earlier in this report.[35] Administration of the test article did not result in any reproductive or developmental effects or any general signs of toxicity.

Diisostearyl Citrate

A multigeneration study was performed in which 4 generations of rats were fed a diet containing 0, 1.9, or 9.5% of the diisostearyl citrate ester mixture that was described earlier in this report.[35] Administration of the test article did not result in any reproductive or developmental effects or any general signs of toxicity.

In-Vitro

Sodium Citrate

The embryotoxic potential of sodium citrate was evaluated in a whole rodent embryo culture system using 9.5-day-old embryos from female Han Wistar rats without metabolic activation.[39] The no-effect concentration for all parameters evaluated, including crown-rump length and abnormalities, was >115 µM sodium citrate.

Spermicidal Effects

Citric Acid

The spermicidal effect of citric acid was determined by suspending human sperm in a solution of citric acid.[40] Addition of 0.1% citric acid to human sperm reduced pH and rendered sperm immotile within 30 min, while 1% was almost instantly spermicidal. The effect on sperm penetration of cervical mucus was also evaluated by adding the acid to human cervical mucus in capillary tubes. Addition of 0.01% citric acid reduced, and addition of 0.1% completely abolished, sperm penetration.

GENOTOXICITY

Citric acid and its salts and esters gave mostly negative reports in in vitro and in vivo genotoxicity tests. Exceptions were weakly positive results in in vitro and in vivo host-mediated assays with citric acid, equivocal results in an Ames test with aluminum citrate, and a weak dose-related response in a suspension test in S.

typhimurium *TA1537 that was not reproducible. Citric acid had anti-mutagenic effects, inhibiting the mutagenicity of 4-nitro*-o-*phenylenediamine and sodium azide.*

Genotoxicity studies are summarized in Table 7. Citric acid and its salts and esters gave mostly negative reports in in vitro and in vivo genotoxicity tests. Exceptions were weakly positive results in in vitro and in vivo host-mediated assays with citric acid, equivocal results in an Ames test with aluminum citrate, and a weak dose-related response in a suspension test in *S. typhimurium* TA1537 that was not reproducible.

Anti-Mutagenic Effects

Citric Acid

The anti-mutagenic effect of citric acid was evaluated in an Ames test, with 4-nitro-*o*-phenylenediamine and sodium azide used as mutagens.[41] Using *S. typhimurium* strain TA97, concentrations of 1-1000 µg/0.1 ml/plate citric acid inhibited the mutagenicity of 20 µg/0.1 ml/plate 4-nitro-*o*-phenylenediamine by 3.54-67.72% without metabolic activation and 55.34-71.97% with metabolic activation. Using strain TA100, concentrations of 1-1000 µg/0.1 ml/plate citric acid inhibited the mutagenicity of 1.5 µg/0.1 ml/plate sodium azide by 15.47-50.65% without metabolic activation and 37.47-67.10% with metabolic activation.

CARCINOGENICITY

Aluminum Citrate

The National Toxicology Program (NTP) has planned toxicity/carcinogenicity testing for aluminum citrate.[42] The rationale for testing is a that aluminum is aluminum is listed by the EPA as a drinking water contaminant with a high health research priority.

IRRITATION AND SENSITIZATION

In irritation studies in rabbits, 30% citric acid was not a primary irritant, 60% produced some erythema and edema that subsided with time, and undiluted citric acid produced mild to severe erythema and mild to moderate edema. Triethyl citrate, at concentrations up to 100%, was not an irritant in guinea pigs or rabbits, and trioctyldodecyl citrate applied neat was not a primary skin irritant in rabbits. In human studies, citric acid was not a dermal irritant at concentrations of up to 5% aq., and 20% triethyl citrate was not irritating in humans. Sodium citrate did not produce any immediate (non-immunologic contact urticaria) reactions. In sensitization testing, citric acid produced positive results in 3 of 91 patients. Triethyl citrate was a strong sensitizer in a guinea-pig maximization test, but it was not a primary irritant in human studies. Trioctyldodecyl citrate was a mild sensitizer in a local lymph node assay, but it was not an irritant or sensitizer in human studies. Tributyl citrate was not a sensitizer in animal studies. In human studies, tristearyl citrate, triisostearyl citrate, and laureth-7 citrate were not irritants or sensitizers in repeated insult patch tests. Citric acid was predicted to be a moderate/severe to severe/extreme ocular irritant in in vitro studies, and was minimally to mildly irritating at concentrations of 10 and 30%, respectively, in studies using rabbits. In in vitro studies, tri-isostearyl citrate was predicted to be non-irritating and laureth-7 citrate was predicted to be slightly irritating to eyes. Triethyl citrate did produce irritation in rabbit eyes, and trioctyldodecyl citrate was non-irritating.

Skin Irritation/Sensitization

Non-human and human skin irritation and sensitization studies are summarized in Table 8. In non-human studies, irritation and sensitization study results varied, while no irritation or sensitization was reported in human studies.

Mucosal Irritation

Mucosal irritation studies are summarized in Table 9. In Draize tests, citric acid and triethyl citrate produced some irritation and trioctyldodecyl citrate was non-irritating to rabbit eyes.

Case Reports

Citric Acid

A woman reported difficulty breathing and severe facial pain 4 h after a professionally-administered cosmetic peel procedure with a product containing 10% citric acid (and other compounds that were not identified).[43] The facial peel was applied for 4 h. The patient also had first and second degree burns to the face and anterior neck. Permanent facial and neck scars, but no airway pathology, resulted.

MISCELLANEOUS STUDIES

Citric acid increased cell renewal and epidermal thickness in human skin, and there appeared to be a greater increase at higher concentrations and/or lower pH of citric acid. Citric acid is a tussive agent. The cough reflex to citric acid is produced by irritation of the larynx and the trachea, and is thought to be mediated by receptors that are distributed mainly in the larynx and upper airways. Triethyl and tributyl citrate had an anesthetic effect in rabbit eyes.

Effects in Skin

Citric Acid

The effect of 1M citric acid on skin cell renewal and irritation (as stinging) was determined at pHs of 3, 5, and 7.[44] The dansyl chloride method was used to determine skin cell renewal and irritation was evaluated subjectively as stinging in the nasal fold area; stinging was scored on a scale of 1-5 every minute for 15 min. Two mg/cm^2 of the citric acid test product were applied to the test area on the volar forearmoof human subjects 2x/daily. The vehicle consisted of 15% ethanol (SD 40), 5% ethoxydiglycol, 5% butylene glycol, and water. Cell renewal was measured in at least 8 subjects; citric acid increased cell renewal by 16.1, 12.8, and 3% at pH 3, 5, and 7, respectively. Using a minimum of 10 subjects, the irritation scores for 1 M citric acid at pH 3, 5, and 7 were 39.4, 37.1, and 23.1, respectively.

The effect of 5% citric acid on skin cell renewal and irritation was also evaluated at the same pH levels.[45] Cell renewal was greater at this higher concentration; 18, 14, and 8% increases were seen with 5% citric acid at pH 3, 5, and 7, respectively. Irritation scores (as stinging) were 2.3, 2.1, and 1.1 (on a scale of 1-5) at pH 3, 5, and 7, respectively. (Details of application were not provided.)

Five male subjects participated in a 30-day study to evaluate the effects of citric acid on skin morphology.[46] Cream formulations containing 10, 20, or 25% citric acid were evaluated, and 0.2 ml of each cream were applied to a 2 cm x 2 cm area of the ventral forearm of each subject. A fourth site on the forearm was used as an untreated control. Occlusive patches, 3x/wk, were applied during wk 1 and non-occlusive patches, 3x/wk, were applied during wks 2-3. Open applications were made daily during wk 4. At the end of dosing, a 3 mm punch biopsy was taken from each site. Irritation was observed with the 20 and 25% formulations. (Details as to the extent of irritation was not provided, other than it was "visible"). Microscopically, an increase in viable epidermal thickness that increased with dose was observed at all dose levels, a "substantial" increase in Langerhans cells was observed with the 20 and 25% citric acid creams, and glycosaminoglycan (GAG) content was "markedly" increased at the sites dosed with 20 and 25% citric acid compared to that seen at the untreated and 10% citric acid sites.

A 20% citric acid lotion, pH 3.5, was applied twice daily for 3 mos to photodamaged skin of the forearm of 6 female subjects.[47] The lotion vehicle without citric acid was applied to the contralateral arms as a control. A 4-mm punch biopsy specimen was taken from each site after 3 mos of application. Application of the lotion containing citric acid produced a statistically significant increase in skin-fold thickness, with a 16.3% increase from baseline recorded. The skin fold thickness of the vehicle-treated skin decreased slightly. Viable epidermis thickness also increased in a statistically significant manner, increasing 40% as compared to untreated skin. A statistically significant increase in GAG content was evidenced by a 2.5-

fold increase in epidermal hyaluronic acid staining, a 57% increase in dermal hyaluronic acid staining, and a 66% increase in dermal chondroitin sulfate staining, as compared to skin treated with vehicle only. (While the % increase in staining was greater for chondroitin sulfate; staining for hyaluronic acid was approximately double that of chondroitin sulfate in both vehicle and citric-acid treated sites.)

Seven subjects with moderate to severe photoaged skin applied a lotion containing 25% citric acid, pH 3.5, to one forearm and a placebo lotion to the other forearm twice daily for 6 mos.[48] (Similar lotions containing glycolic or lactic acid were also evaluated.) Skin thickness measurements were performed in triplicate throughout the study. The two-skin-layer thickness of the forearm treated with citric acid (and the other AHAs) increased 25%, while the thickness of the control forearm decreased 2%; the difference between the citric acid and control sites was statistically significant. (There was no statistically significant difference in skin thickness among the three AHAs tested.) Microscopically, the mean epidermal thickness of skin and the mean thickness of papillary dermis in samples of skin treated with the citric acid lotion were statistically significantly greater than controls. (Total number of samples examined microscopically not given). There was no indication of inflammation. The amount of ground substance was variably increased in the citric acid-treated samples. Collagen fibers appeared to be increased in treated skin samples, but there was not a statistically significant difference in collagen fiber density in the papillary dermis between AHA-treated and untreated sites.

