

Final Report on the Safety Assessment of Malic Acid and Sodium Malate¹

Malic Acid functions in cosmetic formulations as a pH adjuster, and Sodium Malate functions as a skin conditioning agent-humectant. Malic Acid is reportedly used in almost 50 cosmetic formulations across a range of product types at low concentrations, whereas Sodium Malate is used in only one. As a pH adjuster, Malic Acid is used at low concentrations. One commercial method of preparing Malic Acid is hydration of fumaric acid or maleic acid, and then purified to limit the amount of the starting material present. Because Malic Acid is a component of the Krebs cycle, another method is fermentation. Malic Acid was relatively nontoxic in acute toxicity studies using animals. In a chronic oral study, feeding Malic Acid to rats resulted only in weight gain changes and changes in feed consumption. Malic Acid did not cause reproductive toxicity in mice, rats, or rabbits. Malic Acid was a moderate to strong skin irritant in animal tests, and was a strong ocular irritant. Malic Acid was not mutagenic across a range of genotoxicity tests. Malic Acid was irritating in clinical tests, with less irritation seen as pH of the applied material increased. Patients patch tested with Malic Acid, placed on a diet that avoided foods containing Malic or citric acid, and then challenged with a diet high in Malic and citric acid had both immediate urticarial and delayed contact dermatitis reactions. These data were considered sufficient to determine that Malic Acid and Sodium Malate would be safe at the low concentrations at which these ingredients would be used to adjust pH (even though Sodium Malate is not currently used for that purpose). The data, however, were insufficient to determine the safety of these ingredients when used in cosmetics as other than pH adjusters and specifically, the data are insufficient to determine the safety of Sodium Malate when used as a skin conditioning agent-humectant. The types of data required for the Expert Panel to determine the safety of Sodium Malate as a skin-conditioning agent are: concentration of use data; dermal irritation and sensitization data; and ocular irritation data, if available. The data needed to assess the safety of Malic Acid or Sodium Malate for some function other than as a skin-conditioning agent cannot be specified without knowing the intended function. Were these ingredients to be used as exfoliants, for example, data similar to that included in the Cosmetic Ingredient Review safety assessment of Glycolic Acid would be needed. Until these data are available, it is concluded that the available data are insufficient to support the safety of these ingredients in cosmetic formulations for functions other than use as a pH adjuster.

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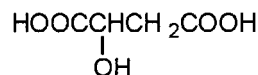
INTRODUCTION

The safety of Malic Acid and Sodium Malate as used in cosmetic formulations is reviewed in this report. Malic Acid functions in cosmetics as a pH adjuster and Sodium Malate functions as a skin conditioning agent-humectant (Wenninger, Canterbury, and McEwen 2000).

CHEMISTRY

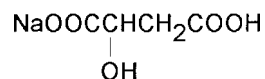
Definition and Structure

Malic Acid (CAS No. 97-67-6, Wenninger, Canterbury, and McEwen 2000; 6915-15-7, Lewis 1993a; 1993b) is the organic acid that conforms to the formula (Wenninger, Canterbury, and McEwen 2000):



Malic Acid is also known as (±)-Malic Acid (US Pharmacopeial Convention, Inc. 1995); D,L-Malic Acid (Food and Agriculture Organization of the United Nations/World Health Organization [FAO/WHO] 1994; Food and Drug Research Labs, Inc. [FDRL] 1973a); DL-Malic Acid (Wenninger, Canterbury, and McEwen 2000); Hydroxysuccinic Acid; Hydroxybutanedioic Acid (Wenninger, Canterbury, and McEwen 2000; FAO/WHO 1994; FDRL 1973a); (±)-Hydroxysuccinic Acid; Hydroxybutanedioic Acid, (±)- (US Pharmacopeial Convention, Inc. 1995); Butanedioic Acid, Hydroxy- (Wenninger, Canterbury, and McEwen 2000); Succinic Acid, Hydroxy-; alpha-Hydroxysuccinic Acid; Deoxytetraric Acid (Registry of Toxic Effects of Chemical Substances [RTECS] 1997); 1-Hydroxy-1,2-Ethanedicarboxylic Acid; Methyl Tartronic Acid (FDRL 1973a); Oxyethylenesuccinic Acid (Grant 1972); Pomalous Acid (FAO/WHO 1994); and Apple Acid (Lewis 1993b).

