Tentative Safety Assessment

Citric Acid, Inorganic Citrate Salts and Alkyl Citrate Esters As Used in Cosmetics

December 19, 2011

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 C. 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, CIR.

1101 17th Street, NW, Suite 412 ♢ Washington, DC 20036-4702 ♢ ph 202.331.0651 ♢ fax 202.331.0088 ♢ cirinfo@cir-safety.org

TABLE OF CONTENTS

ABSTRACT

The CIR Expert Panel assessed the safety of citric acid, 12 inorganic citrate salts, and 20 alkyl citrate esters as used in cosmetics. Citric acid is reported to function as a pH adjuster, chelating agent, or fragrance ingredient. Some of the salts are also reported to function as chelating agents, and a number of the citrates are reported to function as skin conditioning agents. The Panel reviewed available animal and clinical data; however, for citric acid and the other GRAS ingredients, oral toxicity was not a focus in this assessment. The Panel concluded that citric acid, the inorganic salts, and the alkyl esters are safe in the present practices of use and concentration.

INTRODUCTION

This assessment reviews the safety of citric acid, an α (and β)-hydroxytricarboxylic acid, as used in cosmetics. The following 12 inorganic citrate salts and 20 alkyl citrate esters also are included in this safety assessment, for a total of 33 ingredients:

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 Esters

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

Citric acid is reported to function in cosmetics as a chelating agent, pH adjuster, or fragrance ingredient. While some of the inorganic citrate salts are also reported to function as a pH adjuster or chelating agent, there are many other reported functions, including skin conditioning agent, buffering agent, cosmetic astringent, oral care agent, cosmetic biocide, or pesticide. The alkyl citrate esters are reported to function primarily as skin conditioning agents, but a few have other possible functions are reported, including plasticizer, solvent, and fragrance ingredient.

As listed by the Food and Drug Administration (FDA), citric acid, calcium citrate, ferric citrate, manganese citrate, potassium citrate, sodium citrate, diammonium citrate, isopropyl citrate, stearyl citrate, and triethyl citrate are generally recognized as safe (GRAS) direct food additives. Since these 10 ingredients have been shown to be safe for ingestion, this report will focus on the non-oral toxicity of these ingredients. For the other ingredients, all available data will be included.

Structurally, citric acid is an α-hydroxy acid (AHA). In the FDA *Guidance for Industry: Labeling for Topically Applied Cosmetic Products Containing Alpha Hydroxy Acids as Ingredients*, from 2005,[1] the FDA specifically mentions citric acid containing products, for which the following labeling may be warranted:

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.[1]

CHEMISTRY

Definition, Structure, and Properties

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.[2] It precipitates as white, translucent crystals of monoclinic holohedra form. Citric acid is a polyprotic 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).

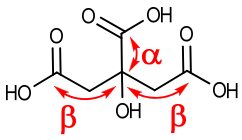


Figure 1. Citric Acid

Citric acid differs structurally from the AHAs reviewed previously (i.e., glycolic and lactic acid) by having three carboxylic acid functional groups, instead of just one. Citric acid is therefore triprotic, and thus has three different pK_as, making it a prime buffer component. Even for the most acidic of these carboxylates, i.e., the center acid functional group, is only a weak acid with a pKa of 3.1.

Citric acid is soluble in water, is soluble in some organic liquids, and is very hydrophilic, with an octanol/water partition coefficient around -1. Citric acid and its salts are solids. The citrate alkyl 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 and are generally hydrophobic, with octanol/water partition coefficients estimated between 1 and 12.

The definitions and structures of the ingredients included in this review are provided in Table 1. It is worth noting that the terminology is not always intuitive, in that monosodium citrate, for example, is the monosodium salt, but sodium citrate is the trisodium salt. The available physical and chemical property information is found in Table 2. Impurities and composition data are provided in Table 3.

Methods of Manufacture

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*.[3] A common problem associated with these fermentation methods is the co-synthesis of isocitric acid (***1***-hydroxy-1,2,3-propanetricarboxylic acid). However, isocitric acid can be separated using a variety of crystallization techniques. Careful control of the trace element content is very important for high production.[2,4] (While citric acid can also be extracted from citrus fruits, over 99% of the world's citric acid output is produced by microbial fermentation.[4]) 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).

Citrate alkyl esters are typically produced via the condensation of the appropriate alcohol with citric acid (e.g., condensing with butyl alcohol to produce tributyl citrate).[5] Some ingredient-specific methods of manufacture are described in Table 4.

USE

Cosmetic

Citric acid is reported to function in cosmetics as a chelating agent, pH adjuster, or fragrance ingredient.[6] Some of the inorganic salts of citric acid are reported to function as a pH adjuster or chelating agent; these salts also have many other reported functions, including skin conditioning agent, buffering agent, cosmetic astringent, oral care agent, cosmetic biocide, or pesticide. The alkyl esters are reported to function primarily as skin conditioning agents, but a few of these have other reported functions, including plasticizer, solvent, and fragrance ingredient. The various cosmetic functions of these ingredients are provided in Table 5; some ingredients have more than one reported function.

Voluntary Cosmetic Registration Program (VCRP) data obtained from the FDA in 2011,[7] and concentration of use information received in response to a survey conducted by the Personal Care Products Council (Council),[8] indicate that 22 of the 33 citrates named in this report are currently used in cosmetic formulations. Citric acid is used in almost every category of cosmetic product, with 6795 reported uses[7] at concentrations up to 4% in leave-on formulations, 10% in rinse-off formulations, and 39% in products diluted for (bath) use.[9] Sodium, tributyl, and triethyl citrate are reported to be used in 980, 331, and 244 cosmetic formulations, respectively.[7] 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.[9] 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. All other in-use ingredients are used at concentrations of ≤12%.

Frequency and concentration of use data are provided in Table 6a. The ingredients not in use, according to the VCRP and Council survey, are listed in Table 6b.

Products containing citric acid and some of its salts and esters may be applied to baby skin or used near the eye area or mucous membranes. Additionally, citric acid and some of its salts and esters are used in cosmetic sprays, including hair, deodorant, body, and other propellant and pump spray products, and could possibly be inhaled. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 μm, with propellant sprays yielding a greater fraction of droplets/particles <10 μm compared with pump sprays.[10,11] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and thoracic regions of the respiratory tract and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[12,13] However, the potential for inhalation toxicity is not limited to respirable droplets/particles deposited in the lungs. Inhaled droplets/particles deposited in the nasopharyngeal and thoracic regions may cause toxic effects depending on their chemical and other properties. There is some evidence indicating that deodorant spray products can release substantially larger fractions of particulates having aerodynamic equivalent diameters in the range considered to be respirable.[13] However, the information is not sufficient to determine whether significantly greater lung exposures result from the use of deodorant sprays, compared to other cosmetic sprays.

All of the ingredients included in this review are listed in the European Union inventory of cosmetic ingredients.[14] "Water-soluble zinc compounds" are listed in Annex III of the Cosmetic Directive, with a maximum authorized concentration in the finished cosmetic product of 1% calculated as zinc; therefore, zinc citrate has a maximum authorized concentration of use of 1%, calculated as zinc, in finished cosmetic products in the European Union.[15]

Non-Cosmetic

The following 10 ingredients are GRAS direct food additives, restricted only by good manufacturing practices: citric acid (21CFR184.1033); calcium citrate (21CFR184.1195); ferric citrate (21CFR184.1298); manganese citrate

(21CFR184.1449); potassium citrate (21CFR184.1625); sodium citrate (21CFR184.1751); diammonium citrate (21CFR184.1140), isopropyl citrate (21CFR184.1386) stearyl citrate (21CFR184.1851) and triethyl citrate (21CFR184.1911). 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.[16] Citrate-containing ingredients are allowed as active ingredients, at a maximum daily dosage of 8 g, in antacid over-the-counter (OTC) products (21CFR331.11).

Examples of other non-cosmetic uses of citric acid and some of the citrates are provided in Table 7.

TOXICOKINETICS

Citric acid is well absorbed and largely metabolized when administered orally; it is an intermediate in the Krebs 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. 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.[18] 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.[19] Ten to 35% of filtered citrate is excreted in the urine. The normal blood citrate level in humans is approximately 25 mg/l.[20]

In Vitro

Trihexyl Citrate

Trihexyl citrate is not a cosmetic ingredient. This information is presented because trihexyl citrate is structurally similar to cosmetic ingredients included in this review, and may provide data that can be extrapolated.

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.[21] 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/ml was used with all three preparations; a concentration of 1000 nmol/ml was also used with rat serum. In rat serum, at concentrations of 50 and 1000 nmol/ml, 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. 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

Eight male Sprague-Dawley rats were dosed by gavage with 100 mg aluminum/kg bw, as aluminum citrate, 6 days/wk for 4 wks.[22] 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 cortex of the brain, the hippocampus, and the cerebellum 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. (In this study, groups

of rats were also dosed with citric acid for 4 wks or aluminum hydroxide for 9 wks. The aluminum content in the cortex of the brain of rats dosed with citric acid was statistically significantly increased compared to controls. There were no statistically significant differences in aluminum content of the brain between control rats and those dosed with aluminum hydroxide.)

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.[23] 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.

Stearyl/Distearyl Citrate

Stearyl citrate is hydrolyzed readily to stearyl alcohol and citric acid in dogs, and to a lesser extent, in rats.[24] Stearyl citrate, predominantly as distearyl citrate, added to the feed of rats at a concentration of 2.5-10% was poorly absorbed.[17] (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.[25] 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 (pet.) or silicone as the vehicle. A 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. Administration of 80 mmol/l aluminum citrate in water for 8 mos 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 produce adverse effects in rats, rabbits, or dogs. Repeated oral dosing with tributyl citrate did not have an adverse effect on rats (10% in the diet for 6 wks) or cats (5 ml/kg for 2 mos).

Single Dose (Acute) Toxicity

Acute toxicity studies are summarized in Table 8. Acute toxicity testing did not raise any toxicological concerns.