It has been hypothesized that AHAs have the following mechanism of action.[49] In the stratum corneum, a low concentration of AHAs diminish corneocyte cohesion. In keratinocytes, AHAs stimulate epidermal proliferation, possibly by improving energy and redox status of the keratinocytes. In fibroblasts, high concentrations of AHA in an appropriate vehicle is thought to induce epidermolysis and epidermal separation, and impact the papillary dermis and reticular dermis, leading to dermal changes that include the synthesis of new collagen.

Lipid Bilayer Permeation

Aluminum Citrate

The lipid bilayer permeation of neutral aluminum citrate was determined by measuring the flux across unilamellar phospholipid vesicles, or liposomes, using two independent procedures.[50] The permeation of aluminum citrate was then compared to that of citric acid (as well as malic and lactic acids). Lipid bilayer permeation of 1.82 mM aluminum citrate was slow; the permeability coefficient was, at most, 2×10^{-11} cm/s. Comparison of permeation of aluminum citrate to the acids indicated that the flux of aluminum citrate is limited by diffusion across the water/lipid interface. (The permeability coefficient for 6.0 mM citric acid was 3.1×10^{-11} cm/s.)

Cough Reflex

Citric Acid

Citric acid is used as a tussive agent.[51] Ten human subjects were exposed to incremental doses of citric acid (10-1000 mM) using an air-driven nebulizer. Using the mean cough frequency, a statistically significant dose-response relationship was observed. Individuals had different threshold and maximum tolerable concentrations; using interpolated values, the concentration that caused five coughs was 141.3 mM citric acid. Using 10 Dunkin Hartley guinea-pigs exposed to 0.9% saline and then, 10 min later, a single challenge of 30-300 mM citric acid for 2 min, the calculated concentration producing five coughs (in 10 min) was 74.1 mM citric acid.

The cough reflex to citric acid is produced by irritation of the larynx and the trachea, and thought to be mediated by receptors that are distributed mainly in the larynx and upper airways.[52] In human subjects, the cough reflex was reduced with higher inspiratory flow rates as opposed to lower rates. The researchers were not able to definitively state a reason the decrease was seen, but did state an important factor may be laryngeal deposition of the aerosol.

Anesthetized guinea pigs were administered 10% w/v aq. citric acid for 1 min; airway resistance increased 79% and lung compliance decreased 68%.[53] In anesthetized guinea pigs in which the vagi had been cut, a 5% increase in resistance and compliance was seen following exposure to citric acid. In conscious guinea pigs exposed to a 10% w/v aq. aerosol of citric acid for 2 min using a glass nebulizer (particle size, 0.5-4 μm), the animals coughed 1-2 times in the first 30 sec, and then a short period of hyperventilation was observed. The researchers theorized that the bronchoconstriction was due to an increase in airway resistance and involved parasympathetic innervation.

Anesthetic Effects

Triethyl and Tributyl Citrate

The corneal reflex in rabbit eyes was temporarily eliminated upon instillation of 3 drops of a 5% suspension of triethyl or tributyl citrate in 3% acacia; the number of animals used was not stated.[37] The anesthetic effect was confirmed by the intradermal administration of 0.1 ml of a 2% solution of triethyl or tributyl citrate into an area of the shaved back of guinea pigs; the number of animals used was not stated. Triethyl citrate resulted in insensitivity to pricking of the area for 12-20 min, while tributyl citrate produced a "deadened area" for a period greater than 2 h.

INFORMATION SOUGHT

In that citric acid is an AHA, the Expert Panel might be interested in the same types of information that was focused on in the Discussion section of the report on the AHAs glycolic and lactic acids.[3] The areas of concern that were discussed are irritation potential, potential penetration enhancement of other ingredients, and the potential increase in sensitivity to sunlight. Additionally, dermal absorption data on citric acid and its salts and esters have not been found in the published literature. If citric acid does absorb through the skin, dermal reproductive and carcinogenicity data may be needed. If citric acid does not appreciably absorb, these data may not be crucial, but if available, they would improve the resulting safety assessment. (Please note that although certain types of information are stated above as desirable for this report, the Expert Panel may or may not ask for these types of data, and they may ask for additional types of data).

SUMMARY

Citric acid is an α-hydroxy tricarboxylic acid that functions in cosmetics as a chelating agent, pH adjuster, or fragrance ingredient. (Citric acid can also be classified as a β-hydroxy acid.) The 12 inorganic salts have many diverse functions, while the 33 alkyl and glycol esters function mostly as skin conditioning agents, although they can have other functions. Citric acid is used in almost every category of cosmetic ingredient, with 6795 reported uses[19191918] at concentrations up to 39%. With the exception of sodium, tributyl, and triethyl citrate, all other in-use ingredients have less than 50 uses. Triisostearyl citrate is used at up to 80% in lipstick formulations. Trioctyldodecyl and tricaprylyl citrate are used at concentrations of 30 and 27%, respectively; all other in-use ingredients are used at ≤12%.

Citric acid, calcium citrate, ferric citrate, manganese citrate, potassium citrate, sodium citrate, diammonium citrate, and triethyl citrate are GRAS direct food additives.

Citric acid is ubiquitously found in nature in virtually all organisms as an intermediate of the Krebs cycle. Orally administered citric acid is well absorbed and largely metabolized. Oral administration of aluminum citrate to male Sprague-Dawley rats, 6 days/wk for 4 wks, resulted in a statistically significant increase in levels of aluminum in the brain in one study. In another study in which Sprague-Dawley rats were given aluminum citrate in the drinking water for 8 mos, aluminum levels were increased in other parts of the body, but not in the brain. Distearyl citrate, when added to the diet of rats,

was poorly absorbed, while nearly complete absorption was observed when isopropyl citrate was administered in the diet of rats.

The dermal LD_{50} values for citric acid and triethyl citrate were >5 g/kg in rabbits. Results of oral, inhalation, and other parenteral single-dose studies with various citrates did not indicate any notable toxic effects in mice, rats, rabbits, or dogs. Oral dosing with aluminum citrate for 6 wks did not affect the body weights of rats. Repeated oral dosing with an isostearyl citrate ester mixture or a distearyl citrate ester mixture did not have adverse effects on rats, rabbits, or dogs. Repeated oral dosing with tributyl citrate did not have an adverse effect on rats or cats.

Oral administration of aluminum citrate concurrent with citric acid to rats was not maternally-, embryo-, or feto-toxic; the aluminum concentration was statistically significantly increased in the liver, bone, and placenta of the test animals, but no aluminum was detected in the fetus. Oral administration of an isopropyl citrate or diisostearyl citrate ester mixture did not produce any reproductive or developmental effects in multigenerational studies.

Citric acid and its salts and esters gave mostly negative reports in in vitro and in vivo genotoxicity tests. Exceptions were weakly positive results in in vitro and in vivo host-mediated assays with citric acid, equivocal results in an Ames test with aluminum citrate, and a weak dose-related response in a suspension test with sodium citrate in *S. typhimurium* TA1537 that was not reproducible. Citric acid had anti-mutagenic effects, inhibiting the mutagenicity of 4-nitro-*o*-phenylenediamine and sodium azide.

In irritation studies in rabbits, 30% citric acid was not a primary irritant, 60% produced some erythema and edema that subsided with time, and undiluted citric acid produced mild to severe erythema and mild to moderate edema. Triethyl citrate, at concentrations up to 100%, was not an irritant in guinea pigs or rabbits, and trioctyldodecyl citrate applied neat was not a primary skin irritant in rabbits. In human studies, citric acid was not an irritant at concentrations of up to 5% aq. or in a cream containing 10% citric acid; creams containing 20 or 25% citric acid did produce irritation in human subjects. Tiethyl citrate, 20%, was not irritating in humans. Sodium citrate did not produce any immediate (non-immunologic contact urticaria) reactions.

In sensitization testing, citric acid produced positive results in 3 of 91 patients. Triethyl citrate was a strong sensitizer in a GPMT, but it was not a primary irritant in human studies. Trioctyldodecyl citrate was a mild sensitizer in a LLNA, but it was not an irritant or sensitizer in human studies. Tributyl citrate was not a sensitizer in animal studies. In human studies, tristearyl citrate, triisostearyl citrate, and laureth-7 citrate were not irritants or sensitizers in HRIPTs.

Citric acid was predicted to be a moderate/severe to severe/extreme ocular irritant in in vitro studies, and was minimally to mildly irritating at concentrations of 10 and 30%, respectively, in studies using rabbits. In in vitro studies, triisostearyl citrate was predicted to be non-irritating and laureth-7 citrate was predicted to be slightly irritating to eyes. In Draize tests, triethyl citrate did produce irritation, and trioctyldodecyl citrate was non-irritating, to rabbit eyes.

Citric acid increased cell renewal and epidermal thickness in human skin, and there appeared to be a greater increase at higher concentrations and/or lower pH of citric acid. Citric acid is a tussive agent. The cough reflex to citric acid is produced by irritation of the larynx and the trachea, and is thought to be mediated by receptors that are distributed mainly in the larynx and upper airways. Triethyl and tributyl citrate had an anesthetic effect in rabbit eyes.