Sodium Malate (CAS No. not available) is the sodium salt of Malic Acid (q.v.) that conforms to the formula (Wenninger, Canterbury, and McEwen 2000):



Sodium Malate is also known as Malic Acid, Monosodium Salt (Wenninger, Canterbury, and McEwen 2000).

TABLE 1
Physical and chemical properties of Malic Acid

Property	Description	Reference
Physical characteristics	White crystals	Nikitakis and McEwen 1990
	White or nearly white crystalline powder or granules with a strongly acidic taste	National Academy of Sciences (NAS) 1996
	Colorless crystals with a sour taste	Lewis 1993a
	White or colorless crystals with an acid taste	Lewis 1993b
	White odorless triclinic crystals with a smoothly tart taste	Furia 1972
Molecular weight	134.09 Da	NAS 1996; Budavari 1989
Grades	Technical, active, and inactive	Lewis 1993a
Melting point		
	DL-form	126–132°C
		128°C
		131–132°C
	D-(+)-form	101°C
	L-(–)-form	100°C
Boiling point		
	DL-form	150°C (decomposes)
	D- or L-form	140°C (decomposes)
Density		
	DL-form	1.601
	D- or L-form	1.595 (20°/4°C)
Solubility	Soluble in water; slightly soluble in alcohol and ether	Nikitakis and McEwen 1990
	Very soluble in water and alcohol; slightly soluble in ether	Lewis 1993a; 1993b
	Soluble in water, methanol, ethanol, acetone, diethyl ether, and dioxane; practically insoluble in benzene	Budavari 1989
Optical rotation		
	L-(–)-form	$[\alpha]_D - 2.3^\circ$ (8.5 g in 100 ml water)
Ionization constants		
	K_{A1} ; K_{A2}	3.9×10^{-4} ; 1.4×10^{-5}
	K_1 ; K_2	4×10^{-4} ; 9×10^{-6}
Reactivity	Combustible	Lewis 1993a

Physical and Chemical Properties

The physical and chemical properties of Malic Acid are described in Table 1.

Manufacture and Production

DL-Malic Acid is made by the catalytic oxidation of benzene to maleic acid, which is converted to Malic Acid by heating with steam under pressure (Lewis 1993b). Malic Acid can be prepared by fermentation from sugars (Anonymous 1975). L-Malic Acid is available through the microbiological fermentation of fumaric acid (Miltenberger 1989). The L-form of Malic Acid is the naturally occurring isomer and is found in unripe apples and other fruits (Lewis 1993b).

Analytical Methods

Malic Acid has been detected and quantitated in biological fluids using gas chromatography (GC), enzymatic methods, and fluorometry; in general foods and in fruits and fruit

derivatives using fluorometry, GC, gas-liquid chromatography, thin-layer chromatography (TLC), paper chromatography, polarimetry, manometry, and ion exchange plus ultraviolet (UV); and in synthetic mixtures of food acids using TLC, thin-layer electrophoresis plus chromatography, and fluorometry (FDRL 1973a). Liquid chromatography (Agarwal 1988; Eisele 1996), GC (Agarwal 1988), and ligand-exchange photometric ion chromatography (Yamamoto, Matsunaga, and Mizukami 1991) have been used to determine Malic Acid in apple juice. A spectrophotometric method with use of a malic enzyme was used to determine Malic Acid in other liquids (Suye, Yoshihara, and Inuta 1992).

Impurities

Maleic and fumaric acids are by-products of the manufacture of Malic Acid (Miltenberger 1989). Malic Acid is generally purified until the amounts of fumaric and maleic acid are 7.5 and <500 ppm, respectively.

USE

Cosmetic

Malic Acid functions as a pH adjuster and Sodium Malate functions as a skin conditioning agent—humectant in cosmetic formulations (Wenninger, Canterbury, and McEwen 2000). The product formulation data submitted to the FDA in 1998 stated that Malic Acid was contained in 47 cosmetic product formulations and that Sodium Malate was contained in one cosmetic formulation (FDA 1998). Concentration of use values are no longer reported to the FDA by the cosmetics industry (FDA 1992) and no current concentration of use data were provided by industry; however, historical product formulation data submitted to the FDA in 1984 stated that Malic Acid was used at concentrations of $\leq 1\%$ (FDA 1984). Such low concentrations are expected to correspond to use as a pH adjuster. Sodium Malate was not reported to be used in 1984. This information is summarized in Table 2.