Repeated Dose Toxicity

Oral

Aluminum Citrate

In a toxicokinetics study described previously, a group of 8 male Sprague-Dawley rats was dosed by gavage with 100 mg aluminum/kg bw, as aluminum citrate, 6 days/wk for 4 wks.[22] 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. Body weights of test animals were similar to those of controls after 4 wks of dosing. Body weights of treated animals decreased compared to controls during the recovery period, but the difference was not statistically significant.

In another toxicokinetics study described previously in this report, a group of 10 female Sprague-Dawley rats was given aluminum citrate in the drinking water at a concentration of 80 mmol/l for 8 mos.[23] Final body weights of animals of the test group were statistically significantly decreased compared to the controls. Kidney function was not affected by dosing.

Isopropyl Citrate Ester Mixture

A 6-wk feeding study of an isopropyl citrate ester mixture consisting of 27% isopropyl citrate, 9% diisopropyl citrate, and 2% triisopropyl citrate, in a vehicle consisting of mono- and diglycerides (1:1) vegetable oil was performed using rats.[26] Male rats had an average daily intake of 0.78 g and females 0.54 g of the citrate mixture, 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.[26] 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.[26] Signs of toxicity were 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 dosed 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.[26] Adverse effects were not observed when dogs were fed a diet containing 0.06% of the test article for 12 wks.

Distearyl Citrate Ester Mixture

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.[26] Male rats had an average daily intake of 1.32 g and females 1.06 g of the mixture, 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.[26] 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.[26] 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.[26] 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.[27] 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.[27] No significant effects were observed.

Intraperitoneal

Tributyl Citrate

A test group of 20 mice (sex not stated) was 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 was dosed with vehicle only.[28] 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 1064 mg/kg bw aluminum citrate concurrent with 62 mg/kg bw 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 control or test group fetuses. Dietary administration of up to 9.5% of a diisostearyl citrate ester mixture did not produce any reproductive or developmental effects in a multi-generation study.

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.[29] 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 xiphoids 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 (detection limit 0.05 µg/g) in the whole fetuses of control or treated animals.

Distearyl Citrate Ester Mixture

A multi-generation study was performed in which 4 generations of rats were fed a diet containing 0, 1.9, or 9.5% of the distearyl citrate ester mixture that was described earlier in this report.[26] 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.[30] 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.[31] 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

Genotoxicity studies are summarized in Table 9. Citric acid and its salts and esters were mostly negative in in vitro and in vivo genotoxicity tests. Exceptions were weakly positive results for 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.[32] 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 by 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.[33] The rationale for testing is that aluminum is listed by the EPA as a drinking water contaminant with a high health research priority.

IRRITATION AND SENSITIZATION

Skin Irritation/Sensitization

Non-human and human skin irritation and sensitization studies are summarized in Table 10. 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 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, a cuticle cream containing 4% citric acid was not an irritant or a sensitizer in humans; 2.5% aq. citric acid produced positive results in skin prick test in 3 of 91 urticaria or anigoedema patients. Triethyl citrate, applied undiluted during epidermal induction, was a strong sensitizer in a guinea-pig maximization test, but 20% in pet. was not a primary irritant or sensitizer in human studies. Trioctyldodecyl citrate was a mild sensitizer in a local lymph node assay when applied neat, but the same concentration was not an irritant or sensitizer in human studies. Tributyl citrate (concentration not stated) was not a sensitizer in animal studies. In human studies, 25% tristearyl citrate and 100% triisostearyl citrate were not irritants or sensitizers in repeated insult patch tests.

Ocular Irritation

Ocular irritation studies are summarized in Table 11. Citric acid was predicted to be a moderate/severe to severe/extreme ocular irritant in in vitro studies, and it was minimally irritating to rabbit eyes at a concentration of 10% and mildly irritating at a concentrations 30%. In in vitro studies, triisostearyl citrate was predicted to be non-irritating to eyes. Triethyl citrate, 33.3%, did produce irritation in rabbit eyes, and undiluted trioctyldodecyl citrate was non-irritating.

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).[34] 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, ≥5%, 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 (16% w/w) citric acid on skin cell renewal and irritation (as stinging) was determined at a pH of 3, 5, and 7.[35] 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 0-4 every minute for 15 min. (It is not stated, but the assumed maximum score is 60). Two mg/cm^2 of the citric acid test product were applied to the test area on the volar forearm of 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 38, 35.4, and 23.6, respectively.

The effect of 5% citric acid on skin cell renewal and irritation was also evaluated at the same pHs.[36] Cell renewal was greater at this 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.[37] 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.[38] 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 pro-

duced 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.[39] (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 was 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.[40] 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 are 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.[41] 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 in cough challenge testing.[42] 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.[43] In human subjects, the cough reflex was decreased 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.

The mechanism of irritant properties was examined by comparing the cough response of isotonic citric acid in saline, isotonic sodium citrate, sodium citrate in saline, isotonic D-glucose, and distilled water.[44] All solutions were nebulized and inhaled by 7 subjects for 1 min periods. Cough occurred in response to inhalation of every test article except sodium citrate in saline (616 mOsmol/l). The mean cough frequency (coughs/min) was 11.4 for 0.69% citric acid in 0.79% saline (308 mOsmol/l), 12.5 for sodium citrate (308 mOsmol/l), 18.1 for D-glucose (308 mOsmol/l), and 15.7 for water (0 mOsmol/l).

Citric acid induced airway constriction in anesthetized Hartley guinea pigs.[45] A citric acid aerosol was generated from a 0.6 M citric acid solution, and each animal received 50 breaths of 4 ml of the solution using a nebulizer. At 2-3 min following exposure to citric acid, the aerosol induced significant airway constriction that persisted to the end of the study (20 min following administration).

In another study, anesthetized guinea pigs were administered 10% w/v aq. aerosol citric acid for 1 min using a nebulizer; airway resistance increased 79% and lung compliance decreased 68%.[46] In anesthetized guinea pigs in which the vagal nerve 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.[28] 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; again, the number of animals used was not stated. Triethyl citrate resulted in insensitivity to pricking of the area lasting 12-20 min, while tributyl citrate produced a “deadened area” for a period greater than 2 h.

SUMMARY

Citric acid is an α-hydroxy tricarboxylic acid that is reported to function 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 are reported to have many diverse functions, while the 20 alkyl esters are reported to function mostly as skin conditioning agents, although they can have other functions. Citric acid is used in almost every category of cosmetic product and has 6795 reported uses. Citric acid is reported to be used at concentrations up to 39% in products that are diluted for (bath) use and up to 4% in leave-on products. 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, in leave-on formulations; all other in-use ingredients are used at ≤12%.

Citric acid, calcium citrate, ferric citrate, manganese citrate, potassium citrate, sodium citrate, diammonium citrate, isopropyl citrate, stearyl citrate, and triethyl citrate are GRAS direct food additives. These ingredients, plus magnesium citrate; distearyl citrate; tristearyl citrate; and tributyl citrate are FDA-approved indirect 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. Administration of 80 mmol/l aluminum citrate in water for 8 mos 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 (10% in the diet for 6 wks) or cats (5 ml/kg for 2 mos).

Oral administration of 1064 mg/kg bw aluminum citrate concurrent with 62 mg/kg bw 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 control or treated-group fetuses. Dietary administration of up to 9.5% of a distearyl citrate ester mixture did not produce any reproductive or developmental effects in a multigenerational study.

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 a dermal irritant at concentrations 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, a cuticle cream containing 4% citric acid was not an irritant or a sensitizer in humans; 2.5% aq. citric acid produced positive results in skin prick test in 3 of 91 urticaria or anigoedema patients. Triethyl citrate, applied undiluted during epidermal induction, was a strong sensitizer in a guinea-pig maximization test, but 20% in pet. was not a primary irritant or sensitizer in human studies. Trioctyldodecyl citrate was a mild sensitizer in a local lymph node assay when applied neat, but the same concentration was not an irritant or sensitizer in human studies. Tributyl citrate (concentration not stated) was not a sensitizer in animal studies. In human studies, 25% tristearyl citrate and 100% triisostearyl 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 it was minimally irritating to rabbit eyes at a concentration of 10% and mildly irritating at a concentration of 30%. In in vitro studies, triisostearyl citrate was predicted to be non-irritating to eyes. Triethyl citrate, 33.3%, did produce irritation in rabbit eyes, and undiluted trioctyldodecyl citrate was non-irritating.

Citric acid, ≥5%, 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 used in inhalation challenge tests. 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.

DISCUSSION

The CIR Expert Panel considered that the oral safety of citric acid, calcium citrate, ferric citrate, manganese citrate, potassium citrate, sodium citrate, diammonium citrate, isopropyl citrate, stearyl citrate, and triethyl citrate has been well substantiated in that these ingredients are GRAS direct food additives. Therefore, the focus of this safety assessment was on the non-oral toxicity of these ingredients. Although there are data gaps, the chemical structures, physicochemical properties, and functions and concentrations in cosmetics allow grouping these ingredients together and extending the available toxicological data to support the safety of the entire group.

Because citric acid and some of its salts and esters can be used in products that may be sprayed, the Panel discussed the issue of incidental inhalation exposure. In the absence of inhalation data, the Panel considered other pertinent data that were available, including e.g., data characterizing the potential for citric acid and its salts and alkyl esters to cause systemic toxicity, ocular or dermal irritation or sensitization, and other effects. The Panel noted that 95% – 99% of droplets/particles produced in cosmetic aerosols would not be respirable to any appreciable amount. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, this information suggested that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic toxic effects. The tussive effects observed with citric acid appear to be due to irritant properties, and pulmonary toxicity is not expected.

The Panel discussed whether citric acid or any of its salts or alkyl esters would be irritants. Available repeated insult patch testing at the highest leave-on concentration of 4% citric acid demonstrated an absence of both dermal irritation and sensitization, suggesting that these ingredients would not be irritants in formulation.