TABLES

Table 1. Definitions and structures of citric acid, salt and esters

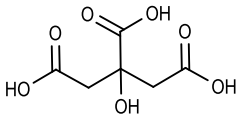
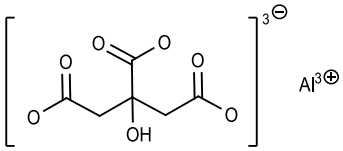
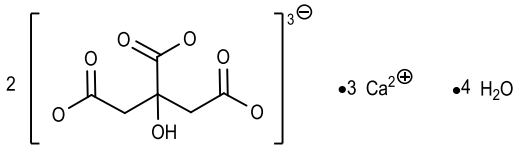
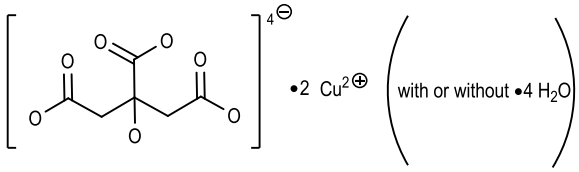
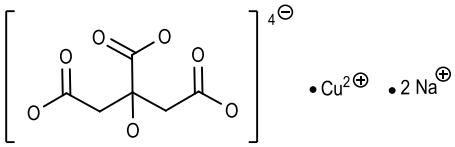
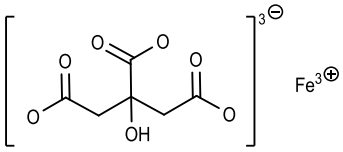
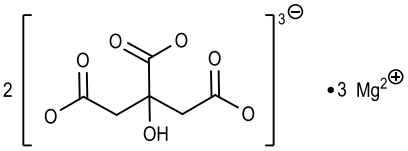
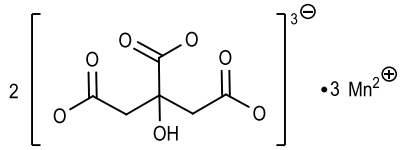
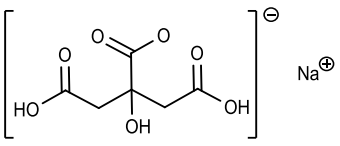
Ingredient CAS No.	Definition	Formula/structure
Citric Acid and inorganic salts		
Citric Acid 77-92-9 5949-29-1 [hydrate]	an α-hydroxy tricarboxylic acid	
Aluminum Citrate 813-92-3 31142-56-0	a complex salt of aluminum hydroxide and citric acid	
Calcium Citrate 5785-44-4	the calcium salt of citric acid	
Copper Citrate 10402-15-0 866-82-0 (hemitrihydrate)	the complex copper (II) salt of citric acid. Herein, copper complexes with the carboxylates and the hydroxyl group.	
Disodium Cupric Citrate 38218-87-0 65330-59-8	the disodium salt of the complex formed between copper (II) and citric acid. Herein, copper complexes with the hydroxyl group and one of the carboxylates.	
Ferric Citrate 2338-05-8 3522-50-7 [hydrate] 28633-45-6	the iron (III) salt of citric acid	
Magnesium Citrate 144-23-0 6150-79-4 7779-25-1	the magnesium salt of citric acid	
Manganese Citrate 10024-66-5	the manganese (II) salt of citric acid	
Monosodium Citrate 994-36-5 18996-35-5	the monosodium salt of citric acid	

Table 1. Definitions and structures of citric acid, salt and esters

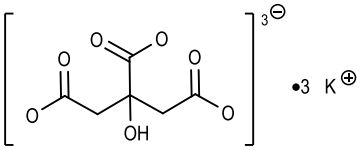
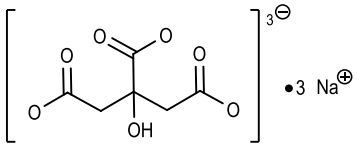
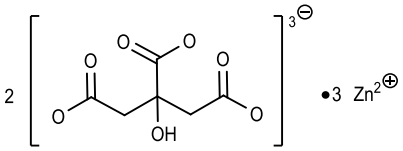
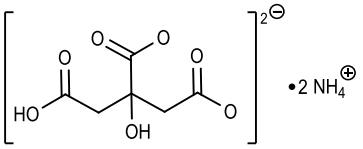
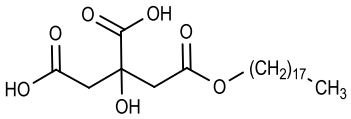
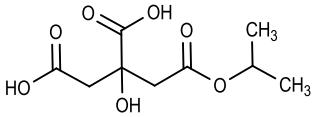
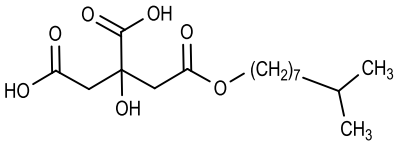
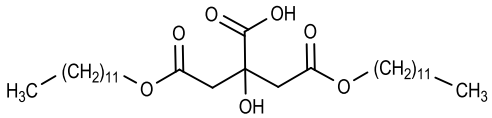
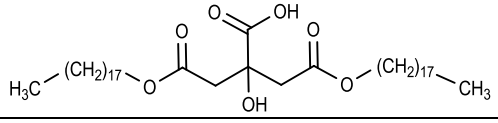
Ingredient CAS No.	Definition	Formula/structure
Potassium Citrate 866-84-2	the tripotassium salt of citric acid	
Sodium Citrate 68-04-2 (anhydrous) 6132-04-3 (dihydrate)	the trisodium salt of citric acid	
Zinc Citrate 546-46-3	the zinc (II) salt of citric acid	
Diammonium Citrate 3012-65-5	the diammonium salt of citric acid	
Alkyl Esters		
-Monoesters		
Stearyl Citrate 1323-66-6 1337-33-3 [CAS No. is not specific to monoester]	the ester of stearyl alcohol and citric acid	
Isopropyl Citrate 39413-05-3 [CAS No. is not specific to monoester]	the ester of isopropanol and citric acid	
Isodecyl Citrate 90605-17-7 [CAS No. is not specific to monoester]	the ester of branched chain decyl alcohols and citric acid	 one example of an "iso"
-Diesters		
Dilauryl Citrate 25637-88-1	the diester of lauryl alcohol and citric acid	
Distearyl Citrate 29589-99-9	the diester of stearyl alcohol and citric acid	

Table 1. Definitions and structures of citric acid, salt and esters

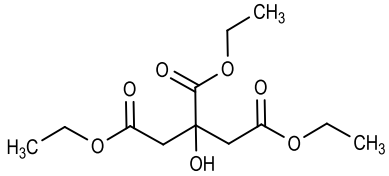
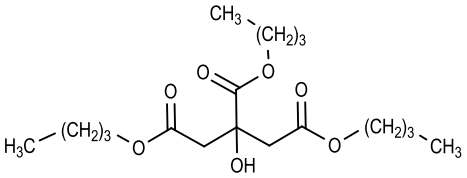
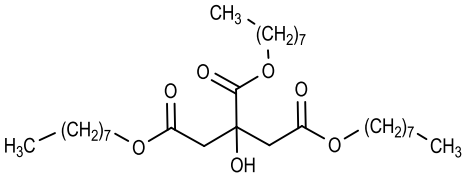
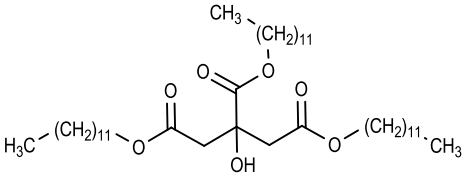
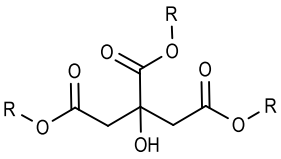
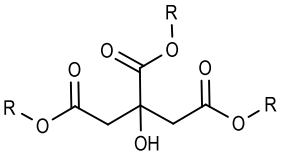
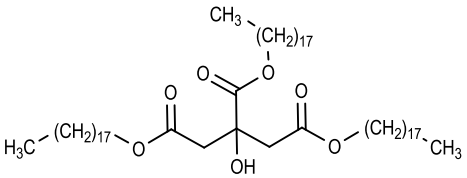
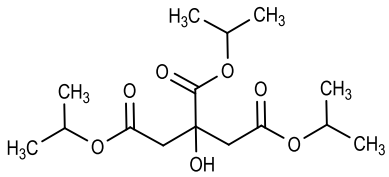
Ingredient CAS No.	Definition	Formula/structure
-Triesters		
Triethyl Citrate 77-93-0	the triester of ethyl alcohol and citric acid	
Tributyl Citrate 77-94-1	the triester of butyl alcohol and citric acid	
Tricaprylyl Citrate 76414-35-2	the triester of capryl alcohol and citric acid	
Trilauryl Citrate 65277-53-4	the triester of lauryl alcohol and citric acid	
Tri-C12-13 Alkyl Citrate	the triester of C12-13 alcohols and citric acid	 wherein R is a 12 or 13 carbon chain
Tri-C14-15 Alkyl Citrate 222721-94-0	the triester of C14-15 alcohols and citric acid	 wherein R is a 14 or 15 carbon chain
Tristearyl Citrate 7775-50-0	the triester of stearyl alcohol and citric acid	
Triisopropyl Citrate 74592-76-0	the triester of isopropyl alcohol and citric acid	

Table 1. Definitions and structures of citric acid, salt and esters

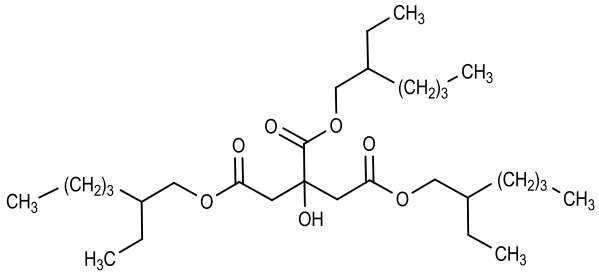
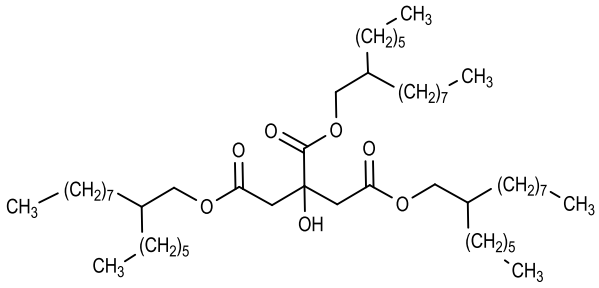
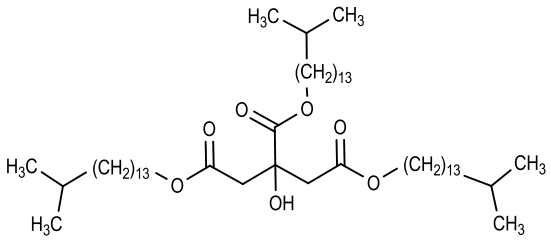
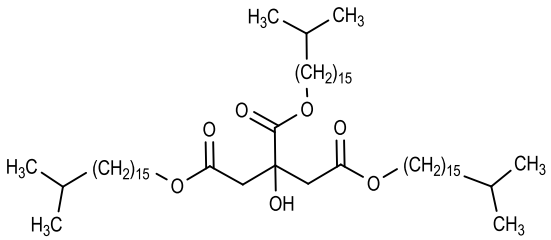
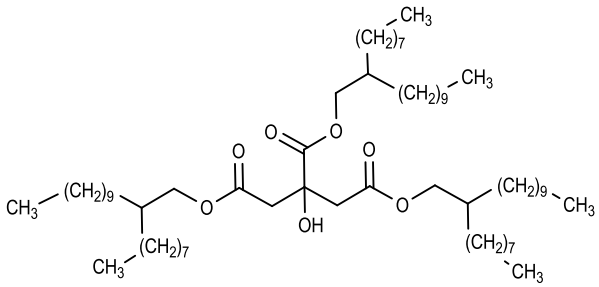
Ingredient CAS No.	Definition	Formula/structure
Triethylhexyl Citrate 7147-34-4	the triester of 2-ethylhexanol and citric acid	
Trihexyldecyl Citrate	the triester of 2-hexyldecanol and citric acid.	
Triisocetyl Citrate 93385-14-9	the triester of isocetyl alcohol and citric acid	 one example of an "iso"
Triisostearyl Citrate 113431-54-2	the triester of isostearyl alcohol and citric acid	 one example of an "iso"
Trioctyldodecyl Citrate 126121-35-5	the triester of 2-octyldodecanol and citric acid	