International

Malic Acid is listed in the *Japanese Comprehensive Licensing Standards of Cosmetics by Category (CLS)* as DL-Malic Acid (Rempe and Santucci 1997). DL-Malic Acid, which conforms to the specifications of the *Japanese Cosmetic Ingredients Codex* or *Japanese Standards of Food Additives*, has precedent for use without restriction in all CLS categories except eyeliner prepa-

rations, for which there is no precedent for use. Malic Acid does not appear in Annex II (list of substances which must not form part of the composition of cosmetic products) or Annex III (list of substances which cosmetic products must not contain except subject to restrictions and conditions) of the Cosmetics Directive of the European Union (European Economic Community 1995).

Noncosmetic

DL- and L-Malic Acid, when meeting Food Chemicals Codex specifications, are generally recognized as safe (GRAS) as direct food additive for use as a flavor enhancers, flavoring agents, and adjuvants, and as pH control agent, but are not GRAS for use in baby foods (FDA 1997). Using good manufacturing practices, the following maximum concentrations are allowed in foods as served: hard candy, 6.9%; processed fruits and fruit juices, 3.5%; nonalcoholic beverages, 3.4%; soft candy, 3.0%; chewing gum, 3.0%; jams and jellies, 2.6%; gelatins, puddings, and fillings, 0.8%; and all other food categories, 0.7%. Malic Acid can be used as an acidifying ingredient in milk and cream, and can be used in French dressing, mayonnaise, and salad dressing. There is no set limit on the human acceptable daily intake (ADI) of L-Malic Acid, and the ADI for D-Malic Acid is limited only by good manufacturing practice (FAO/WHO 1967; 1969). Neither D- or DL-Malic Acid should be added to food of young infants.

TABLE 2
Product formulation and concentration of use data

Product category (number of formulations reported to FDA) (FDA 1984)	Number of formulations containing ingredient (FDA 1998)	Historical concentration of use (FDA 1984)
Malic Acid		
Other baby products (29)	1	
Hair conditioners (636)	8	
Hair sprays (aerosol fixatives) (261)	2	
Shampoos (noncoloring) (860)	7	
Tonics, dressings, and other hair-grooming aids (549)	1	
Wave sets (55)	—	0.1–1.0%
Hair rinses (coloring) (33)	—	<0.1–1.0%
Basecoats and undercoats (48)	9	<0.1%
Nail polish and enamel (80)	9	<0.1–1.0%
Other manicuring preparations (61)	4	<0.1–1.0%
Face and neck preparations (excluding shaving preparations) (263)	2	
Body and hand preparations (excluding shaving preparations) (796)	1	
Moisturizing preparations (769)	1	
Night preparations (188)	1	
Paste masks (mud packs) (255)	1	
1998 total for Malic Acid	47	
Sodium Malate		
Body and hand preparations (excluding shaving preparations) (796)	1	
1998 total for Sodium Malate	1	

Malic Acid is used in foods as an acidifier and flavoring agent (National Academy of Sciences [NAS] 1996). It can also be used as a discoloration inhibitor and a synergist with antioxidants (Furia 1972). It is used in the manufacture of various esters and salts, in wine manufacturing, and as a chelating agent (Lewis 1993a). Malic Acid is also used in medicine and in the preparation of esters and salts (Patty 1981-2).

GENERAL BIOLOGY

Absorption, Distribution, Metabolism, and Excretion

Male albino Wistar Alderly Park SPF rats were given 2.5 mg/kg ^{14}C -L-Malic Acid (diluted with L-Malic Acid to a specific activity of 61 $\mu\text{Ci}/\text{mmol}$) or 4- ^{14}C -DL-Malic Acid (specific activity 93 $\mu\text{Ci}/\text{mmol}$) in an aqueous solution by gavage or by intraperitoneal (IP) injection (Daniel 1969). (The number of animals per group was not specified.) Urine, feces, and expired carbon dioxide were collected. Most of the radioactivity was excreted as carbon dioxide; after 24 hours, 91.6% and 83.4% of orally and intraperitoneally administered DL-Malic Acid, respectively, and 88.0% and 86.6% of orally and intraperitoneally administered L-Malic Acid, respectively, was found in expired air. The amount of radioactivity recovered after oral and IP administration of DL-Malic Acid was 3.1% and 8.8% in the urine and 0.6% and 0.3% in the feces, respectively, and the amount recovered after oral and IP administration of L-Malic Acid was 3.2% and 3.1% in the urine and 1.4% and 1.4% in the feces, respectively. After 24 hours, the total amount of radioactivity recovered was 95.3% and 92.5% after oral and IP administration of DL-Malic Acid, respectively, and 92.6% and 91.1% after oral and IP administration of L-Malic Acid, respectively.