While citric acid can be considered an alpha-hydroxy acid (AHA), it is also a beta-hydroxy acid. Structurally, citric acid is a tricarboxylic acid, and as such, has a unique functionality and is chemically and biologically distinct from the AHAs considered in the CIR safety assessment of AHAs (i.e., glycolic and lactic acid). Therefore, the concerns that stem from the mode of action of AHAs are not relevant to citric acid and its inorganic salts and alkyl esters.

CONCLUSION

The CIR Expert Panel concluded that citric acid, inorganic citrate salts, and alkyl citrate esters, listed below, are safe in the present practices of use and concentration.

Citric Acid

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 Esters

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

Were ingredients in this group not in current use (as indicated by *) to be used in the future, the expectation is that they would be used at concentrations comparable to others in this group.

TABLES

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

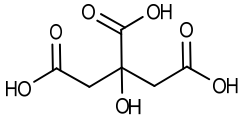
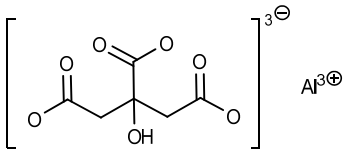
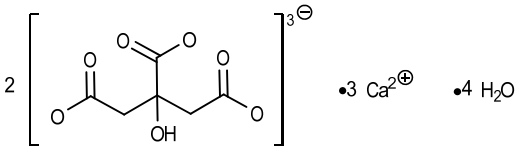
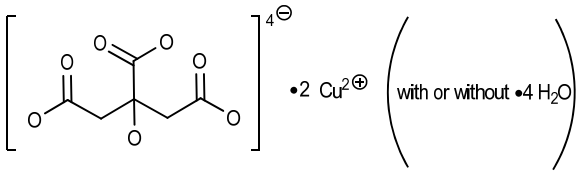
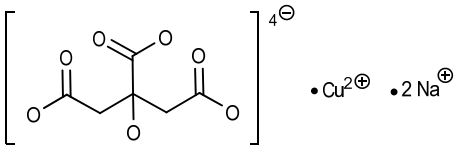
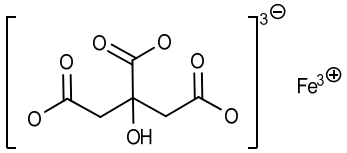
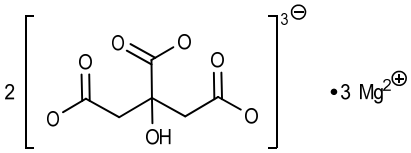
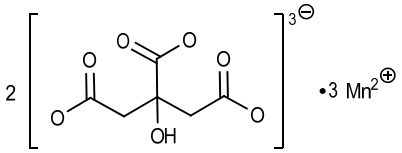
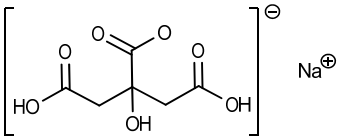
Ingredient/CAS No.	Definition	Formula/structure
Citric Acid and inorganic salts		
Citric Acid 77-92-9 5949-29-1 [hydrate]	an α-hydroxy tricarboxylic acid	
Aluminum Citrate 813-92-3 31142-56-0	a complex salt of aluminum hydroxide and citric acid[6]	
Calcium Citrate 5785-44-4	the calcium salt of citric acid[6]	
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[6]	
Manganese Citrate 10024-66-5	the manganese (II) salt of citric acid[6]	
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

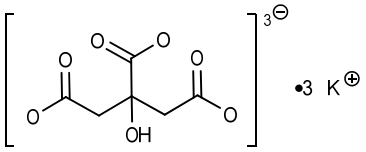
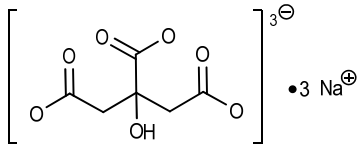
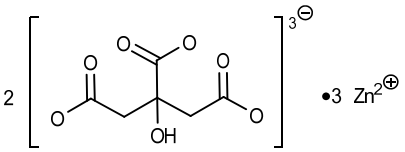
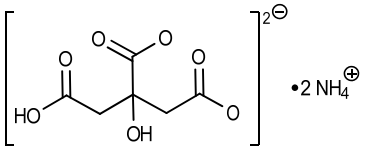
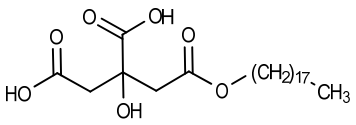
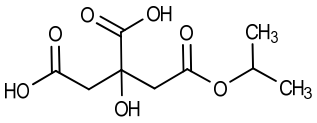
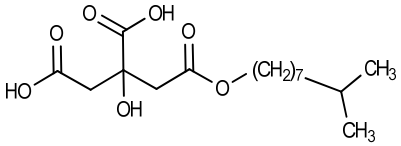
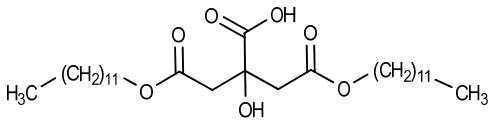
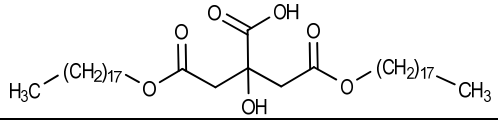
Ingredient/CAS No.	Definition	Formula/structure
Potassium Citrate 866-84-2	the tripotassium salt of citric acid	
Sodium Citrate 68-04-2 (anhydrous) 6132-04-3 (dihydrate)	the trisodium salt of citric acid	
Zinc Citrate 546-46-3	the zinc (II) salt of citric acid[6]	
Diammonium Citrate 3012-65-5	the diammonium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

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

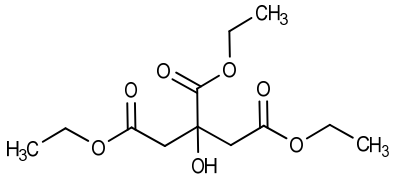
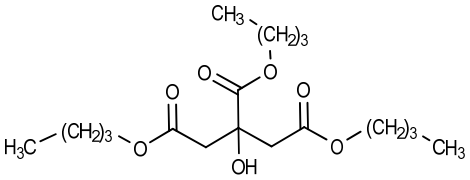
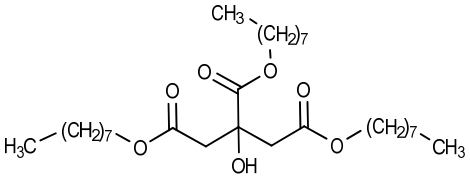
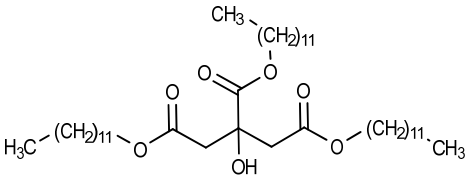
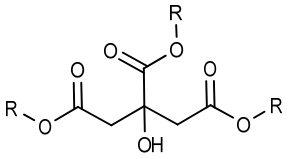
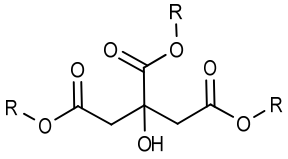
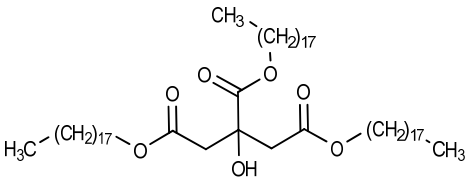
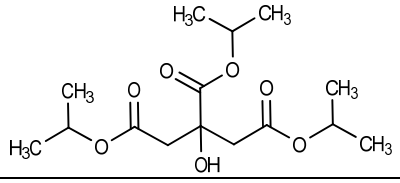
Ingredient/CAS No.	Definition	Formula/structure
-Triesters		
Triethyl Citrate 77-93-0	the triester of ethyl alcohol and citric acid[6]	
Tributyl Citrate 77-94-1	the triester of butyl alcohol and citric acid[6]	
Tricaprylyl Citrate 76414-35-2	the triester of capryl alcohol and citric acid[6]	
Trilauryl Citrate 65277-53-4	the triester of lauryl alcohol and citric acid[6]	
Tri-C12-13 Alkyl Citrate	the triester of C12-13 alcohols and citric acid[6]	 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[6]	 wherein R is a 14 or 15 carbon chain
Tristearyl Citrate 7775-50-0	the triester of stearyl alcohol and citric acid[6]	
Triisopropyl Citrate 74592-76-0	the triester of isopropyl alcohol and citric acid	