Table 1. Definitions and structures of citric acid, salt and esters

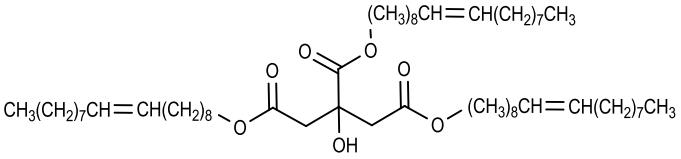
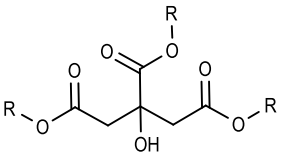
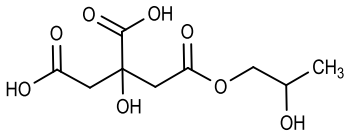
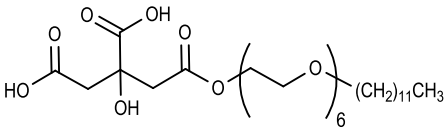
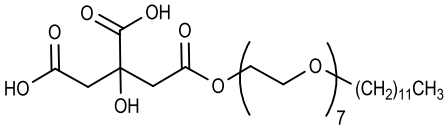
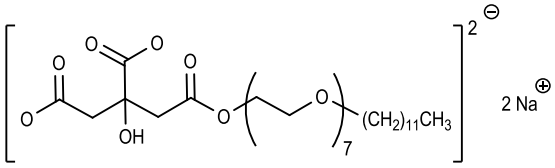
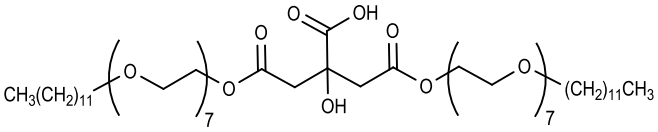
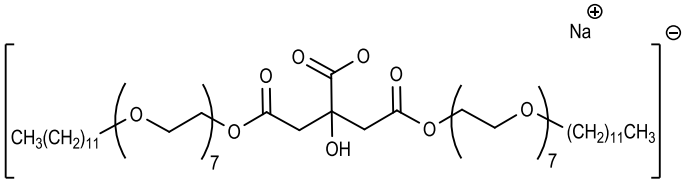
Ingredient CAS No.	Definition	Formula/structure
Trioleyl Citrate 175831-77-3	the triester of oleyl alcohol and citric acid	
Ethyl Citrates 172820-60-9	a mixture of mono-, di- and triesters of ethanol and citric acid	 wherein R is a hydrogen atom or an ethyl group
Glycol Esters		
-Monoesters		
Propylene Glycol Citrate 10444-00-4 [CAS No. is not specific to monoester]	the ester of citric acid and propylene glycol	
Laureth-6 Citrate 161756-30-5 [CAS No. is generic to any laureth-n citrate]	the ester of citric acid and laureth-6	
Laureth-7 Citrate 161756-30-5 [CAS No. is generic to any laureth-n citrate]	the ester of citric acid and laureth-7	
Disodium Laureth-7 Citrate	the disodium salt of the ester of citric acid and laureth-7	
-Diesters		
Dilaureth-7 Citrate	the diester of citric acid and laureth-7	
Sodium Dilaureth-7 Citrate 134096-11-0 53421-98-8	the sodium salt of the diester of citric acid and laureth-7	

Table 1. Definitions and structures of citric acid, salt and esters

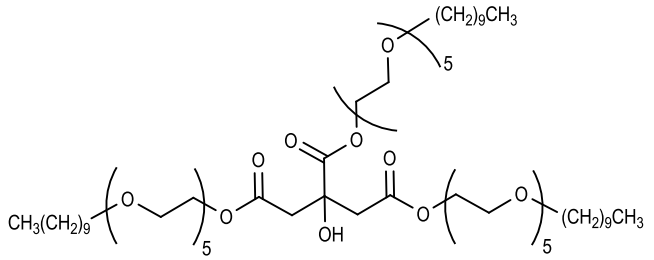
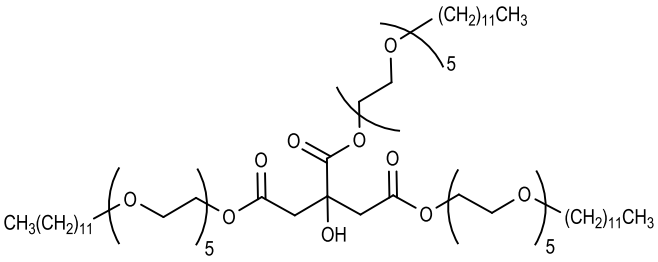
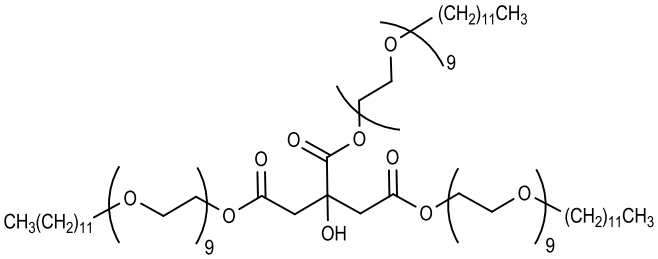
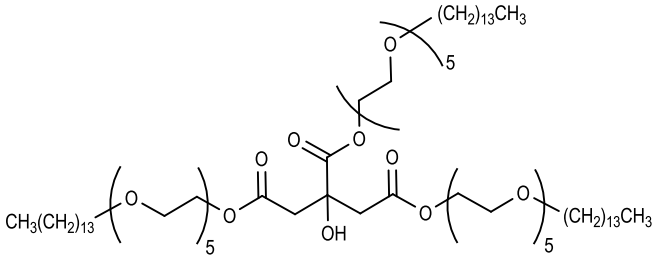
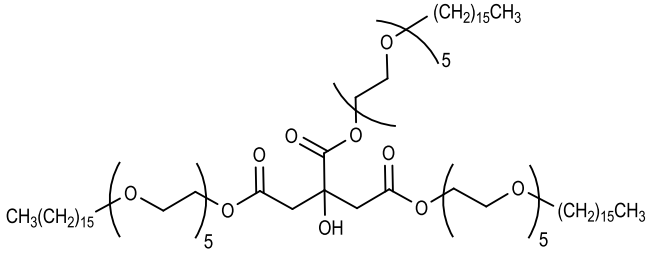
Ingredient CAS No.	Definition	Formula/structure
-Triesters		
PEG-5 Tricapryl Citrate	the triester of citric acid and PEG-5 decanol alcohol	
PEG-5 Trilauryl Citrate	the triester of citric acid and PEG-5 dodecanol	
Trilaureth-9 Citrate	the triester of laureth-9 and citric acid	
PEG-5 Trimyristyl Citrate	the triester of citric acid and PEG-5 myristyl alcohol	
PEG-5 Tricetyl Citrate	the triester of citric acid and PEG-5 cetyl alcohol	

Table 1. Definitions and structures of citric acid, salt and esters

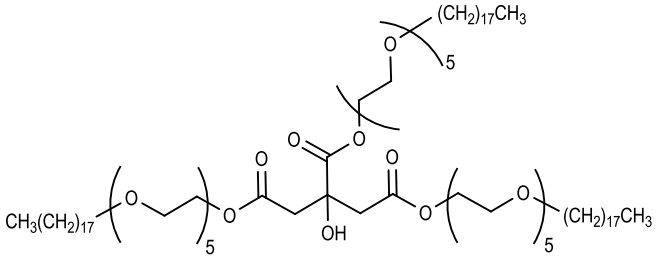
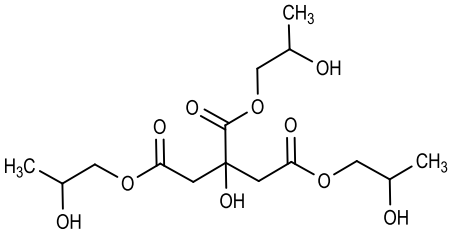
Ingredient CAS No.	Definition	Formula/structure
PEG-5 Tristearyl Citrate	the triester of citric acid and PEG-5 stearyl alcohol	
Tripropylene Glycol Citrate	a triester of propylene glycol and citric acid	