Daily oral administration of 4 g/kg Malic Acid resulted in increased glucuronic acid excretion in the urine (Martin and Stenzel 1944).

Biochemistry

Malic Acid is an intermediate in the tricarboxylic acid (Kreb's) cycle (Taylor 1988). It is formed from fumaric acid and is oxidized to oxaloacetic acid (Patty 1981-2). Malic Acid plays an essential role in carbohydrate metabolism (Liebrand 1992).

ANIMAL TOXICOLOGY

Acute Toxicity

Oral

The oral LD_{50} values of Malic Acid for albino CD-1 outbred mice, albino Wistar rats, and Dutch-Belted rabbits were approximately 2.66 (FDRL 1973b), 3.5 (FDRL 1973c), and 3 g/kg (FDRL 1973d) respectively. Each study used 50 animals, consisting of five groups of 5 males and 5 females, and Malic Acid was administered as a 25% aqueous solution. Mortality was observed for 14 days. Signs of toxicity included ataxia, prostration, convulsions, and death.

In a review of studies done in the 1920s, FAO/WHO (1967) stated that the oral lethal dose of L-Malic Acid for rabbits was 5 g/kg, and for Sodium Malate in dogs was 1 g/kg. In a more recent review, the oral LD_{50} of Malic Acid for rabbits was 5 g/kg (Sax 1979). In a review of industrial chemicals, Patty (1981-2) stated that the oral LD_{50} values of Malic Acid for mice and rats were reported to be 1.6 to 3.2 and >3.2 g/kg, respectively. The signs of acute poisoning in rats and mice were weakness, retraction of the abdomen, respiratory distress, and cyanosis.

Parenteral

The acute toxicity of intravenously administered 0.25 N Malic Acid aqueous solution to four rabbits was 2.4 g/kg (FDRL 1973a).

The IP administration to rats of 1 g/kg L-Malic Acid was not lethal, but the same dose of D-Malic Acid killed rats within 20 to 25 minutes (Brookdale Dental Center of New York University 1973). The vehicle was not reported. A mixture of 1 g/kg D-Malic Acid and 1 g/kg L-malic Acid was lethal, and death occurred sooner than it did with D-Malic Acid alone. The IP administration of 2 g/kg DL-Malic Acid was not lethal to rats.

In a review of hazardous substances, Patty (1981-2) reported that the IP LD_{50} of Malic Acid for mice and rats as 50 to 100 and 100 to 200 mg/kg, respectively.

Chronic Toxicity

Oral

Groups of 30 male and 30 female Charles River rats were fed 500, 5000, or 50,000 ppm (0.05%, 0.5%, and 5.0%, respectively) Malic Acid for 104 weeks, and a control group of 60 male and 60 female rats was given untreated feed (TRW/Hazleton Laboratories 1971a). Animals were observed daily for mortality. Clinical observations were made and body weights and feed consumption were determined weekly for the first 26 weeks, biweekly for the second 26 weeks, and monthly thereafter. Clinical pathology studies were performed on five males and five females per group prior to study initiation and at 13, 26, 52, and 104 weeks. After 26 and 52 weeks, 5 male and 5 female test animals per group and 10 male and 10 female control animals were killed; the remaining animals were killed at study termination.

Physical appearance, behavior, and survival were similar for test and control animals. Body weight gains were significantly decreased for males and females of the high-dose group during weeks 0 to 52. Feed consumption was statistically significantly decreased for males of the high-dose group during this period. For females of the high-dose group, feed consumption was significantly decreased during weeks 0 to 26 and decreased, but not to a significant degree, during weeks 27 to 52, as compared to controls. These differences were less distinct during the second year; terminal body weights of the high-dose group were similar to controls for male animals and decreased, but not significantly, for female animals. Significant changes were not observed in hematological, blood, or urine parameters. Significant lesions were not found at gross and microscopic examination. For males

of the high-dose group, relative thyroid weights were significantly decreased at week 26, relative testes weights were significantly increased and liver weights were significantly decreased at week 52, and spleen weights were significantly increased and relative kidney weights were significantly decreased at study termination as compared to control animals. For females of the high-dose group, heart and body weights were significantly decreased at week 26, body weights were significantly decreased at week 52, and thyroid gland weights were significantly decreased at study termination. These differences were considered incidental.