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

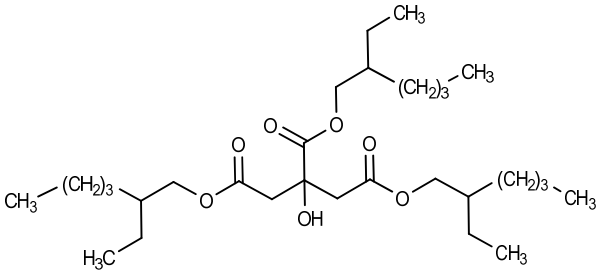
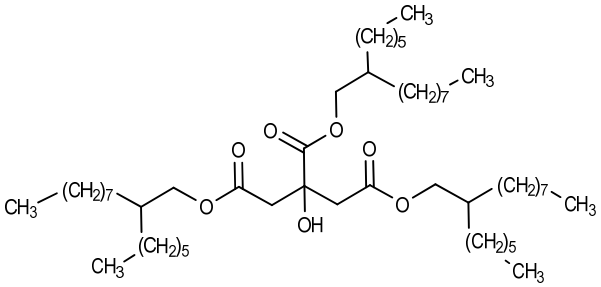
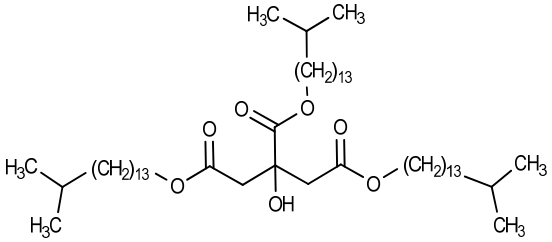
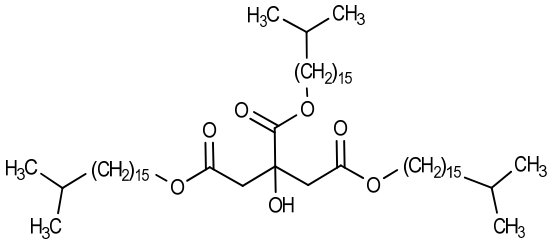
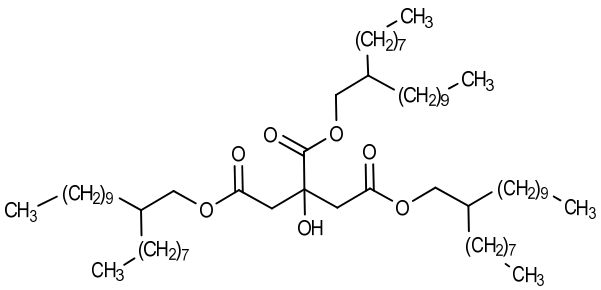
Ingredient/CAS No.	Definition	Formula/structure
Triethylhexyl Citrate 7147-34-4	the triester of 2-ethylhexanol and citric acid	
Trihexyldecyl Citrate	the triester of 2-hexyldecanol and citric acid.	
Triisocetyl Citrate 93385-14-9	the triester of isocetyl alcohol and citric acid	 one example of an "iso"
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

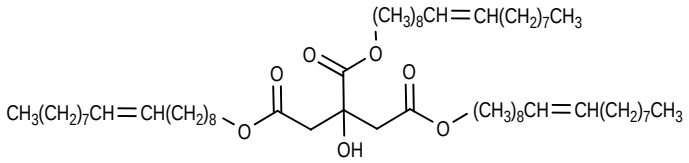
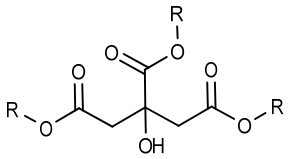
Ingredient/CAS No.	Definition	Formula/structure
Trioleyl Citrate 175831-77-3	the triester of oleyl alcohol and citric acid	
Ethyl Citrates 172820-60-9	a mixture of mono-, di- and triesters of ethanol and citric acid[6]	 wherein R is a hydrogen atom or an ethyl group

Table 2. Chemical and physical properties

Property	Description	Reference
	Citric Acid	
molecular weight	192.12 monohydrate: 210.14	3
appearance and form	monoclinic holohedrism crystals monohydrate: orthorhombic crystals	3
	free-flowing, colorless, translucent crystals or as a white granular to fine powder	47
melting point	153°C monohydrate: ≈100°C	3
boiling point	decomposes above 175°C	18
log P	-1.198±0.396 (at 25°C)	48
log K_{ow}	-1.75	49
vapor pressure	<0.001 mm Hg (20°C) 3.7 x 10^{-9} mm Hg (25°C)	50 49
solubility	solubility in water increases with temperature (from 54% w/w/ at 10°C to 84%)	3
	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)	47
	solubility in water increases with temperature from ~54 wt percentage at 10°C to ~88 wt percentage at 100°C	51
density	1.665 monohydrate: 1.542	3
pK_a	pK_1 = 3.128; pK_2 = 4.761; pK_3 = 6.396 (25°C)	3
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)	52
	Aluminum Citrate	
density	1.5 g/cm^3	3
	Calcium Citrate	
molecular weight	498.43	3
appearance and form	fine white, odorless powder	53
solubility	soluble in 1050 parts cold water, somewhat soluble in hot water; insoluble in alcohol	3

Table 2. Chemical and physical properties

Property	Description	Reference
	Copper Citrate	
molecular weight	315.18	3
appearance and form	green or bluish-green crystalline powder; odorless	3
solubility	slightly soluble in water; soluble in ammonia, diluted acids, and cold alkali citrate solutions; freely soluble in hot alkali citrate solutions	3
	Diammonium Citrate	
molecular weight	226.18	3
appearance and form	granules or crystals	3
solubility	soluble in 1 part water; slightly soluble in alcohol	3
	Ferric Citrate	
appearance and form	garnet-red transparent scales or pale brown powder	3
solubility	slowly but completely soluble in cold water; readily soluble in hot water, practically insoluble in alcohol	3
	Magnesium Citrate	
molecular weight	dibasic: 214.41 tribasic: 451.11	3
	Monosodium Citrate	
molecular weight	214.12	54
melting point	decomposes	54
solubility	570 g/l (at 25°C); insoluble in ethanol and ether	54
	Potassium Citrate	
molecular weight	306.39 monohydrate: 324.41	3
appearance and form	monohydrate: white crystals, granules, or powder; odorless monohydrate: white coarse powder	3 55
boiling point	211°C (calculated)	49
log K_{ow} (calculated)	-0.28	49
vapor pressure	2.09 x 10^{-12} mm Hg (25°C)	49
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	3 55
stability	monohydrate: very hygroscopic; readily deliquesces in moist air	55
	Sodium Citrate	
molecular weight	258.07 dihydrate: 294.10	3
appearance and form	dihydrate: white crystals, granules, or powder; odorless	3
melting point	anhydrous: >300°C dihydrate: 150°C	56 57
density	monohydrate: 1.814	3
log K_{ow} (calculated)	-0.28	58
vapor pressure	2.09 x 10^{-12} mm Hg (25°C)	49
solubility	soluble in water, ~425 g/l (25°C) monohydrate: soluble in 1.3 parts water; insoluble in alcohol	49 3
	Zinc Citrate	
molecular weight	574.43	3
appearance and form	powder; odorless	3
solubility	slightly soluble in water; soluble in diluted mineral acids and alkali hydroxides	3

Table 2. Chemical and physical properties

Property	Description	Reference
	Stearyl Citrate	
molecular weight	458.60	59
	Distearyl Citrate	
melting point	70-72°C	60
	Triethyl Citrate	
molecular weight	276.29	61
appearance and form	clear, colorless, oily liquid	27
melting point	-55°C	62
boiling point	294°C	62
vapor pressure	6.4 x 10^{-3} mm Hg (20°C)	63
density	1.137 (20°C)	3
refractive index	1.440 -1.442 (@25°C/D)	63
solubility	6.5 g/100 ml water (25°C) 5.5 g/100 ml water (25°C); insoluble in hexane miscible with alcohol, ether	27 63 3
log K_{ow}	1.3 (35°C) (measured) 0.33 (calculated)	61
	Tributyl Citrate	
molecular weight	360.44	3
appearance and form	colorless or pale yellow liquid; odorless	3
melting point	-20°C	3
boiling point	170°C (1 mm Hg) 233°C (22 mm Hg)	27 3
vapor pressure	9.6 x 10^{-2} mm Hg (20°C)	63
density	1.045 (20°C)	3
refractive index	1.443-1.445 (@25°C/D)	63
solubility	insoluble in water; miscible with most organic liquids	3
log P (predicted)	4.324 ± 0.411 (25°C)	48
pK_a (predicted)	11.3 ± 0.29 (25°C)	48
	Tricaprylyl Citrate	
molecular weight	528.76	48
boiling point	250-255°C (6-7 mm Hg)	64
density	0.9498 g/cm^3	64
log P (predicted)	10.438 ± 0.411 (25°C	48
pK_a (predicted)	11.30 ± 0.29	48
	Trilauryl Citrate	
molecular weight	697.08	48
boiling point (predicted)	675.9°C	48
density (predicted)	0.955 g/cm^3 (20°C)	48
log P (predicted)	16.551 (25°C)	48
pK_a (predicted)	11.29 (25°C)	48
	Tristearyl Citrate	
molecular weight	949.56	48
boiling point (predicted)	840.3°C	48
density (predicted)	0.924 g/cm^3 (20°C)	48

Table 2. Chemical and physical properties

Property	Description	Reference
log P (predicted)	25.722 (25°C)	48
pK_a (predicted)	11.29 (25°C)	48
	Triisopropyl Citrate	
molecular weight	318.36	48
boiling point (predicted)	331°C	48
density (predicted)	1.116 g/cm^3 (20°C)	48
log P (predicted)	2.328 (25°C)	48
pK_a (predicted)	11.69 (25°C)	48
	Triisostearyl Citrate	
molecular weight	944	65
appearance	clear viscous liquid	66
	Trioctyldodecyl Citrate	
molecular weight	1032	65
boiling point (predicted)	883.3°C	48
density (predicted)	0.917 g/cm^3 (20°C)	48
log P (predicted)	29.634 (25°C)	48
pK_a (predicted)	11.25 (25°C)	48
	Trioleyl Citrate	
molecular weight	943.51	48
boiling point (predicted)	845.8°C	48
density (predicted)	0.936 g/cm^3 (20°C)	48
log P (predicted)	25.443 (25°C)	48
pK_a (predicted)	11.28 (25°C)	48

Table 3. Impurities and Composition

Ingredient	Impurities/Composition	Reference
Stearyl Citrate	10-15% monostearyl, 70-80% distearyl, and 10-15% tristearyl derivatives	17
Isopropyl Citrate	65-80% monoisopropyl, 15-30% diisopropyl, and 5-10% triisopropyl citrate	17
Triisostearyl Citrate	supplied as >90% triisostearyl citrate	65
Trioctyldodecyl Citrate	impurities include residual isostearyl alcohol (<10%) and citric acid (<0.5%) supplied as ~100% trioctyldodecyl citrate (according to one supplier) impurities include residual octyldodecyl alcohol (<5%) and citric acid	65