Table 2. Chemical and physical properties

Property	Description	Reference
	Citric Acid	
molecular weight	192.12 monohydrate: 210.14	4
appearance and form	monoclinic holohedrism crystals monohydrate: orthorhombic crystals	4
	free-flowing, colorless, translucent crystals or as a white granular to fine powder	15
melting point	153°C monohydrate: ≈100°C	4
boiling point	decomposes above 175°C	27
log P	-1.198±0.396 (at 25°C)	54
log K_{ow}	-1.75	55
vapor pressure	<0.001 mm Hg (20°C) 3.7×10^{-9} mm Hg (25°C)	56 55
solubility	solubility in water increases with temperature (from 54% w/w/ at 10°C to 84%)	4
	at 100°C; freely soluble in alcohol; very slightly soluble in ether in water: 162 g/100 ml (at 25°C); in alcohol: 59.1 g/100 ml (at 25°C)	15
	solubility in water increases with temperature from ~54 wt percentage at 10°C to ~88 wt percentage at 100°C	57
density	1.665 monohydrate: 1.542	4
pK_a	$pK_1 = 3.128$; $pK_2 = 4.761$; $pK_3 = 6.396$ (25°C)	4
pH (citric acid-sodium citrate solution)	pH of water solutions with equal percentages of citric acid and sodium citrate ranged from 4.15 (0.25% each chemical) to 3.54 (15% of each chemical)	58
	Aluminum Citrate	
density	1.5 g/cm^3	4
	Calcium Citrate	
molecular weight	498.43	4
appearance and form	fine white, odorless powder	7
solubility	soluble in 1050 parts cold water, somewhat soluble in hot water; insoluble in alcohol	4
	Copper Citrate	
molecular weight	315.18	4
appearance and form	green or bluish-green crystalline powder; odorless	4
solubility	slightly soluble in water; soluble in ammonia, diluted acids, and cold alkali citrate solutions; freely soluble in hot alkali citrate solutions	4
	Ferric Citrate	
appearance and form	garnet-red transparent scales or pale brown powder	4
solubility	slowly but completely soluble in cold water; readily soluble in hot water, practically insoluble in alcohol	4
	Magnesium Citrate	
molecular weight	dibasic: 214.41 tribasic: 451.11	4
	Monosodium Citrate	
molecular weight	214.12	59
melting point	decomposes	59
solubility	570 g/l (at 25°C); insoluble in ethanol and ether	59

Table 2. Chemical and physical properties

Property	Description	Reference
	Potassium Citrate	
molecular weight	306.39 monohydrate: 324.41	4
appearance and form	monohydrate: white crystals, granules, or powder; odorless monohydrate: white coarse powder	4 16
boiling point	211°C (calculated)	55
log K_{ow} (calculated)	-0.28	55
vapor pressure	2.09 x 10^{-12} mm Hg (25°C)	55
solubility	1 g dissolves slowly in 0.65 ml water; practically insoluble in alcohol monohydrate: 190 g/100 ml water (at 25°C); insoluble in alcohol and ether	4 16
stability	monohydrate: very hygroscopic; readily deliquesces in moist air	16
	Sodium Citrate	
molecular weight	258.07 dihydrate: 294.10	4
appearance and form	dihydrate: white crystals, granules, or powder; odorless	4
melting point	anhydrous: >300°C dihydrate: 150°C	60 61
density	monohydrate: 1.814	4
log K_{ow} (calculated)	-0.28	62
vapor pressure	2.09 x 10^{-12} mm Hg (25°C)	55
solubility	soluble in water, ~425 g/l (25°C) monohydrate: soluble in 1.3 parts water; insoluble in alcohol	55 4
	Zinc Citrate	
molecular weight	574.43	4
appearance and form	powder; odorless	4
solubility	slightly soluble in water; soluble in diluted mineral acids and alkali hydroxides	4
	Diammonium Citrate	
molecular weight	226.18	4
appearance and form	granules or crystals	4
solubility	soluble in 1 part water; slightly soluble in alcohol	4
	Distearyl Citrate	
melting point	70-72°C	63
	Triethyl Citrate	
molecular weight	276.29	12
appearance and form	clear, colorless, oily liquid	36
melting point	-55°C	64
boiling point	294°C	64
vapor pressure	6.4 x 10^{-3} mm Hg (20°C)	65
density	1.137 (20°C)	4
refractive index	1.440 -1.442 (@25°C/D)	65
solubility	6.5 g/100 ml water (25°C) 5.5 g/100 ml water (25°C); insoluble in hexane miscible with alcohol, ether	36 65 4
log K_{ow}	1.3 (35°C) (measured) 0.33 (calculated)	12

Table 2. Chemical and physical properties

Property	Description	Reference
	Tributyl Citrate	
molecular weight	360.44	4
appearance and form	colorless or pale yellow liquid; odorless	4
melting point	-20°C	4
boiling point	170°C (1 mm Hg) 233°C (22 mm Hg)	36 4
vapor pressure	9.6×10^{-2} mm Hg (20°C)	65
density	1.045 (20°C)	4
refractive index	1.443-1.445 (@25°C/D)	65
solubility	insoluble in water; miscible with most organic liquids	4
log P (predicted)	4.324 ± 0.411 (25°C)	54
pK_a (predicted)	11.3 ± 0.29 (25°C)	54
	Tricaprylyl Citrate	
molecular weight	528.76	54
boiling point	250-255°C (6-7 mm Hg)	66
density	0.9498 g/cm^3	66
log P (predicted)	10.438 ± 0.411 (25°C	54
pK_a	11.30 ± 0.29	54
	Trilauryl Citrate	
molecular weight	697.08	54
boiling point (predicted)	675.9°C	54
density (predicted)	0.955 g/cm^3 (20°C)	54
log P (predicted)	16.551 (25°C)	54
pK_a (predicted)	11.29 (25°C)	54
	Tristearyl Citrate	
molecular weight	949.56	54
boiling point (predicted)	840.3°C	54
density (predicted)	0.924 g/cm^3 (20°C)	54
log P (predicted)	25.722 (25°C)	54
pK_a (predicted)	11.29 (25°C)	54
	Triisopropyl Citrate	
molecular weight	318.36	54
boiling point (predicted)	331°C	54
density (predicted)	1.116 g/cm^3 (20°C)	54
log P (predicted)	2.328 (25°C)	54
pK_a (predicted)	11.69 (25°C)	54
	Triisostearyl Citrate	
molecular weight	944	13
appearance	clear viscous liquid	67
	Trioctyldodecyl Citrate	
molecular weight	1032	13
boiling point (predicted)	883.3°C	54
density (predicted)	0.917 g/cm^3 (20°C)	54
log P (predicted)	29.634 (25°C)	54
pK_a (predicted)	11.25 (25°C)	54

Table 2. Chemical and physical properties

Property	Description	Reference
	Trioleyl Citrate	
molecular weight	943.51	[54]
boiling point (predicted)	845.8°C	[54]
density (predicted)	0.936 g/cm^3 (20°C)	[54]
log P (predicted)	25.443 (25°C)	[54]
pK_a (predicted)	11.28 (25°C)	[54]
	Laureth-7 Citrate	
molecular weight	677	[14]
appearance and form	clear, slightly yellow liquid	[14]
acid number	130-170	[14]
saponification value	210-250	[14]
pH value (10%)	1.8-2.8	[14]

Table 3. Reported functions of citric acid and its salts and esters

pH adjuster
Citric Acid
Calcium Citrate
Monosodium Citrate
Potassium Citrate
Sodium Citrate

Chelating Agent
Citric Acid
Diammonium Citrate
Potassium Citrate
Sodium Citrate

Fragrance Ingredient
Citric Acid
Sodium Citrate
Triethyl Citrate

Buffering Agent
Diammonium Citrate
Potassium Citrate
Sodium Citrate

Skin Conditioning Agent – Emollient
Dilauryl Citrate
Distearyl Citrate
Isodecyl Citrate
PEG-5 Tricapryl Citrate
PEG-5 Tricetyl Citrate
PEG-5 Trilauryl Citrate
PEG-5 Trimyristyl Citrate
PEG-5 Tristearyl Citrate
Stearyl Citrate
Tri-C12-13 Alkyl Citrate
Tri-C14-15 Alkyl Citrate
Triethylhexyl Citrate
Triisopropyl Citrate
Trioleyl Citrate

Skin Conditioning Agent – Humectant
Propylene Glycol Citrate

Skin Conditioning Agent – Occlusive
Tricaprylyl Citrate
Trihexyldecyl Citrate
Triisocetyl Citrate
Triisostearyl Citrate
Trilauryl Citrate
Trioctyldodecyl Citrate
Tristearyl Citrate

Skin Conditioning Agent – Miscellaneous
Dilaureth-7 Citrate
Ferric Citrate
Magnesium Citrate
Tripropylene Glycol Citrate

Surfactant Cleansing Agent
Disodium Laureth-7
Laureth-6 Citrate
Laureth-7 Citrate
Sodium Dilaureth-7 Citrate
Trilaureth-9 Citrate

Surfactant – Emulsifying Agent
Dilaureth-7 Citrate
Disodium Laureth-7 Citrate
PEG-5 Tricapryl Citrate
PEG-5 Tricetyl Citrate
PEG-5 Trilauryl Citrate
PEG-5 Trimyristyl Citrate
PEG-5 Tristearyl Citrate
Trilaureth-9 Citrate

Hair Fixative
Ethyl Citrates

Plasticizer
Isodecyl Citrate
Isopropyl Citrate
Tributyl Citrate
Triethyl Citrate
Triethylhexyl Citrate

Cosmetic Astringent
Aluminum Citrate

Oral Care Agent
Zinc Citrate

Cosmetic Biocide
Zinc Citrate

Pesticide
Copper Citrate

Solvent
Isopropyl Citrate
Tributyl Citrate

Not Reported
Disodium Cupric Citrate
Manganese Citrate

Reference[18]

Table 4a. Frequency and concentration of use according to duration and type of exposure

	# of Uses	*Conc of Use (%)*	*# of Uses*	*Conc of Use (%)*	*# of Uses*	*Conc of Use (%)*
	Citric Acid		**Aluminum Citrate**		**Diammonium Citrate**	
Totals*	**6795**	**0.0000005-39**	**4**	**NR**	**6**	**NR**
Duration of Use						
Leave-On	*2851*	*0.0000005-35*	*3*	*NR*	*2*	*NR*
Rinse-Off	*3753*	*0.000002-10*	*1*	*NR*	*4*	*NR*
Diluted for Use	*191*	*0.3-39*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	580	*0.0000005-2*	NR	NR	1	NR
Possible Ingestion	214	0.0006-3	NR	NR	NR	NR
Inhalation	71	0.003-35	NR	NR	NR	NR
Dermal Contact	4323	0.000008-35	4	NR	2	NR
Deodorant (underarm)	22	0.000008-0.2	NR	NR	NR	NR
Hair - Non-Coloring	1945	0.0001-5	NR	NR	3	NR
Hair-Coloring	210	0.08-10	NR	NR	NR	NR
Nail	290	0.001-30	NR	NR	NR	NR
Mucous Membrane	1487	0.0002-3	NR	NR	1	NR
Bath Products	191	0.3-39	1	NR	NR	NR
Baby Products	112	0.2	NR	NR	NR	NR