Groups of four male and female beagle dogs were fed 500, 5000, or 50,000 ppm Malic Acid for 104 weeks, and a control group was given untreated feed (TRW/Hazleton Laboratories 1971b). Clinical observations were made daily. Body weights and feed consumption were determined weekly for the first 26 weeks, biweekly for the second 26 weeks, and monthly thereafter. Clinical pathology studies were performed prior to study initiation and at 4, 13, 26, 52, 78, and 104 weeks. One male and one female from each group was killed after 52 weeks, and the remaining animals were killed at study termination.

Body weight gains were normal for all animals. Significant changes were not observed in hematological, blood, or urine parameters. Significant lesions were not observed at necropsy or at microscopic examination, and dose-related differences in absolute and relative organ weights were not found.

Dermal Irritation

In a review of industrial chemicals, Patty (1981-2) stated that Malic Acid was moderately irritating to rabbit skin (500 mg/24 h) and was a strong irritant to guinea pigs.

Ocular Irritation

In a review of industrial chemicals, Patty (1981-2) stated that application of Malic Acid, 750 μ g, to the conjunctival sac of rabbits caused severe ocular irritation.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Groups of 25 albino CD-1 outbred mice were mated and dosed orally with 2.66, 12.4, 57.3, or 266 mg/kg Malic Acid on days 6 through 15 of gestation (FDRL 1974a). A negative-control group was given vehicle (water) and a positive-control group was given 150 mg/kg aspirin. All animals were observed daily. Body weights were determined on days 0, 6, 11, 15, and 17 of gestation. On day 17 of gestation, the number of implantation sites, resorption sites, and live and dead neonates were determined. The body weights of live pups were recorded, and all neonates were examined grossly.

At gross examination, 19, 22, 21, and 21 animals of the 2.66, 12.4, 57.3, and 266 mg/kg dose groups, respectively, were gravid. All animals except one of the 12.4 mg/kg test group survived until study termination. The researchers concluded that "the administration of up to 266 mg/kg (body weight) of the test

material to pregnant mice for 10 consecutive days had no clearly discernible effect on nidation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in sham-treated controls."

A study following a similar procedure was conducted using groups of 25 to 29 Wistar albino rats dosed orally with 3.5, 16.2, 75.4, or 350 mg/kg Malic Acid (FDRL 1974b). The number of implantation sites, resorption sites, and live and dead neonates were determined on day 20 of gestation. At gross examination, 20/25, 21/29, 22/25, and 26/28 animals of the 3.5, 16.2, 75.4, and 350 mg/kg dose groups, respectively, were gravid. All animals except three of the 350-mg/kg test group (two were gravid) survived until study termination. The researchers concluded that "the administration of up to 350 mg/kg (body weight) of the test material to pregnant rats for 10 consecutive days had no clearly discernible effect on nidation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in sham-treated controls."

A study was also conducted using groups of 15 to 23 Dutch-belted rabbits that were inseminated artificially and dosed orally with 3, 14, 65, or 300 mg/kg Malic Acid on days 6 to 18 of gestation (FDRL 1974c). A negative-control group was given water and a positive-control group was dosed with 6-aminonicotinamide. All animals were observed daily and body weights were determined on days 0, 6, 12, 18, and 29 of gestation. On day 29 of gestation, the number of corpora lutea, implantation sites, resorption sites, and live and dead fetuses were determined.

At gross examination, 12/15, 10/20, 13/15, and 13/23 animals of the 3, 14, 65, and 300 mg/kg dose groups, respectively, were gravid. All animals of the negative and positive control groups and the 3 and 14 mg/kg dose groups, 12/15 of the 65-mg/kg dose group (two were gravid), and 15/23 of the 300-mg/kg dose group (four were gravid) survived until study termination. The researchers concluded that "the administration of up to 300 mg/kg (body weight) of the test material to pregnant rabbits for 13 consecutive days had no clearly discernible effect on nidation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in sham-treated controls."