Table 4. Ingredient-Specific Methods of Manufacture

Ingredient	**Method of Manufacture**	**Reference**
Calcium Citrate	neutralization of citric acid with calcium hydroxide or calcium carbonate	21CFR184.1195
Copper Citrate	prepared by the interaction of hot aqueous solutions of copper sulfate and sodium citrate	[3]
Ferric Citrate	prepared from reaction of citric acid with ferric hydroxide	21CFR184.1298
Manganese Citrate	obtained by precipitating manganese carbonate from manganese sulfate and sodium carbonate solutions. 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	21CFR184..1449
Potassium Citrate	crystallizing and drying of a potassium citrate solution that is prepared using a citric acid solution and potassium hydroxide	[67]
Sodium Citrate	neutralization of citric acid with sodium hydroxide or sodium carbonate	21CFR184.1751
Zinc Citrate	prepared from zinc carbonate and citric acid	[3]
Diammonium Citrate	partial neutralization of citric acid with ammonia	21CFR184.1140
Isopropyl Citrate	esterification of citric acid with isopropanol	21CFR184.1386
Stearyl Citrate	esterification of citric acid with stearyl alcohol	21CFR184.1851
Triethyl Citrate	esterification of ethyl alcohol with citric acid	21CFR184.1911
Tributyl Citrate	synthesized from *n*-butyl alcohol and citric acid	[3]
Triisostearyl Citrate	manufactured from isostearyl alcohol and citric acid in a proprietary esterification process, without the use of heavy metal catalysts	[65]
Trioctyldodecyl Citrate	manufactured from octyldodecyl alcohol and citric acid in a proprietary esterification process, without the use of heavy metal catalysts	[65]

Table 5. Reported cosmetic 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
Stearyl Citrate
Tri-C12-13 Alkyl Citrate
Tri-C14-15 Alkyl Citrate
Triethylhexyl Citrate
Triisopropyl Citrate
Trioleyl Citrate

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

Skin Conditioning Agent – Miscellaneous
Ferric Citrate
Magnesium 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[6]

Table 6a. Frequency and concentration of use according to duration and type of exposure

	# of Uses[7]	Max. Conc of Use (%)[8]	# of Uses[7]	Max. Conc of Use (%)[8]	# of Uses[7]	Max. Conc of Use (%)[8]
	Citric Acid		**Aluminum Citrate**		**Diammonium Citrate**	
Totals*	**6795**	**0.0000005-39**	**4**	**NR**	**6**	**NR**
Duration of Use						
Leave-On	*2851*	*0.0000005-4*	*3*	*NR*	*2*	*NR*
Rinse-Off	*3753*	*0.000002-10*	*1*	*NR*	*4*	*NR*
Diluted for (Bath) Use	*191*	*0.3-39*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	580	0.0000005-2	NR	NR	1	NR
Incidental Ingestion	214	0.0006-3	NR	NR	NR	NR
Incidental Inhalation-Spray	149[a]	0.004-0.7[a] aerosol:0.05-0.7 pump: 0.003-0.1	NR	NR	NR	NR
Incidental Inhalation-Powder	35	0.0006-0.3	NR	NR	NR	NR
Dermal Contact	4055	0.000008-10	4	NR	2	NR
Deodorant (underarm)	22[b]	0.000008-0.2(not spray) 0.002[b] pump: 0.01	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	0.001-4 5% diluted to 0.025%	NR	NR	NR	NR
Mucous Membrane	1875	0.0002-39 (20-39% is diluted prior to bath use)	1	NR	1	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 (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Powder	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
Baby Products	NR	NR	NR	NR	NR	NR

Table 6a. Frequency and concentration of use according to duration and type of exposure

	# of Uses[7]	*Max. Conc of Use (%)*[8]	*# of Uses*[7]	*Max. Conc of Use (%)*[8]	*# of Uses*[7]	*Max. Conc of Use (%)*[8]
	Isodecyl Citrate		**Magnesium Citrate**		**Monosodium Citrate**	
Totals*	**4**	**NR**	**9**	**0.01-2**	**16**	**0.004-5**
Duration of Use						
Leave-On	*4*	*NR*	*NR*	*0.01-2*	*NR*	*0.004-5*
Rinse-Off	*NR*	*NR*	*9*	*0.5*	*2*	*0.8-5*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*14*	*5*
Exposure Type						
Eye Area	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	5
Dermal Contact	4	NR	NR	0.01-2	16	0.004-5
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	9	0.5	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	14	5 (diluted prior to use)
Baby Products	NR	NR	NR	NR	NR	5
	Potassium Citrate		**Sodium Citrate**		**Stearyl Citrate**	
Totals*	**8**	**0.002-0.6**	**980**	**0.000005-10**	**23**	**0.007-12**
Duration of Use						
Leave-On	*2*	*0.002-0.5*	*587*	*0.000005-10*	*1*	*0.3-12*
Rinse Off	*6*	*0.002-0.6*	*386*	*0.0001-10*	*22*	*0.007-2*
Diluted for (Bath) Use	*NR*	*NR*	*7*	*0.9*	*NR*	*NR*
Exposure Type						
Eye Area	1	NR	47	0.02-2	NR	1-2
Incidental Ingestion	1	0.6	7	0.003-0.4	NR	12
Incidental Inhalation-Spray	NR	0.06-0.07	30[b]	0.000005-0.3; 0.4[a]	NR	1-3[a]
Incidental Inhalation-Powder	NR	0.02	6	0.03	NR4	NR
Dermal Contact	4	0.002-0.5	718	0.0001-10	20	0.007-5
Deodorant (underarm)	NR	NR	1[a]	0.02; 0.1[b]	NR	3[b]
Hair - Non-Coloring	3	0.002-0.07	206	0.000005-4	3	1
Hair-Coloring	NR	NR	5	0.1	NR	NR
Nail	NR	NR	2	0.08-0.5	NR	NR
Mucous Membrane	4	0.002	96	0.003-1	7	0.007-12
Baby Products	NR	NR	9	NR	NR	NR

	Tributyl Citrate		**Tri-C12-13 Alkyl Citrate**		**Tri-C14-15 Alkyl Citrate**	
Totals*	**331**	**0.0005-9**	**1**	**NR**	**19**	**0.1-5**
Duration of Use						
Leave-On	*35*	*0.0005-9*	*1*	*NR*	*19*	*0.1-5*
Rinse-Off	*267*	*0..0009-5*	*NR*	*NR*	*NR*	*NR*
Diluted for (Bath) Use	*29*	*0.0005*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	NR	NR	1	NR	1	3
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	6	NR	NR	NR	13[a]	0.1-5[a]
Incidental Inhalation-Powder	1	NR	NR	NR	NR	NR
Dermal Contact	260	0.0005- <0.05	1	NR	19	0.1-5
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	14	NR	NR	NR	NR	NR
Hair-Coloring	55	NR	NR	NR	NR	NR
Nail	2	0.01-9	NR	NR	NR	NR
Mucous Membrane	233	0.0005-0.001	NR	NR	NR	NR
Baby Products	1	NR	NR	NR	NR	NR

Table 6a. Frequency and concentration of use according to duration and type of exposure

	# of Uses[7]	*Max. Conc of Use (%)*[8]	*# of Uses*[7]	*Max. Conc of Use (%)*[8]	*# of Uses*[7]	*Max. Conc of Use (%)*[8]
	Tricaprylyl Citrate		**Triethyl Citrate**		**Triethylhexyl Citrate**	
Totals*	**19**	**0.3-27**	**244**	**0.0008-6**	**1**	**NR**
Duration of Use						
Leave-On	*16*	*0.3-27*	*215*	*0.004-6*	*1*	*NR*
Rinse-Off	*3*	*0.5-0.8*	*29*	*0.0008-0.2*	*NR*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	1	3	2	0.2-0.6	NR	NR
Incidental Ingestion	3	14-19	11	0.3	NR	NR
Incidental Inhalation-Spray	NR	NR	96[a]	0.2-2	NR	NR
Incidental Inhalation-Powder	1	NR	NR	3	NR	NR
Dermal Contact	13	0.3-27	127	0.0008-6	1	NR
Deodorant (underarm)	NR	NR	48[b]	2 (spray)	NR	NR
Hair - Non-Coloring	3	0.5-0.8	106	0.1-2	NR	NR
Hair-Coloring	NR	NR	NR	0.5	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	3	14-19	18	0.2-0.3	NR	NR
Baby Products	NR	NR	NR	0.009	NR	NR
	Triisocetyl Citrate		**Triisostearyl Citrate**		**Trioctyldodecyl Citrate**	
Totals*	**33**	**0.6-3**	**47**	**0.3-80**	**56**	**1-30**
Duration of Use						
Leave-On	*33*	*0.6-3*	*44*	*0.3-80*	*56*	*1-30*
Rinse Off	*NR*	*NR*	*3*	*NR*	*NR*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	NR	NR	1	NR	8	5-21
Incidental Ingestion	7	NR	39	9-80	37	1-19
Incidental Inhalation-Spray	NR	NR	NR	NR	1	4
Incidental Inhalation-Powder	11	2	NR	NR	2	1-3
Dermal Contact	26	0.6-3	5	0.3-9	19	1-30
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	3	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	7	NR	39	9-80	37	1-19
Baby Products	NR	NR	NR	NR	NR	NR
	Zinc Citrate					
Totals*	**9**	**0.05-2**				
Duration of Use						
Leave-On	*5*	*0.05*				
Rinse-Off	*4*	*0.3-2*				
Diluted for (Bath) Use	*NR*	*NR*				
Exposure Type						
Eye Area	NR	NR				
Incidental Ingestion	4	0.3-2				
Incidental Inhalation-Spray	NR	NR				
Incidental Inhalation-Powder	NR	0.05				
Dermal Contact	5	0.05				
Deodorant (underarm)	4[b]	NR				
Hair - Non-Coloring	NR	NR				
Hair-Coloring	NR	NR				
Nail	NR	NR				
Mucous Membrane	4	0.3-2				
Baby Products	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.

[a] Includes suntan products, in that it is not known whether or not the reported product is a spray.

[b] It is not known whether or not the product is a spray.