	Dilauryl Citrate		**Ethyl Citrates**		**Ferric Citrate**	
Totals*	**1**	**NR**	**NR**	**0.5-1**	**7**	**0.5**
Duration of Use						
Leave-On	*NR*	*NR*	*NR*	*NR*	*4*	*NR*
Rinse Off	*1*	*NR*	*NR*	*0.5-1*	*3*	*0.5*
Diluted for Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	NR	NR	NR	NR	NR	NR
Possible Ingestion	NR	NR	NR	NR	NR	NR
Inhalation	NR	NR	NR	NR	NR	NR
Dermal Contact	1	NR	NR	0.5-1	5	0.5
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	2	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	1	NR	0.5
Bath Products	NR	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR

	Isodecyl Citrate		**Laureth-7 Citrate**		**Magnesium Citrate**	
Totals*	**4**	**NR**	**1**	**NR**	**9**	**0.01-2**
Duration of Use						
Leave-On	*4*	*NR*	*NR*	*NR*	*NR*	*0.01-2*
Rinse-Off	*NR*	*NR*	*1*	*NR*	*9*	*0.5*
Diluted for Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	NR	NR	NR	NR	NR	NR
Possible Ingestion	NR	NR	NR	NR	NR	NR
Inhalation	NR	NR	NR	NR	NR	NR
Dermal Contact	4	NR	NR	NR	NR	0.01-2
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	1	NR	9	0.5
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	NR	NR
Bath Products	NR	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR

Table 4a. Frequency and concentration of use according to duration and type of exposure

	# of Uses	*Conc of Use (%)*	*# of Uses*	*Conc of Use (%)*	*# of Uses*	*Conc of Use (%)*
	Monosodium Citrate		**Potassium Citrate**		**Sodium Citrate**	
Totals*	**16**	**0.004-5**	**8**	**0.002-0.6**	**980**	**0.000005-10**
Duration of Use						
Leave-On	*NR*	*0.004-5*	*2*	*0.002-0.5*	*587*	*0.000005-10*
Rinse Off	*2*	*0.8-5*	*6*	*0.002-0.6*	*386*	*0.0001-10*
Diluted for Use	*14*	*5*	*NR*	*NR*	*7*	*0.9*
Exposure Type						
Eye Area	NR	NR	1	NR	47	0.02-2
Possible Ingestion	NR	NR	1	0.6	7	0.003-0.4
Inhalation	NR	NR	NR	0.06-0.07	8	0.000005-0.3
Dermal Contact	16	0.004-5	5	0.002-0.5	758	0.0001-10
Deodorant (underarm)	NR	NR	NR	NR	1	0.02-0.1
Hair - Non-Coloring	NR	NR	3	0.002-0.07	206	0.000005-4
Hair-Coloring	NR	NR	NR	NR	5	0.1
Nail	NR	NR	NR	NR	2	0.08-0.5
Mucous Membrane	NR	NR	3	0.002	88	0.02-1
Bath Products	14	5	NR	NR	7	0.9
Baby Products	NR	5	NR	NR	9	NR

	Stearyl Citrate		**Tributyl Citrate**		**Tri-C12-13 Alkyl Citrate**	
Totals*	**23**	**0.007-12**	**331**	**0.0005-9**	**1**	**NR**
Duration of Use						
Leave-On	*1*	*0.3-12*	*35*	*0.0005-9*	*1*	*NR*
Rinse-Off	*22*	*0.007-2*	*267*	*0..0009-5*	*NR*	*NR*
Diluted for Use	*NR*	*NR*	*29*	*0.0005*	*NR*	*NR*
Exposure Type						
Eye Area	NR	1-2	NR	NR	1	NR
Possible Ingestion	NR	12	NR	NR	NR	NR
Inhalation	NR	3	6	0.0005	NR	NR
Dermal Contact	20	0.007-12	260	0.0005- <0.05	1	NR
Deodorant (underarm)	NR	3	NR	NR	NR	NR
Hair - Non-Coloring	3	1	14	NR	NR	NR
Hair-Coloring	NR	NR	55	NR	NR	NR
Nail	NR	NR	2	0.01-9	NR	NR
Mucous Membrane	7	0.007-1	204	0.0009-0.001	NR	NR
Bath Products	NR	NR	29	0.0005	NR	NR
Baby Products	NR	NR	1	NR	NR	NR

	Tri-C14-15 Alkyl Citrate		**Tricaprylyl Citrate**		**Triethyl Citrate**	
Totals*	**19**	**0.1-5**	**19**	**0.3-27**	**244**	**0.0008-6**
Duration of Use						
Leave-On	*19*	*0.1-5*	*16*	*0.3-27*	*215*	*0.004-6*
Rinse-Off	*NR*	*NR*	*3*	*0.5-0.8*	*29*	*0.0008-0.2*
Diluted for Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	1	3	1	3	2	0.2-0.6
Possible Ingestion	NR	NR	3	14-19	11	0.3
Inhalation	NR	NR	NR	NR	86	0.2-2
Dermal Contact	19	0.1-5	16	0.3-27	138	0.0008-6
Deodorant (underarm)	NR	NR	NR	NR	48	2
Hair - Non-Coloring	NR	NR	3	0.5-0.8	106	0.1-2
Hair-Coloring	NR	NR	NR	NR	NR	0.5
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	7	0.2
Bath Products	NR	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	0.009

Table 4a. Frequency and concentration of use according to duration and type of exposure						
	# of Uses	*Conc of Use (%)*	*# of Uses*	*Conc of Use (%)*	*# of Uses*	*Conc of Use (%)*
	Triethylhexyl Citrate		**Triisocetyl Citrate**		**Triisostearyl Citrate**	
Totals*	**1**	**NR**	**33**	**0.6-3**	**47**	**0.3-80**
Duration of Use						
Leave-On	*1*	*NR*	*33*	*0.6-3*	*44*	*0.3-80*
Rinse Off	*NR*	*NR*	*NR*	*NR*	*3*	*NR*
Diluted for Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	NR	NR	NR	NR	1	NR
Possible Ingestion	NR	NR	7	NR	39	9-80
Inhalation	NR	NR	NR	NR	NR	NR
Dermal Contact	1	NR	33	0.6-3	44	0.3-80
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	3	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	NR	NR
Bath Products	NR	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR

	Trioctyldodecyl Citrate		**Tripropylene Glycol Citrate**		**Zinc Citrate**	
Totals*	**56**	**1-30**	**1**	**NR**	**9**	**0.05-2**
Duration of Use						
Leave-On	*56*	*1-30*	*1*	*NR*	*5*	*0.05*
Rinse-Off	*NR*	*NR*	*NR*	*NR*	*4*	*0.3-2*
Diluted for Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	8	5-21	NR	NR	NR	NR
Possible Ingestion	37	1-19	NR	NR	4	0.3-2
Inhalation	1	4	NR	NR	NR	NR
Dermal Contact	56	1-30	1	NR	5	0.05
Deodorant (underarm)	NR	NR	NR	NR	4	NR
Hair - Non-Coloring	NR	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	4	0.3-2
Bath Products	NR	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR

* Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.

NR – no reported uses

Table 4b. Ingredients not reported to be used

Calcium Citrate	PEG-5 Trilauryl Citrate
Copper Citrate	PEG-5 Trimyristyl Citrate
Citrate Dilaureth-7	PEG-5 Tristearyl Citrate
Disodium Cupric Citrate	Propylene Glycol Citrate
Disodium Laureth-7 Citrate	Sodium Dilaureth-7 Citrate
Distearyl Citrate	Trihexyldecyl Citrate
Isopropyl Citrate	Triisopropyl Citrate
Laureth-6 Citrate	Trilaureth-9 Citrate
Manganese Citrate	Trilauryl Citrate
PEG-5 Tricapryl Citrate	Trioleyl Citrate
PEG-5 Tricetyl Citrate*	Tristearyl Citrate

*not yet included in an industry survey

Table 5. Examples of non-cosmetic uses

Ingredient	Non-Cosmetic Use	Reference
Citric Acid	used in the food, beverage, and pharmaceutical industries; active ingredient in pesticide products; manufacture of ecologically compatible detergents; chemical cleaning; metal cleaning; concrete admixtures; plasticizers; photography	1,5,15,68
Calcium Citrate	calcium fortifier in foods; anti-caking agent in dry mixes	4
Copper Citrate	as an astringent or antiseptic	4
Diammonium Citrate	determination of phosphate, especially in fertilizers	4
Potassium Citrate	as a replacement for sodium citrate in foods; as a buffering agent in foods; as a source of potassium ion in a nutritional supplement; sequestering or emulsifying agent	4,16
Sodium Citrate	anticoagulant; acidulant in beverages, confectionery, effervescent salts, powders, and tablets, pharmaceutical syrups, and elixirs; pH adjuster in food; as an synergistic oxidant; in processing cheese; in the manufacture of alkyd resins; in the manufacture of citric acid salts as a sequestering agent to remove trace metals; in electroplating; in special inks	4
Triethyl Citrate	plasticizer for cellulose derivatives and natural resins; plasticizer in pharmaceutical excipients	65,69
Tributyl Citrate	plasticizer and solvent for nitrocellulose lacquers; in polishes, inks, and similar preparations; plasticizer in pharmaceutical excipients; as an anti-foam agent	4
Zinc Citrate	used in toothpaste and mouthwash	4