Groups of 10 male and 20 female weanling albino rats were fed 1000 or 10,000 ppm Malic Acid for 9 weeks prior to mating for the F_{1A} litter through weaning of the F_{1B} litter, and a control group was fed untreated feed (Hazleton Laboratories, Inc. 1970). The F_{1A} litters were culled to a maximum of eight pups, reproductive indices were monitored, and after 21 days, approximately one third of the pups were necropsied. One week after weaning of the last F_{1A} litter, the P₁ parents were remated to produce the F_{1B} litter, which was also culled and monitored. After 21 days, 10 male and 20 female weanlings from each group were selected for the P₂ generation. Approximately one third of the remaining pups were necropsied. The P₂ generation was

fed the appropriate diet and mated when the animals reached approximately 100 days of age to produce the F_{2A} generation, and the same procedures were followed as above. One half of the F_{2B} litters were delivered naturally and held until weaning, whereas the other half were delivered by caesarean section on day 19 of gestation.

Prior to mating of the P₁ generation, body weight gains of males of the test groups were slightly decreased compared to control animals; female body weights were comparable. Feed consumption and survival were similar for test and control animals. Appearance and behavior were similar for P₁ test and control rats. For all litters, the various indices, litter sizes, and pup body weights were comparable among test and control animals. In the F_{1A} litters, all of the necropsied pups in three of the low-dose litters had rough surfaces on the spleen. In the F_{2A} litters, the number of pups that were weak or had labored respiration during lactation was increased in the high-dose group. Abnormal findings were not reported at necropsy. None of the P₁ animals died during the F_{1A} or F_{1B} phase. The P₂ test and control animals were similar throughout the study; wheezing was observed in all groups during the F_{2B} phase. In the F_{2A} litters, renal discoloration (two animals), dark renal medullas (four animals), rough surfaces on the spleen (four animals), and white foci on the spleen (three animals) were found in low-dose weanling animals. Renal discoloration (three animals), dark red corticomedullary zones (three animals), dark renal medullas (three animals), rough surfaces on the spleen (two animals), and a firm, enlarged, irregularly-shaped cecum with a hole penetrating it (one animal) were found in high-dose weanling animals at necropsy. In the F_{2B} litters, weakness and labored respiration were reported for a few low-dose pups, and the renal pelvis of one high-dose pup was dilated at necropsy. The animals of the F_{2B} generation delivered by caesarean section had no "meaningful differences" between test and control animals in the number and placement of implantation and resorption sites or in the number, weight, or length of live neonates, and none of the neonates died. The skeletal development of the F_{2B} neonates was similar between test and control animals. Slight differences in developmental indices were "considered to be within the range of normal variations in fetal development. No trends toward lesser or greater skeletal development were observed."

GENOTOXICITY

The mutagenic potential of 0.001% Malic Acid was determined in a plate test using *Salmonella typhimurium* strains TA1535, TA1537, and TA1538 without and with metabolic activation (Litton Bionetics, Inc. 1974). Negative and positive controls were used, and duplicate testing was done. Malic Acid was not mutagenic.

An Ames test was performed to determine the mutagenic potential of Malic Acid in phosphate buffer, ≤ 10.0 mg/plate, using *S. typhimurium* strains TA92, TA1535, TA100, TA1537, TA94, and TA98 with metabolic activation (Ishidate et al. 1984). Testing was done in duplicate. Malic Acid was not mutagenic.

The mutagenic potential of 1100 to 2000 $\mu\text{g}/\text{plate}$ Malic Acid in distilled water was determined in a plate test using *S. typhimurium* TA97, TA98, TA100, and TA104 with and without metabolic activation (Al-Ani and Al-Lami 1988). Distilled water was used as a negative control and 2-aminoanthracene was used as a positive control. Testing was done in triplicate. Malic Acid was not mutagenic.

The mutagenic potential of Malic Acid was examined in a suspension test using *S. typhimurium* strains TA1535, TA1537, and TA1538 and *Saccharomyces cerevisiae* strain D4 without and with metabolic activation (Litton Bionetics, Inc. 1974). Malic Acid was tested at concentrations of 0.0005% and 0.001% using *S. typhimurium* and 0.05% and 0.1% using *S. cerevisiae*. Negative and positive controls were used. Malic Acid was not mutagenic for either *S. typhimurium* or *S. cerevisiae*.

A chromosomal aberration test was performed without metabolic activation using a Chinese hamster fibroblast cell line to determine the mutagenic potential of ≤ 1.0 mg/ml Malic Acid in physiological saline (Ishidate et al. 1984). The incidence of polyploid cells and cells with structural chromosomal aberrations was 0% and 1%, respectively, after 48 hours. Malic Acid was not mutagenic.