NR – no reported uses

Table 6b. Ingredients not reported to be used

Calcium Citrate
Copper Citrate
Disodium Cupric Citrate
Distearyl Citrate
Isopropyl Citrate
Manganese Citrate
Trihexyldecyl Citrate
Triisopropyl Citrate
Trilauryl Citrate
Trioleyl Citrate
Tristearyl Citrate

Table 7. 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	2,4,47,68
Calcium Citrate	calcium fortifier in foods; anti-caking agent in dry mixes	3
Copper Citrate	as an astringent or antiseptic	3
Diammonium Citrate	determination of phosphate, especially in fertilizers	3
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	3,55
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	3
Triethyl Citrate	plasticizer for cellulose derivatives and natural resins; plasticizer in pharmaceutical excipients; solvent in paint removers; emulsifier in food industry; flavor-preserving agent	59,63,69
Tributyl Citrate	plasticizer and solvent for nitrocellulose lacquers; in polishes, inks, and similar preparations; plasticizer in pharmaceutical excipients; as an anti-foam agent	3
Zinc Citrate	used in toothpaste and mouthwash	3

Table 8. Acute toxicity studies

Ingredient	Animals*	No./Group	Dose	LD_{50}	Reference
			DERMAL		
Citric Acid					
Citric Acid	rabbits	10	5 g/kg tested	>5 g/kg	50
Triethyl Citrate					
Triethyl Citrate	rabbits	4	not stated	>5 g/kg	61
Triethyl Citrate	guinea pig	not stated	not stated	>10 ml/kg	70
			ORAL		
Tributyl Citrate					
Tributyl Citrate	rats	5	10-30 ml/kg	no deaths reported	27
Tributyl Citrate	cats	4	30-50 ml/kg	no deaths reported	27
Trioctyldodecyl Citrate					
Trioctyldodecyl Citrate	rats	10 (5/sex)	5 g/kg	no deaths reported	71
			INHALATION		
Triethyl Citrate	rats	not stated	6-h exposure to vapor	1300-3500 ppm	70
			INTRAPERITONEAL		
Monosodium Citrate					
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					
Tributyl Citrate	Swiss albino mice	not stated	chosen from a logarithmic scale	2900 mg/kg	28
			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 9. 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	[33]
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]

Table 9. Genotoxicity studies

Concentration	Vehicle	Procedure	Test System	Results	Reference
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]
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]
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, oral	Saccharomyces D3 mice	weakly positive	[75]
3500 mg/kg (acute & subacute)	saline	host-mediated assay, oral	*S. typhimurium* TA1530 and G46 mice	neg. (acute); weakly pos. (subacute)	[75]
1.2, 12, 120 mg/kg (subacute)	saline	dominant lethal assay, oral, 1x/day for 5 days	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, oral, 1 dose (acute) or 1x/day for 5 days (subacute)	rats	negative	[75]

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

Table 10. Dermal irritation and sensitization

Test Article	Concentration	Test Pop.	Procedure	Results	Reference
NON-HUMAN					
IRRITATION					
Citric Acid					
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	[83]
Citric Acid	not stated	rabbits	acute dermal irritation/corrosion study	slightly irritating; avg erythema score = 0.33	[84]
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	[85]
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	[50]
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	[86]

Table 10. Dermal irritation and sensitization

Test Article	Concentration	Test Pop.	Procedure	Results	Reference
Triethyl Citrate					
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; no irritation with 40 or 70%	87
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	87
Triethyl Citrate	100%	4 rabbits	5 g/kg were applied in an acute study (details not provided)	no irritation	61
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	61
Triethyl Citrate	33.3% in pet	3 albino rabbits	as above	not a primary irritant; PII = 0	61
Trioctyldodecyl Citrate					
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					
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	87
Tributyl Citrate					
Tributyl Citrate	not provided	not provided	GPMT or LLNA (add'l details not provided)	negative	81
Trioctyldodecyl Citrate					
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
			HUMAN IRRITATION		
Citric Acid					
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	88
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	89

Table 10. Dermal irritation and sensitization

Test Article	Concentration	Test Pop.	Procedure	Results	Reference
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	89
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	90
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	90
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)	90
Citric Acid	1% aq.	133 oral disease patients	48 h patch test, occlusive	no positive reactions	91
Citric Acid	2.5% aq.	49 atopic; 56 non-atopic patients	20 min occlusive application	no immediate (non-immunologic contact urticaria) reactions	92
Citric Acid	not stated (most likely 100%)	702 contact dermatitis patients	Finn chambers were applied the back using Scanpor tape; 48 h	no reactions	93
Sodium Citrate					
Sodium Citrate	10% aq.	49 atopic; 56 non-atopic patients	20 min occlusive application	no immediate (non-immunologic contact urticaria) reactions	92
Triethyl Citrate					
Triethyl Citrate	20% in pet.	22 subjects	48- closed patch test	not irritating	61
			SENSITIZATION		
Citric Acid					
Citric Acid	4% in a cuticle cream	56 subjects	HRIPT; semi-occlusive patches applied 3x/wk for 3 wks; a challenge patch was applied after 2 wks	not an irritant or a sensitizer	94
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					
Triethyl Citrate	4.8% in a blush	106 subjects	HRIPT; 0.2 g applied to a ¾" x ¾" occlusive patch and then moistened; applied 3x/wk for 3 wks; a challenge patch was applied after 2 wks	not a dermal irritant or a sensitizer	96

Table 10. Dermal irritation and sensitization

Test Article	Concentration	Test Pop.	Procedure	Results	Reference
Triethyl Citrate	concentration range tested not specified (vehicle – 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 or sensitizer; no effects observed with 15%	61
Triethyl Citrate	concentration ranged tested not specified (vehicle – alcohol 39C)	41 subjects 10 males 31 females	HRIPT; as above	not a primary irritant or sensitizer; no effects observed with 33.33%	61
Triethyl Citrate	concentration range tested not specified (vehicle –pet.)	45 subjects 10 males 35 females	HRIPT; as above, except that 0.4 ml was applied	not a primary irritant or sensitizer; no effects observed with 33.33%	61
Triethyl Citrate	concentration range tested not specified (vehicle – 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; irritant effects with 15% at induction ranged from mild erythema to erythema and edema with vesiculation and/ or ulceration; rxns at challenge included minimal to well-defined erythema; no sensitization at 15%	61
Triethyl Citrate	concentration range tested not specified (vehicle – 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; no effects at 33.33%	61
Triethyl Citrate	concentration range tested not specified (vehicle – pet.)	22 subjects	maximization test: induction: 5 alternate 48-h occlusive patches applied to the forearm, with 5% aq. pretreatment with the 1st patch only; challenge: 48-h semi-occlusive patch, with 5% SLS pretreatment (occlusive)	not effects observed with 20%	61
Triethyl Citrate	neat	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	97
Tristearyl Citrate					
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	98

Table 10. Dermal irritation and sensitization

Test Article	Concentration	Test Pop.	Procedure	Results	Reference
Triisostearyl Citrate					
Triisostearyl Citrate	15.5% in a lip gloss	110 subjects	HRIPT; 0.2 g 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 an irritant or a sensitizer	[99]
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	[66]
Trioctyldodecyl Citrate					
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]

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 11. Ocular irritation studies

Test Article	Concentration/Dose	Animals/Gp	Method	Results	Reference
ALTERNATIVE STUDIES					
Citric Acid					
Citric Acid	2% in NaCl	---	luminescent bacteria toxicity test (Microtox® test)	moderate/ severe ocular irritant; EC_{50} =14 mg/l	100
Citric Acid	undiluted	---	EYTEX assay	severe/extreme irritant; EDE>51	101
Triisostearyl Citrate					
Triisostearyl Citrate	10% in corn oil	---	MatTek EpiOcular *in vitro* toxicity assay ; 100 µl	non-irritating; ET_{50} >256 min	102
NON-HUMAN STUDIES					
Citric Acid					
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	84
Triethyl Citrate					
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	61
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	61
Trioctyldodecyl Citrate					
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

REFERENCES

1. Food and Drug Administration (FDA). Guidance: Labeling for Cosmetics Containing Alpha Hydroxy Acids. Guidance for Industry, Labeling for Topically Applied Cosmetic Products Containing Alpha Hydroxy Acids as an Ingredient. http://www.fda.gov/Cosmetics/GuidanceComplianceRegulatoryInformation/GuidanceDocuments/ucm090816.htm. 2005. Date Accessed 6-7-2011.

2. Anastassiadis, S., Morgunov, I. G., Kamzolova, S. V., and Finogenova, T. V. Citric acid production patent review. *Recent Pat Biotechnol.* 2008;2:(2):107-123.

3. Merck & Co., Inc. The Merck Index. http://themerckindex.cambridgesoft.com/themerckindex/Forms/Home/ContentArea/Home.aspx. 2010. Date Accessed 4-8-2011.

4. Berovic, M. and Legisa, M. Citric acid production. *Biotechnol Annu Rev*. 2007;13:303-343.

5. de Guertechin, Luis Oldenhove. Surfactants: Classification. Chapter: 71. Barel, Andre O., Paye, Marc, and Maibach, Howard I.In: *Handbook of Cosmetic Science and Technology*. 3rd ed. Informa Healthcare; 2009:769-770.

6. Gottschalck T.E. and Bailey, J. E. International Cosmetic Ingredient Dictionary and Handbook. Washington, DC: Personal Care Products Council, 2010.

7. Food and Drug Administration (FDA). Frequency of use of cosmetic ingredients. *FDA Database.* 2011. Washington, DC: FDA.Updated February.

8. Personal Care Products Council. Concentration of use by FDA product category. 11-1-2011. Unpublished data submitted by the Council on Nov. 1, 2011. (9 pages).

9. Personal Care Products Council. Updated concentration of use by FDA product category: Citric acid and its salts and esters. 1-28-2011. Unpublished data submitted by the Council of Jan 28, 2011. (9 pp).