Table 6. Acute toxicity studies

Ingredient	Animals*	No./Group	Dose	LD_{50}	Reference
			DERMAL		
Citric Acid	rabbits	10	5 g/kg tested	>5 g/kg	56
Triethyl Citrate	rabbits	4	not stated	>5 g/kg	12
Triethyl Citrate	guinea pig	not stated	not stated	>10 ml/kg	70
			ORAL		
Isopropyl Citrate Esters, mostly mono- + vehicle[#]	rats	6M/4-11F	M: 2.1-20.7 g/kg F: 2.7-27.0 g/kg	M: >20.7 g/kg (>7.0 g/kg[##]) F: 18.8 g/kg (7.2 g/kg)	35
as above, in cottonseed oil (2:1)	rats	9-10M/ 10-20 F	M: 11.1-17.2 g/kg F: 12.0-22.2 g/kg	M: >17.2 g/kg (>6.5 g/kg) F: 19.2 g/kg (7.3 g/kg)	35
7.5% Isopropyl Citrate Esters, mostly mono-, in 10% ethanol	rats	10 M	2.1-3.9 g/kg	3.7 g/kg	35
15% Isopropyl Citrate Esters, mostly mono-, in 10% ethanol	rats	10F	2.1-3.9 g/kg	2.8 g/kg	35
75% aq. Isopropyl Citrate Esters, mostly mono-,	rats	10F	2.25-5.25 g/kg	3.6 g/kg	35
Isopropyl Citrate Esters, mostly mono- + vehicle	dogs	4	12 g/kg	>12 g/kg; not fatal at this dose	35
Isopropyl Citrate Esters, mostly mono-	dogs	4	2.25 g/kg	>2.25 g/kg; not fatal at this dose	35
Stearyl Citrate Esters, predominantly distearyl[@] 20% in cottonseed oil	rats	2-13M/ 2-13 F	M/F: 0.9-5.4 g/kg	M/F: >5.4 g/kg	35
Stearyl Citrate Esters, predominantly distearyl	dogs	4	5 g/kg	>5 g/kg; not fatal at this dose	35
Tributyl Citrate	rats	5	10-30 ml/kg	no deaths reported	36
Tributyl Citrate	cats	4	30-50 ml/kg	no deaths reported	36
Trioctyldodecyl Citrate	rats	10 (5/sex)	5 g/kg	no deaths reported	71
			INHALATION		
Triethyl Citrate	rats	no stated	6-h exposure to vapor	1300-3500 ppm	70
			INTRAPERITONEAL		
Monosodium Citrate	white mice	not stated	0.0477 M solution	7.6 mmol/kg	72
Monosodium Citrate	albino rats	not stated	0.381 M solution	6.3 mmol/kg	72
Tributyl Citrate	Swiss albino mice	not stated	chosen from a logarithmic scale	2900 mg/kg	37
			INTRAVENOUS		
Monosodium Citrate	white mice	not stated	0.019 M; rapid administration	0.23 mmol/kg	72
Monosodium Citrate	white mice	20	0.25 M administered at rate of 1.5 mmol/min (6 ml/min)	2.01 mmol/kg	72
Monosodium Citrate	rabbits	not stated	0.477 M; administered at a rate of 0.358 mmol/min (0.75 ml/min)	1.76 mm/kg	72

*unless it is given, the sex of the animals was not stated

[#] - this test material is composed of 27% isopropyl citrate, 9% diisopropyl citrate, and 2% triisopropyl citrate; when + vehicle - vehicle consisting of mono- and diglycerides (1:1) of vegetable oil

[##] - when available, the isopropyl citrate ester content without vehicle is given in ( )

[@]- the test material is composed of 12.5% stearyl citrate, 75% distearyl citrate, and 12.5% tristearyl citrate

Table 7. Genotoxicity studies

Concentration	Vehicle	Procedure	Test System	Results	Reference
IN VITRO					
Citric Acid					
500-2000 µg/plate	distilled water	Ames test, in triplicate; negative and positive controls	*S. typhimurium* TA97, TA98, TA100, TA104,+/- met act	negative	[73]
≤5000 µg/plate	phosphate buffer	Ames test	*S. typhimurium* TA92, TA94, TA98, TA100, TA1535, TA1537, +/- met act	negative	[74]
≤1000 µg/ml	saline	chromosome aberration assay	Chinese hamster fibroblast cells	negative	[74]
6-600 µg/ml	saline	cytogenetic study	human embryonic lung cultures, WI-38	negative	[75]
not given	saline	host-mediated assay	*S. typhimurium* TA1530, G46; *S. cerevisiae* D3	negative in *S. typhimurium*; weakly positive in *S. cerevisiae*	[75]
1.0 mg/ml	not stated	RK bacterial assay; was used as a non-mutagenic control	*E. coli* CHY832	negative	[76]
Aluminum Citrate					
10-10,000 µg/plate	water	Ames test	*S. typhimurium* TA100, TA1535, TA97, TA98, TA102, TA104 +/- met act; TA1537, without met act	equivocal in TA97 w/met act	[42]
Ferric Citrate					
≤25,000 µg/plate	phosphate buffer	Ames test	*S. typhimurium* TA92, TA94, TA98, TA100, TA1535, TA1537, +/- met act	negative	[74]
≤500 µg/ml	sodium CMC	chromosome aberration assay	Chinese hamster fibroblast cells	negative	[74]
≤2 mM	not stated	DNA strand break	Chinese hamster V79 cells	no reduction in double-stranded DNA	[77]
Monosodium Citrate					
≤5000 µg/plate	phosphate buffer	Ames test	*S. typhimurium* TA92, TA94, TA98, TA100, TA1535, TA1537, +/- met act	negative	[74]
≤3000 µg/ml	saline	chromosome aberration assay	Chinese hamster fibroblast cells	negative	[74]
Potassium Citrate					
0.001-0.004%	DMSO	Ames test	*S. typhimurium* TA1535, TA1537, TA1538; +/- met act	negative	[78]
0.001-0.004% (*S. typhimurium*) 0.002-0.004% (*S. cerevisiae*)	DMSO	suspension test	*S. typhimurium* TA1535, TA1537, TA1538, *S. cerevisiae* D4; +/- met act	negative	[78]
Sodium Citrate (Dihydrate)					
6.25 x 10^{-4} – 25 x 10^{-4} %	DMSO	Ames test	*S. typhimurium* TA1535, TA1537, TA1538, +/- met act	negative	[79]
6.25 x 10^{-4} – 25 x 10^{-4} %	DMSO	suspension test	*S. typhimurium* TA1535, TA1537, TA1538, *S. cerevisiae* D4	weak dose-related response in *S. typhimurium* TA1537 without activation, repeat trial neg; neg in *S. cerevisiae*; negative w/activation	[79]
Triethyl Citrate					
0.4-1.6%	DMSO	Ames test	*S. typhimurium* TA1535, TA1537, TA1538; +/- met act	negative	[80]
0.4-1.6% (*S. typhimurium*) 0.425-1.7% (*S. cerevisiae*)	DMSO	suspension test	*S. typhimurium* TA1535, TA1537, TA1538, *S. cerevisiae* D4; +/- met act	negative	[80]
Tributyl Citrate					
not given	not given	Ames test	not given	negative	[81]
not given	not given	chromosome aberration assay	human peripheral blood lymphocytes	negative	[81]

Table 7. Genotoxicity studies

Concentration	Vehicle	Procedure	Test System	Results	Reference
Triisostearyl Citrate					
10-10,000 µg/plate	ethanol	Ames test, in triplicate; negative and positive controls	*S. typhimurium* TA1535, TA1537, TA98, TA100,+/- met act	negative	[82]
Laureth-7 Citrate					
3-5000 µg/plate	deionized water	Ames test, in triplicate; negative and positive controls	*S. typhimurium* TA98, TA100,+/- met act	negative	[83]
IN VIVO					
Citric Acid					
1.2-120 mg/kg	saline	cytogenetic assay, oral	rats	negative	[75]
500, 3500 mg/kg (acute); 300, 3000 mg/kg (subacute)	saline	cytogenetic assay, oral	rats	negative	[75]
1.2-120 mg/kg (acute & subacute)	saline	host-mediated assay	mice	weakly positive	[75]
3500 mg/kg (acute & subacute)	saline	host-mediated assay	mice	neg. (acute); weakly pos. (subacute)	[75]
1.2-120 mg/kg	saline	dominant lethal assay	rats	sig. increase in preimplantation loss at wk 4 in high dose group	[75]
500, 3500 mg/kg (acute); 300, 3000 mg/kg (subacute)	saline	dominant lethal assay	rats	negative	[75]

Abbreviations: CMC – carboxymethyl cellulose; DMSO – dimethyl sulfoxide; met act –metabolic activation

Table 8. Dermal irritation and sensitization

Test Article	Concentration	Test Pop.	Procedure	Results	Reference
NON-HUMAN					
IRRITATION					
Citric Acid	30% aq.	3 NZW rabbits	Draize test, 0.5 ml applied for 4 h to intact and abraded; occlusive patch	not a primary irritant; PII=84	84
Citric Acid	not stated	rabbits	acute dermal irritation/corrosion study	slightly irritating; avg erythema score = 0.33	85
Citric Acid	60% pure	NZW rabbits, 5M/3F	0.5 ml; applications to 1 animal for 3 min, to 1 for 60 min, to the remainder for 4 h	3 min: very slight erythema 60 min: very slight erythema 4-hr: very slight-moderate to severe erythema, very slight-moderate edema, subsided to well-defined erythema and no edema after 48 h	86
Citric Acid	100%	10 rabbits	5 g/kg were applied in an acute study (details not provided)	mild (n=3), moderate (n=4), and severe (n=2) erythema; mild (n=8) and moderate (n=2) edema	56
Citric Acid	15%	32 male Wistar rats	Evan's blue test: 2% Evan's blue was injected i.v. into the tail of rats; 0.1 ml was then injected intradermally to a site on the back; animals were killed after 0.5, 1, 3,and 6 h	statistically significantly more dye was extracted with Citric Acid compared to saline	87
Triethyl Citrate	40, 70, 100% in ethanol	4 F guinea pigs/gp	24 h, 8 mm occlusive patch; test sites scored 24 and 48 h after patch removal	barely perceptible erythema at 24 h in 1 animal of the 100% group	88
Triethyl Citrate	0.05-1.0% in 0.01% DBS/ saline	guinea pigs, 4 M/gp	intradermal injection, 0.1 ml; test sites scored after 24h	faint pink reaction at all test sites with all concentrations	88
Triethyl Citrate	100%	4 rabbits	5 g/kg were applied in an acute study (details not provided)	no irritation	12
Triethyl Citrate	15 and 33.3% in alcohol SDA 39C	3 albino rabbits	0.5 ml applied to a 2x2 (unites not given area of intact and abraded skin for 24 h with an occlusive covering	not a primary irritant; PII = 0	12
Triethyl Citrate	33.3% in pet	3 albino rabbits	as above	not a primary irritant; PII = 0	12
Trioctyldodecyl Citrate	neat	6 rabbits (sex not specified)	0.5 ml applied to intact and abraded skin for 24 h under an occlusive patch	not a primary skin irritant; PII = 0.00	71
SENSITIZATION					
Triethyl Citrate	induction: intradermal, 2.5% in 0.01% DBS/ saline epidermal, 100% challenge, 50% in absolute eth.	9 guinea pigs	Magnusson -Kligman GPMT; FCA was used at intradermal induction; occlusive patches were used during intradermal induction and at challenge	strong sensitizer; 9/9 animals sensitized after 2 challenges; primarily intense erythema, with some moderate and diffuse erythema, was observed	88
Tributyl Citrate	not provided	not provided	GPMT or LLNA (add'l details not provided)	negative	81
Trioctyldodecyl Citrate	0, 10, 50, 100% w/v in acetone/ olive oil (4:1, v/v)	5 mice	LLNA; 25 µl/ear were applied daily for 3 days; untreated and positive (α-hexylcinnamic aldehyde) control were used	neat material was considered a mild sensitizer; the SI for the concentrations tested ranged from 1.1 to 3.1	71