The effect of pyrolysis on the mutagenic potential of Malic Acid was first determined using *S. typhimurium* TA98 and TA100 with and without metabolic activation (Yoshida and Okamoto 1982). In this study, pyrolyzates of Malic Acid were not mutagenic. In a study by Kuroda, Yoshida, and Mizusaki (1985), pyrolyzates of Malic Acid were mutagenic when tested using *S. typhimurium* TA97 with and without metabolic activation. The pyrolyzates of Malic Acid were fractionated into neutral, acidic, phenolic, and basic fractions, and the mutagenicity of each fraction was determined using TA97 and TA98. Most of the mutagenicity was found in the neutral fraction, with TA97 being more sensitive, and weak activity was found in the acidic and phenolic fractions. No activity was found in the basic fractions with either strain.

Malic Acid was treated with aqueous solutions of chlorine, pH 2.5, 4, and 7 (Chang et al. 1988). Diethyl ether extraction followed by gas chromatography/mass spectrometry (GC/MS) was performed and the results indicated that "large amounts" of trichloroacetaldehyde were present in the treated Malic Acid. Methyl esters of dichloro- and trichloroacetic acid were detected by GC/MS analysis when comparably treated Malic Acid was reacted with diazomethane. The products that are formed are considered mutagenic.

CARCINOGENICITY

Published data on the carcinogenic potential of Malic Acid and Sodium Malate were not found.

CLINICAL ASSESSMENT OF SAFETY

Irritation

The subjective skin irritation potential of Malic Acid was evaluated by applying 2 mg/cm² of 1 M Malic Acid in vehicle

(15% ethanol [SD 40], 5% ethoxydiglycol, and 5% butylene glycol) to the nasal fold area of at least 10 subjects (Smith 1996). Irritation was graded on a scale of 0 to 4 every minute for 15 minutes. The irritation scores, as an average of the summation of each individual irritation score over the 15-minute test period, were 39.4, 37.1, and 23.1 for pH 3, 5, and 7, respectively.

Sensitization

Predictive Testing

Thirty-four patients with atopic dermatitis were tested to determine their sensitivity to foods containing Malic (and citric) Acid (Walsh 1979). The patients were first patch tested with Malic (and citric) Acid applied as a 10% aqueous solution under occlusive patches for 48 hours. For 2 weeks, the patients followed a diet that avoided processed foods in which Malic (and citric) Acid were used, and then challenged themselves with a diet high in Malic (and citric) Acid during the third week. Eighteen patients reacted to both Malic and citric Acid and 6 patients reacted to only Malic Acid. Both immediate reactions (seasonal allergic rhinitis and urticaria) and delayed reactions (contact dermatitis) were present. Patch-test results were reliable in predicting results of the challenge with diet.

Skin Effects

The effect of Malic Acid on cell renewal was assessed using the dansyl chloride method (Smith 1996). Two mg/cm² of 1 M Malic Acid in a simple liquid vehicle (15% ethanol [SD 40], 5% ethoxydiglycol, and 5% butylene glycol) was applied to the volar forearm which was stained with dansyl chloride twice daily until all the stain was removed. An 18%, 10%, and 5% increase in cell renewal was observed at pH 3, 5, and 7, respectively.

Medical/Therapeutic

The data from clinical use of Malic Acid are included here to provide a complete record of reported dermal effects. Information included in this section represents the opinions of researchers; such information is only included in order to provide the full scope of information available. Inclusion is not an endorsement of validity.

Fourteen patients, 11 males and 3 females, with various forms of ichthyosiform dermatoses were used to evaluate the therapeutic potential of more than 60 chemicals, including Malic Acid (Van Scott and Yu 1974). Malic Acid was dissolved in either water or ethanol and incorporated into a hydrophilic ointment of plain petrolatum. The ointment, containing 5% Malic Acid (pH not specified), was applied twice daily to the appropriate test site for 2 weeks. Daily to weekly observations were made. Malic Acid provided 3+ (disappearance of scales from lesions) or 4+ (restoration to normal looking skin) improvement in all patients except one with epidermolytic hyperkeratosis.