10. Johnsen MA. The influence of particle size. *Spray Technology and Marketing*. 2004;November:24-27.

11. Rothe H. Special Aspects of Cosmetic Spray Evalulation. 9-26-2011. Unpublished data presented at the 26 September CIR Expert Panel meeting. Washington, D.C.

12. Rothe H, Fautz R, Gerber E, Neumann L, Rettinger K, Schuh W, and Gronewold C. Special aspects of cosmetic spray safety evaluations: Principles on inhalation risk assessment. *Toxicol Lett*. 2011;205:(2):97-104.

13. Bremmer HJ, Prud'homme de Lodder LCH, and Engelen JGM. Cosmetics Fact Sheet: To assess the risks for the consumer; Updated version for ConsExpo 4. 2006. Report No. RIVM 320104001/2006. pp. 1-77.

14. European Commission. European Commission Health and Consumers Cosmetic Cosing database. http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.simple. 2011. Date Accessed 2-25-2011.

15. European Commission. European Commission Health and Consumers Cosmetic Cosing [Cosmetics Directive (v.1)] - Annex III/24. http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=28271&back=1. 2011. Date Accessed 2-25-2011.

16. Food and Drug Administration (FDA). Code of Federal Regulations, Title 21. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm. 4-1-2011. Date Accessed 3-14-2011.

17. Life Sciences Research Office. Evaluation of the health aspects of citric acid, sodium citrate, potassium citrate, calcium citrate, ammonium citrate, triethyl citrate, isopropyl citrate, and stearyl citrate as food ingredients. 1977. Prepared for the Bureau of Foods of the Food and Drug Administration, Contract No. FDA 223-75-2004.

18. Organisation for Economic Co-operation and Development (OECD). SIDS Initial Assessment Report - Citric Acid (CAS No. 77-92-9). http://www.chem.unep.ch/irptc/sids/OECDSIDS/77929.pdf. =United Nations Environment Programme (UNEP) Chemicals: 2001. Date Accessed 3-13-2011.

19. Hamm LL. Renal handling of citrate. *Kidney International*. 1990;38:728-735.

20. Tracor-Jitco, Inc. Scientific Literature Reviews on Generally Recognized as Safe (GRAS) food ingredients. Citric acid. 1974. NTIS No. PB-241 967.

21. Fouda HG. Safety assessment of citroflex plasticizers in vitro by serum, liver and intestinal enzymes. 1982. Unpublished data submitted by the Cosmetic, Toiletry,and Fragrance Association on Dec 4, 1998. (31 pp).

22. Slanina P, Falkeborn Y, Frech W, and Cedergren A. Aluminum concentrations int he brain and bone of rats fed citric acid, aluminum citrate or aluminum hydroxide. *Fd Chem Toxic*. 1984;22:(5):391-397.

23. Vittori D, Nesse A, Pérez G, and Garbossa G. Morphologic and functional alterations of erythroid cells induced by long-term ingestion of aluminum. *J Inorg Biochem*. 1999;76:113-120.

24. Madhavi, D. L. and Salunkhe, D. K. Toxicological aspects of food antioxidants. Madhavi, D. L., E, and D.K.SALUNKHE.In: *Food science and technology (New york),71*. NEW YORK,NEW YORK,USA; BASEL,SWITZERLAND: MARCEL DEKKER,INC.; 1996:267-359.

25. Nicolau G, Dahlin DC, Kohlbrenner M, Chan PS, Ronsberg MA, Saunders TK, Yacobi A, and Cervoni P. Skin metabolism and transdermal absorption of viprostol, a synthetic PGE_2 analog, in the rat: Effect of vehicle. *Skin Pharmacol*. 1989;2:22-29.

26. Deuel, H. J., Jr., Greenberg, S. M., Calbert, C. E., Baker, R., and Fisher, H. R. Toxicological studies on isopropyl and stearyl citrates. *Food Res.* 1951;16:(3):258-280.

27. Finkelstein, M. and Gold, H. Toxicology of the citric acid esters: tributyl citrate, acetyl tributyl citrate, triethyl citrate, and acetyl triethyl citrate. *Toxicol Appl Pharmacol*. 1959;1:(3):283-298.

28. Meyers DB, Autian J, and Guess WL. Toxicity of plastics used in medical practice. II. Toxicity of citric acid esters used as plasticizers. *J Pharm Sci*. 1964;53:(7):774-777.

29. Gomez M, Domingo JL, and LLobet JM. Developmental toxicity evaluation of oral aluminum in rats: Influence of citrate. *Neurotoxicol Teratol*. 1991;13:323-328.

30. Bechter, R. and Brouillard, J. F. The effects of different chemical forms of a test compound on embryotoxicity, distribution and metabolism in vitro. *Toxicol In Vitro.* 1988;2:(3):181-188.

31. Brown-Woodman PDC, Post EJ, Chow PYW, and White IG. Effects of malonic, maleic, citric, and caffeic acids onthe motility of human sperm and penetration of cervical mucus. *Int J Fertil*. 1985;30:(3):38-44.

32. Bala S and Grover IS. Antimutagenicity of some citrus fruits in *Salmonella typhimurium*. *Mutat Res*. 1989;222:(141):148.

33. National Toxicology Program. Salmonella study overview with aluminum citrate. Study A14572. http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?fuseaction=salmonella.salmonellaData&endpointlist=SA&study%5Fno=A14572&cas%5Fno=31142%2D56%2D0&activetab=detail. 2003. Date Accessed 4-19-2011.

34. Ghadishah D and Gorchynski J. Airway compromise after routine alpha-hydroxy facial peel administration. *Journal of Emergency Medicine*. 2002;22:(4):353-355.

35. Smith WP. Comparative effectiveness of a-hydroxy acids on skin properties. *Int J Cosmet Sci*. 1996;18:(2):75-83.

36. Smith WP. Hydroxy acids and skin aging. *Cosmetics & Toiletries*. 1994;109:41-48.

37. Green BA and Wildnauer RH. Effect of 10%, 20%, and 25% alpha-hydroxyacid (citric acid) formulations on skin morphology. 58th Annual Meeting of the American Academy of Dermatology, Can Franscisco, March 10-15. 2000. Cited in RIFM (2011) RIFM data synopsis on citric acid.

38. Bernstein, E. F., Underhill, C. B., Lakkakorpi, J., Ditre, C. M., Uitto, J., Yu, R. J., and van Scott, E. Citric acid increases viable epidermal thickness and glycosaminoglycan content of sun-damaged skin. *Dermatol Surg.* 1997;23:(8):689-694.

39. Ditre CM, Griffin TD, Murphy GF, Sueki H, Telegan B, Johnson WC, Yu RJ, and van Scott EJ. Effects of α-hydroxy acids on photoaged skin: A pilot clinical, histologic, and ultrastructural study. *J Am Acad Dermatol*. 1996;34:187-195.

40. Berardesca E. Alpha hydroxy acids. Handb.Cosmet.Sci.Technol. 2001. CAPLUS AN 2001:697206(Conference; General Review).

41. Akeson, M. A. and Munns, D. N. Lipid bilayer permeation by neutral aluminum citrate and by three alpha-hydroxy carboxylic acids. *Biochim Biophys Acta*. 1989;984:(2):200-206.

42. Laude EA, Higgins KS, and Morice AH. A comparative study of the effects of citric acid, capasicin and resiniferatoxin on the cough challenge in guinea-pig and man. *Pulmonayr Pharmacology*. 1993;6:171-175.

43. Barros MJ, Zammattio SJ, and Rees PJ. Importance of inspiratoyr flow rate in the cough response to citric acid inhalation in normal subjects. *Clinical Science*. 1990;78:521-525.

44. Lowry RH, Wood AM, and Higenbottam TW. Effects of pH and osmolarity on aerosol-induced cough in normal volunteers. *Clinical Science*. 1988;74:373-376.

45. Lai Y-L and Huang P-C. Reactive oxygen species in sustained airway constriction induced by citric acid aerosol inhalation. *European Journal of Pharmacology*. 2002;452:229-233.

46. Allott C, Evan DP, and Marshall PW. A model ofr irritant-induced bronchoconstriction in the spontaneously breathing guinea-pig. *Br J Pharmac*. 1980;71:165-168.

47. Archer Daniels Midland Co. Citric acid anhydrous, USP/FCC. 2010. Unpublished data submitted by the Council on Nov. 19, 2010. (1 p).

48. ACD/Labs. Advanced Chemistry Development (ACD/Labs) Software. 2011. (11.02):As cited in Chemical Abstracts Services Registry. Date Accessed 2011

49. American Chemistry Council. U.S. High Production Volume (HPV) Chemical Challenge Program. Robust summaries for acetic acid and salts category. http://www.epa.gov/HPV/pubs/summaries/acetisalt/c13102rt.pdf. 6-28-2001. Date Accessed 4-8-2011.

50. Research Institute for Fragrance Materials (RIFM). RIFM data synopsis on citric acid. 2011. Unpublished document submitted by RIFM on March 21, 2011. (39 pp).

51. Archer Daniels Midland Co. Solubility fo citric acid in water. 2010. Unpublished data submitted by the Council on Nov. 19, 2010. (1 p).

52. Archer Daniels Midland Co. pH of citric acid-sodium citrate solutions. Unpublished data submitted byt the Council on Nov. 19, 2010. (1 p).

53. Food and Drug Administration (FDA). Code of Federal Regulations, 21CFR184.1195 Calcium citrate. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?FR=184.1195&CFRPart=&FRSearch=. 4-1-2010. Date Accessed 4-17-2011.

54. European Commission - European Chemicals Bureau. IUCLID Dataset - Sodium Dihydrogen Citrate. http://ecb.jrc.ec.europa.eu/iuclid-datasheet/18996355.pdf. 2-18-2000. Date Accessed 3-13-2011.

55. Archer Daniels Midland Co. Potassium citrate, USP/FCC. 2010. Unpublished data submitted by the Council on Nov. 19, 2010. (1 p).