Table 8. Dermal irritation and sensitization

Test Article	Concentration	Test Pop.	Procedure	Results	Reference
HUMAN					
IRRITATION					
Citric Acid	0.3N solution (vehicle not specified)	not specified	stinging potential was evaluated by applying 0,1-0.2 ml to an abraded site on the forearm for ≤5 min; sig. change measured as difference from first to last day of dosing	citric acid produced the most painful stinging response: citric, acetic >> aconitic>tartaric>ascorbic; citric acid has scored quite low when intercompared to other acids for primary irritancy	89
Citric Acid	5% aq., pH 2	20 subjects, 14F/6M	50 µl applied to the back using 12 mm occlusive patch each AM; each PM, either the same patch or 0.5% aq SLS was applied; procedure repeated for 4 days; irritation was measured by visual scoring, TEWL, and skin color reflectance	no irritation with citric acid alone; exposure with SLS caused a clear irritant reaction, however, this reaction was less than that seen 1x daily exposure to SLS	90
Citric Acid	5% aq., pH 4	as above	as above	no irritation with citric acid alone; exposure with SLS caused a clear irritant reaction, however, this reaction was less than that seen 1x daily exposure to SLS	90
Citric Acid, in hand cleansers (A and B; % Citric Acid not given)	neat	12 subjects/ group	use test; product was applied ≥20/day for 2 wks; s.c. hydration was measured with a corneometer; TEWL measured with an evaporation meter; sig. determined as above	Δ erythema:A, ~0.3; B, ~0.7 TEWL: A, ~4 g/m^2/h (P≤0.5); B, ~1.25 g/m^2/h Δ s.c. hydration: A, ~ -1; B, ~ -1.9	91
hand cleansers as above (A&B), plus a 3rd cleanser (not def.)	neat	8 subjects/ group	forearm wash test; each group received 2 products to apply simultaneously; forearms were washed for 1 min 2x, then rinsed for 30 sec; sig. changes measured as above	Δ erythema: A, ~0.7 (p≤0.5); B, ~0.45 TEWL: A, ~11 g/m^2/h (p≤ 0.5); B, 8 g/m^2/h (p≤0.5) Δ s.c. hydration: A, ~ -9.5(p ≤0.5); B, ~ -8	91
hand cleansers as above (A&B), 2 addl. cleanser (not def.)	10%	40 subjects	patch test; 50 µl of each cleanser applied using 12 mm Finn chambers; 48 h	Δ erythema: A, ~2.7 (p≤0.5); B, ~2.25 (p≤0.5) TEWL: A, 14 g/m^2/h; B, ~7.9 g/m^2/h, diff. btwn. A&B (p≤0.5) Δ s.c. hydration: A, ~ -7.9 (p ≤0.5); B, ~ -7.7 (p≤0.5)	91
Citric Acid	1% aq.	133 oral disease patients	48 h patch test, occlusive	no positive reactions	92
Citric Acid	2.5% aq.	49 atopic; 56 non-atopic patients	20 min occlusive application	no immediate (non-immunologic contact urticaria) reactions	93
Citric Acid	not stated (most likely 100%)	702 contact dermatitis patients	Finn chambers were applied the back using Scanpore tape; 48 h	no reactions	94
Sodium Citrate	10% aq.	49 atopic; 56 non-atopic patients	20 min occlusive application	no immediate (non-immunologic contact urticaria) reactions	93
Triethyl Citrate	20% in pet.	22 subjects	48- closed patch test	not irritating	12

Table 8. Dermal irritation and sensitization

Test Article	Concentration	Test Pop.	Procedure	Results	Reference
			SENSITIZATION		
Citric Acid	2.5% aq.	91 patients w/chronic urticaria or angioedema	skin prick test	positive results in 3 patients; 1 of the positive reactors also reacted to benzoic and propionic acids	95
Triethyl Citrate	15% in alcohol 39C	41 subjects 5 males 36 females	HRIPT; 0.5 ml applied to a Webril patch affixed to an elastic bandage; 9 24-h patches were applied during induction; challenge patches were applied to the test site and an untested site	not a primary irritant (no information was given regarding sensitization)	12
Triethyl Citrate	33.3% in alcohol 39C	41 subjects 10 males 31 females	HRIPT; as above	not a primary irritant or a sensitizer	12
Triethyl Citrate	33.3% in pet	45 subjects 10 males 35 females	HRIPT; as above, except that 0.4 ml was applied	not a primary irritant or as a sensitizer	12
Triethyl Citrate	15% in alcohol (SDA 39C)	26 subjects	Modified Maximization study: induction: 5 alternate 48-h occlusive patches applied to the back or forearm, with 2.5% SLS pre-treatment; challenge: 48-h semi-occlusive patch, with 2.5% SLS pretreatment	not a sensitizer according to the Kligman scale; rxns at induction ranged from mild erythema to erythema and edema with vesiculation and/or ulceration; rxns at challenge included minimal to well-defined erythema	12
Triethyl Citrate	33.3% in pet	25 subjects	as above	1 subject was not patched during challenge due to rxns to substances during induction; rxns at induction included minimal erythema to erythema and edema; rxns at challenge included minimal to well-defined erythema; not a sensitizer according to the Kligman scale	12
Triethyl Citrate	20% in pet.	22 subjects	maximization test: induction: 5 alternate 48-h occlusive patches applied to the forearm, with 5% aq. pre-treatment with the 1st patch only; challenge: 48-h semi-occlusive patch, with 5% SLS pretreatment (occlusive)	not a sensitizer	12
Triethyl Citrate	100%	59 subjects	HRIPT; 0.4 ml, 20 x 20 mm Webril pad applied with a 40 x 40 mm adhesive square; 9 induction patches	not an irritant or a sensitizer	96
Tristearyl Citrate	25% in olive oil; heated until soluble	110 subjects	HRIPT; 0.2 ml applied to a 1sq. in. pad of a semi-occlusive patch; induction patches applied 3x/wk for 3 wks; a challenge patch was applied after 2 wks	not a primary irritant or sensitizer	97

Table 8. Dermal irritation and sensitization

Test Article	Concentration	Test Pop.	Procedure	Results	Reference
Triisostearyl Citrate	neat	114 subjects	HRIPT; 150 µl applied to a 2 cm^2 absorbent pad of an occlusive patch; induction patches applied 4x/wk for 3 wks; 4 challenge applications were made on a previously untreated site	not an irritant or a sensitizer	[67]
Trioctyldodecyl Citrate	neat	105 subjects	HRIPT; 150 µl applied to a 2 cm^2 absorbent pad under a 4 cm^2 occlusive covering; induction patches applied 4x/wk for 3 wks; 4 challenge applications were made on a previously untreated site	not an irritant or a sensitizer	[71]
Laureth-7 Citrate	10%, with pH adjusted to 5.5 (vehicle not given)	100 subjects	HRIPT; .2 ml applied to a 3/4 sq. in. pad of an occlusive patch; induction patches applied 3x/wk for 3 wks; a challenge patch was applied after 2 wks	not an irritant or a sensitizer	[98]

Abbreviations: DBS – dodecylbenzenesulfonate; FCA – Freund's complete adjuvant; GPMT – guinea pig maximization test; HRIPT – human repeated insult patch test; LLNA – local lymph node assay; pet – petrolatum; PII- primary irritation index; SLS – sodium lauryl sulfate; TEWL – transepidermal water loss

Table 9. Mucosal irritation studies

Test Article	Concentration/Dose	Animals/Gp	Method	Results	Reference
ALTERNATIVE STUDIES					
Citric Acid	2% in NaCl	---	luminescent bacteria toxicity test (Microtox® test)	moderate/ severe ocular irritant; EC_{50} =14 mg/l	99
Citric Acid	undiluted	---	EYTEX assay	severe/extreme irritant; EDE>51	100
Triisostearyl Citrate	10% in corn oil	---	MatTek EpiOcular *in vitro* toxicity assay ; 100 µl	non-irritating; ET_{50} >256 min	101
Laureth-7 Citrate	5% active	---	300 µl; HET-CAM test; reactive-time method	slightly irritating; irritation value of 0.00	102
NON-HUMAN STUDIES					
Citric Acid (hydrate)	5.0% (0.26 M); pH 2.1	6 NZW rabbits.	modified Draize study; test material was placed directly on central portion of cornea; eyes rinsed in 1 gp	no corneal opacity in rinsed or unrinsed eyes; conjunctivitis in all animals through day 7 (details not given)	103
Citric Acid	10 and 30% aq.	3 NZW rabbits	0.1 ml; Draize eye irritation study	10%: PII = 9.3; minimally irritating 30%: PII = 16.0; mildly to moderately irritating	104
Citric Acid	not given	rabbits	acute eye irritation/corrosion study	avg. scores (24-72 h): cornea=2.8; iris = 0.0; conjunctiva = 1.7	85
Triethyl Citrate	15 and 33.3% in alcohol SDA 39C	3 NZW rabbits	0.1 ml; Draize eye irritation study	both concentrations: conjunctival irritation and corneal involvement which did not clear by day 7	12
Triethyl Citrate	33.3% in pet	3 NZW rabbits	0.1 ml; Draize eye irritation study	conjunctival irritation and corneal involvement cleared on day 7	12
Trioctyldodecyl Citrate	neat	6 rabbits	0.1 ml; Draize eye irritation study	non-irritating; MMTS = 0.00	71

Abbreviations: EC_{50} – concentration causing a 50% reduction in light; EDE – EYTEX/Draize equivalent; ET_{50} - % viability 50%; MMTS-maximum mean total score; NZW – New Zealand white

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