An efficacy and safety test of a tablet containing 200 mg Malic Acid (and 50 mg magnesium) was conducted using patients with

primary fibromyalgia syndrome (Russell et al. 1995). In the first part of the test, 24 patients were given three tablets twice daily (bid) for 4 weeks. In the second part, 16 patients started with three tablets bid and increased the dosage every 3 to 5 days as necessary; at month 6, the average dose was 8.8 tablets per day. (For a 50-kg person, ingestion of six tablets would be equivalent to 24 mg of malate/kg of body weight.) In the first part of the study, one test patient reported diarrhea, one reported nausea, and one reported dyspepsia. (In the placebo group, two patients reported diarrhea and one reported dyspepsia.) In the second part of the study, five test patients reported diarrhea, one reported nausea, one reported dyspepsia, one reported panic attacks, and one reported dizziness.

SUMMARY

Malic Acid, an intermediate in the Krebs's cycle, is an organic acid that functions as a pH adjuster and Sodium Malate is an organic salt that functions as a chemical additive. In 1998, it was reported to the Food and Drug Administration (FDA) that Malic Acid was used in 47 cosmetic formulations and that Sodium Malate was used in 1 formulation. In 1984, Malic Acid was reported to be used at concentrations of $\leq 1\%$; Sodium Malate was not reported to be used in 1984.

Malic Acid is generally purified until the amounts of the by-products fumaric and maleic acid are 7.5 and <500 ppm, respectively. Malic Acid is a direct food additive.

Upon oral and IP administration of radioactive Malic Acid to rats, most of the radioactivity was excreted as carbon dioxide.

The oral LD₅₀ values of Malic Acid for mice, rats, and rabbits ranged from 2.66 to >3.2, 1.60 to 3.5, and 3 to 5 g/kg, respectively. The acute LD₅₀ of Malic Acid given intravenously was 2.4 g/kg for rabbits, and the IP LD₅₀ values for mice and rats were 50 to 100 and 100 to 200 mg/kg, respectively. In a chronic oral study, feeding Malic Acid to rats resulted in some changes in body weight gains and feed consumption, but compound-related lesions were not observed. No significant changes or lesions were observed when dogs were fed Malic Acid in a chronic study. Malic Acid did not cause reproductive toxicity in mice, rats, or rabbits.

Malic Acid was moderately irritating to rabbit skin and was a strong irritant to guinea pigs. Malic Acid caused severe ocular irritation in rabbit eyes.

Malic Acid was not mutagenic in plate tests, an Ames test, a suspension test, or a chromosomal aberration assay. In one study, pyrolyzates of Malic Acid were not mutagenic, but in another study they were. Products formed from treatment of Malic Acid with aqueous solutions of chlorine were mutagenic.

In a test determining the subjective skin irritation potential, the average irritation scores over a 15-minute period were 39.4, 37.1, and 23.1 for Malic Acid at pH 3, 5, and 7, respectively. In predictive testing using patients with atopic dermatitis, 18 of 34 patients reacted to a diet high in Malic and citric acids, and 6 reacted to a diet high in Malic Acid. In assessing the effect of

Malic Acid on cell renewal, an 18%, 10%, and 5% increase was observed at pH 3, 5, and 7, respectively.

Malic Acid was not toxic in a clinical efficacy and safety test.

DISCUSSION

The Expert Panel considered separately the ways in which Malic Acid and Sodium Malate are used. As a pH adjuster, Malic Acid historically has been used at concentrations less than 1%. The available data demonstrate that what toxicity has been demonstrated for Malic Acid and Sodium Malate is related to concentration. Accordingly, the Expert Panel concluded that Malic Acid and Sodium Malate are safe for use as pH adjusters (even though Sodium Malate is not currently used for that purpose).

The data included in this report, however, were insufficient to determine the safety of these ingredients when used in cosmetics as other than pH adjusters. Specifically, the data are insufficient to determine the safety of Sodium Malate when used as a skin conditioning agent—humectant. The types of data required for the Expert Panel to determine the safety of Sodium Malate as a skin conditioning agent are:

1. concentration of use data;
2. dermal irritation and sensitization data; and
3. ocular irritation data, if available.

The data needed to assess the safety of Malic Acid or Sodium Malate for some function other than as a skin conditioning agent—humectant cannot be specified without knowing the intended function. Were these ingredients to be used as exfoliants, for example, data similar to that included in the report on Glycolic and Lactic Acid (i.e., the Alpha Hydroxy Acid report) (Andersen 1998) would be needed.

CONCLUSION

On the basis of the animal and clinical data included in this report, the Cosmetic Ingredient Review (CIR) Expert Panel concludes that Malic Acid and Sodium Malate are safe for use as pH adjusters in cosmetic formulations. The Expert Panel determined that the data are insufficient to determine the safety of these ingredients for any other functions.

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