56. National Institute for Occupational Safety and Health. International Chemical Safety Cards: trisodium citrate anhydrous. http://www.cdc.gov/niosh/ipcsneng/neng1218.html. 1994. Date Accessed 3-14-2011.

57. European Commission - European Chemicals Bureau. IUCLID Dataset - Trisodium Citrate. http://ecb.jrc.ec.europa.eu/iuclid-datasheet/68042.pdf. 2-19-2000. Date Accessed 3-13-2011.

58. Research Institute for Fragrance Materials (RIFM). RIFM data synopsis on sodium citrate. 2011. Unpublished document submitted by RIFM on March 21, 2011. (11pp).

59. Patty's Industrial Hygiene and Toxicology. New York: John Wiley & Sons, Inc., 1994.

60. Gooding CM, Vahlteich HW, and Neal RH. Citric acid esters. 1950. (US 2518678):

61. Research Institute for Fragrance Materials (RIFM). RIFM data synopsis on triethyl citrate. 2011. Unpublished document submitted by RIFM on March 21, 2011. (33 pp).

62. National Institute for Occupational Safety and Health. International Chemical Safety Cards: Triethyl Citrate. http://www.cdc.gov/niosh/ipcsneng/neng1350.html. 1994. Date Accessed 3-14-2011.

63. Morflex, Inc. Citroflex® Citric Acid Esters. Technical Bulletin 101. 1998. Unpublished data submitted by the Cosmetic, Toiletry,and Fragrance Association on Dec 4, 1998. (15 pp).

64. Salit NI and Sadykov AS. Esters of citric and malic acid. *Zhurnal Obshchei Khimii*. 1963;33:(8):2746-2748.

65. Personal Care Products Council. Information on trisostearyl citrate and triictyldodecyl citrate. 1-4-2011. Unpublished data submitted by the Council on Jan 4, 2011. (1 p).

66. Product Investigations, Inc. Determination of the irritating and sensitizing propensities of EX-1028 (triisostearyl citrate) on human skin. Report: PII No. 22097. 5-29-2007. Unpublished data submitted by the Council on Jan 4, 2011. (12 pp).

67. Archer Daniels Midland Co. Process stages: potassium citrate, USP/FCC. 2010. Unpublished data submitted by the Council on Nov. 19, 2010. (1 p).

68. Environmental Protection Agency. EPA R.E.D. Facts: Citric Acid. 1992. NTIS No. PB92-221837.

69. Amidon GE, Peck, GE, Block LH, Moreton RC, Katdare A, Lafaver R, and Sheehan C. Proposed new USP general information chapter, excipient performance. *Pharmacopeial Forum*. 2007;33:(6):1311-1323.

70. Opdyke DLJ. Monographs on fragrance raw materials. Triethyl citrate. *Food Cosmet Toxicol.* 1979;17:(4):389-390.

71. Lubrizol. G-66 Guerbet Ester (trioctyldodecyl citrate) toxicology studies. TOX-017. 1-12-2005. Tox summary data submitted by the Council on Jan 4, 2011. (2 pp).

72. Gruber, C. M., Jr. and Halbeisen, W. A. A study on the comparative toxic effects of citric acid and its sodium salts. *J Pharmacol Exp Ther.* 1948;94:(1):65-67.

73. Al-Ani FY and Al-Lami SK. Absence of mutagenic activity of acidity regulators in the Ames Salmonella/microsome test. *Mutat Res*. 1988;206:467-470.

74. Ishidate M, Jr, Sofuni T, Yoshikawa K, Hayashi M, Nohmi T, Sawada M, and Matsuoka A. Primary mutagenicity screening of food additives currently used in Japan. *Fd Chem Toxicol*. 1984;(8):623-636.

75. Litton Bionetics, Inc. Mutagenic evaluation of compound FDA 71-54, citric acid. 1-8-1975. NTIS No. PB-245 463.

76. Hayes S, Gordon A, Sadowski I, and Hayes C. RK bacterial test for independently measuring chemical toxicity and mutagenicity: Short-term forward selection assay. *Mutat Res*. 1984;130:97-106.

77. Hartwig, A. and Schlepegrell, R. Induction of oxidative DNA damage by ferric iron in mammalian cells. *Carcinogenesis*. 1995;162:(12):3009-3013.

78. Litton Bionetics, Inc. Mutagenic evaluation of compound. FDA 75-4. 006100-05-6, Potassium Citrate, NF. FCC Granular. 1975. NTIS #PB254518.

79. Litton Bionetics, Inc. Mutagenic evaluation of compound FDA 75-12. 006132-04-3, Sodium Citrate, USP, FCC hydrous, granular. 12-24-1975. NTIS No. PB254510.

80. Litton Bionetics, Inc. Mutagenic evaluation of compound FDA 75-10. 000077-93-0, Triethyl Citrate, FCC. 1976. NTIS No. PB257866.

81. Wolfreys AM and Basketter DA. Mutagens and sensitizers - An unequal relationship? *J Toxicol Cutaneous Ocul Toxicol*. 2004;23:(3):197-205.

82. NOTOX B.V. Evaluation of the mutagenic activity of EX-1028 (triisostearyl citrate) in the *Salmonella typhimurium* reverse mutation assay and the *Escherichia coli* reverse mutation assay (with independent repeat). NOTOX Project No. 484965. 4-23-2007. Unpublished data submitted by the Council on Jan 4, 2011. (26 pp).

83. F. Hoffmann-LaRoche Ltd. Unpublished report, dermal irritation test, occlusive patch. 1984. Unpublished data cited in OECD 2001.

84. Kowalski RL and Hartnagel RE. Unpublished report; acute dermal and ocular irritation/corrosion study in rabbits. 1991. Unpublished data cited in OECD 2001.

85. Hill Top Biolabs, Inc. D.O.T. corrosivity potential study in rabbits of: citric acid solution, 60%. 1992. Unpublished data cited in American Chemistry Council (2001).

86. Sousa, S. M., Bramante, C. M., and Taga, E. M. Biocompatibility of EDTA, EGTA and citric acid. *Braz.Dent.J.* 2005;16:(1):3-8.

87. Unilever Limited. Sensitization potential of Citroflex A2, Citroflex A4,a nd Citroflex 2 (triethyl citrate) tested in guinea pigs. 1976. Unpublished data submitted by the Cosmetic, Toiletry,and Fragrance Association on May 12, 1999. (31 pp).

88. Laden K. Studies on irritancy and stinging potential. *J Soc Cosmet Chem*. 1973;24:385-393.

89. Schliemann-Willers S, Fuchs S, Kleesz P, Grieshaber R, and Elsner P. Fruit acids do not enhance sodium lauryl sulphate-induced cumulative irritant contact dermatitis in vivo. *Acta Derm Venereol*. 2005;85:206-210.

90. Spoo J, Wigger-Alberti W, Berndt U, Fischer T, and Elsner P. Skin cleansers: Three test protocols for the assessment of irritancy ranking. *Acta Dermato-Venereol*. 2002;82:(1):13-17.

91. Torgerson RR, Davis MDP, Bruce AJ, Farmer SA, and Rogers RS. Contact allergy in oral disease. *J Am Acad Dermatol*. 2007;57:315-321.

92. Lahti, A. Nonimmunologic contact urticaria. *Acta Dermato.-Venereol Suppl*. 1980;60:(91):1-49.

93. Reider N, Issa A, Hawranek T, Schuster C, Aberer W, Kofler H, Fritsch P, and Hausen BM. Absence of contact sensitization to *Aloe veraa* (L.) Burm. f. *Contact Dermatitis*. 2005;53:332-334.

94. Clinical Research Laboratories Inc. 2007. Repeated insult patch test of a cuticle cream containing 4% Citric Acid. CRL Study Number: CRL134907-2. Unpublished data submitted by Personal Care Products Council.

95. Malanin G and KAlimo K. The results of skin testing with food additives and the effect of an elimination diet in chronic ad recurrent urticaria and recurrent angioedema. *Clinical and Experimental Allergy*. 1989;19:539-543.

96. Consumer Product Testing Co. 2002. Repeated insult patch test of a powder blush containing 4.8% Triethyl Citrate. Experiment Reference Number: C02-0969.02. Unpublished data submitted by Personal Care Products Council.

97. Hill Top Research. Repeated insult patch test on Citroflex 2 liquid (triethyl citrate), Citroflex A-2 liquid, and Citroflex A-4 liquid. 2-24-1978. Unpublished data submitted by the Cosmetic, Toiletry,and Fragrance Association on Dec 4, 1998. (3 pp).

98. Consumer Product Testing Co. Repeated insult patch test on test material C-SAT 020029 (tristearyl citrate). Experiment Ref. No. C02-0279.01. 2002. Unpublished data submitted by the Council on Dec 10, 2010. (14 pp).

99. Consumer Product Testing Co. 2009. Repeated insult patch test of a lip gloss containing 15.5% Triisostearyl Citrate. Experiment Reference Number: C09-099 1.01. Unpublished data submitted by Personal Care Products Council.

100. Bulich AA, Tung K-K, and Scheibner G. The luminescent bacteria toxicity test: Its potential as an in vitro alternative. *J Biolumin Chemilumin*. 1990;5:71-77.

101. Gordon VC. Utilization of biomacromolecular *in vitro* assay systems in the prediction of *in vivo* toxic responses. *Lens and Eye Toxicity Research*. 1992;9:(3&4):211-227.

102. Consumer Product Testing Co. The MatTek corporation EpiOcular™ tissue model *in vitro* toxicity testing system. Experiment Ref. No. V04-0142-3. 2004. Unpublished data submitted to the Council on Jan 4, 2011. (5 pp).

103. Murphy JC, Ostenberg RE, Seabaugh VM, and Bierbower GW. Ocular irritancy responses to various pHs of acids and bases with and without irrigation. *Toxicology*. 1982;23:(4):281-291.

104. F. Hoffmann-LaRoche Ltd. Unpublished report; Draize ocular irritation study in rabbits. Unpublished data cited in OECD 2001.