Safety Assessment of Dialkyl Malates as Used in Cosmetics

Status:	Final Report for public distribution
Release Date:	October 5, 2012
Panel Meeting Date:	September 10-11, 2012

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ABSTRACT

The Cosmetic Ingredient Review Expert Panel (the Panel) reviewed the safety of 6 dialkyl malate compounds used in cosmetics, including the widely used diisostearyl malate. These ingredients function mostly as skin-conditioning agents-emollients. The Panel reviewed relevant animal and human data related to the ingredients along with a previous safety assessment of malic acid. The similar structure, properties, functions, and uses of these ingredients enabled grouping them and using the available toxicological data to assess the safety of the entire group. The Panel concluded that the available data support the safety of diisostearyl malate, dibutyloctyl malate, di-C12-13 alkyl malate, diethylhexyl malate, diisoamyl malate, and dioctyldodecyl malate.

INTRODUCTION

Dialkyl malates have a succinate core (a four-carbon, alkyl diacid ester) that is either mono- or di-hydroxy substituted.

The ingredients in this report are:

- Diisostearyl Malate
- Dibutyloctyl Malate
- Di-C12-13 Alkyl Malate
- Diethylhexyl Malate
- Diisoamyl Malate
- Dioctyldodecyl Malate

These ingredients function in cosmetics mostly as skin-conditioning agents-emollient (Table 1).

The similar chemical structures, physicochemical properties, and functions and concentrations used in cosmetics enable grouping these ingredients and reading across the available toxicological data to support the safety assessment of the entire group.

While dibutyl malate is not a cosmetic ingredient, it is a dialkyl malate and data regarding this chemical were considered relevant to the entire group. Where available, data on dibutyl malate were included in the appropriate sections.

Because these ingredients are diesters, esterases in the skin may metabolize them to the monoester or possibly to the free acid and corresponding alcohol. For example, diisostearyl malate may result in isostearyl malate (the monoester), malic acid and isostearyl alcohol, which may penetrate to the dermis. Accordingly, summary data for malic acid are provided in the text below and the available toxicity data on the corresponding alcohols are included in an appendix.

CHEMISTRY

Definition, Structure, and Manufacture

The core of all of these ingredients is succinic acid (a four carbon, alkyl diacid), that is mono-hydroxy substituted. Malic acid (a dicarboxylic acid) is a monohydroxy succinic acid. Because of this diacid structure, these ingredients may be esterified with an alkyl group at each end of the molecule. For instance, diisostearyl malate is monohydroxy substituted succinic acid, which is esterified at each end with a branched, eighteen carbon alkyl chain (i.e. isostearyl chain; Figures 1 and 2).

All of these ingredients have at least one stereocenter denoted by *D, L, DL*, *meso* or racemic in front of many of the names in the literature. The INCI names are defined as ambiguous to these stereochemical details. Stereochemical forms for the ingredients included in this report are identified where provided in the studies.

Dialkyl Esters

The dialkyl esters of malic acid can be manufactured from malic acid by traditional esterification techniques, with the appropriate alcohol, and with or without acid or metal catalyst (Fischer esterification).[1] For example, diethylhexyl malate can be manufactured from malic acid and ethylhexanol with a titanium catalyst.[2] It is likely that all of the diacid is consumed in the reaction and no malic acid is present in the final product.

Malic Acid

Malic acid (monohydroxysuccinic acid), a white crystalline material, has one stereocenter, at the carbon bearing the hydroxyl group.[3] The *L*-isomer is a natural constituent and common metabolite of plants (most commonly found in fruits) and animals.

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.[4] *L*-Malic acid is available through the microbiological fermentation of fumaric acid.[5] The *L*-form of malic acid is the naturally occurring isomer and is found in unripe apples and other fruits.[4]

A mixture of maleic, fumaric, rac-malic (or ±malic) acids heated with water in a closed space will cause the maleic acid to be consumed and the resulting solution to reach an equilibrium between fumaric acid and *D*-malic acid.[6] Maleic and fumaric acids are by-products of the manufacture of malic acid.[5] Malic acid is generally purified until the amounts of fumaric and maleic acid are 7.5 and <500 ppm, respectively.

In 2001, the Cosmetic Ingredient Review Expert Panel (the Panel) reviewed and concluded that the dicaboxylic acid,

malic acid, and its sodium salt (sodium malate) are safe for use as pH adjusters in cosmetic formulations.[7] The Panel determined that the data are insufficient to determine the safety of these ingredients for any other functions. Although these ingredients are not included in this safety assessment, the data on their safety is useful in determining the safety of dialkyl malates. The data from the malic acid and sodium malate safety assessment are summarized in the appropriate sections below.

Chemical and Physical Properties

Chemical and physical properties of these ingredients are provided in Table 2.

Diethylhexyl malate was reported to be 99% pure with the impurities being unreacted raw materials.[8]

Diethylhexyl malate is soluble in oil, ethanol, and silicone, and insoluble in propylene glycol, water, and dimethicone.[8]

USE

Cosmetic

Data on ingredient usage are provided to the Food and Drug Administration (FDA) Voluntary Cosmetic Registration Program (VCRP) and a survey conducted by the Personal Care Products Council (Council) has collected maximum use concentrations for ingredients in this group (Table 3).[9,10]

The total number of VCRP reported uses of diisostearyl malate was 694 (690 uses in leave-on products; 345 uses in lipsticks) and was reported to be used at a maximum of 0.001% - 82% (up to 0.2%-82% in leave-on products and 0.001% - 29% in rinse-off products; up to 82% in lipstick). Di-C12-13 alkyl malate was reported to be used in 27 products (24 in leave-on products; 26 with dermal exposure) and was reported to be used up to 1% - 36% in leave-on products (makeup foundation). Diethylhexyl malate was reported to be used in 12 products (11 leave-on products) and was reported to be used up to 0.4% - 2% in leave-on products and 2% in rinse-off products.

There were no reported uses for: dibutyloctyl malate, diisoamyl malate, and dioctyldodecyl malate.

Diisostearyl malate is reported to be used in cosmetic sprays, including fragrance products, and could possibly be inhaled. These ingredients are reportedly used at concentrations up to 10% (other fragrance preparations). In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 μm.[11-14] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[11,13]

Non-Cosmetic

D-malic acid is not generally recognized as safe (GRAS) for use in baby foods because babies cannot digest *D*-malic acid. However, *D*- and *L*-malic acid, when meeting Food Chemicals Codex specifications, are GRAS as direct food additives for use as flavor enhancers, flavoring agents, and adjuvants, and as a pH control agent.[15-17] Information on non-cosmetic uses of dialkyl malates was not available.

TOXICOKINETICS

Absorption, Distribution, Metabolism, and Excretion

There were no absorption, distribution, metabolism or excretion studies discovered for the ingredients in this safety assessment.

Oral and Intraperitoneal

MALIC ACID

Malic acid plays a part in carbohydrate metabolism and is a precursor of oxalacetic and pyruvic acids.[18]

Most of the radioactivity from 2.5 mg/kg U-^{14}C-*L*-malic acid (sp. act. 61 μCi/mmol) or 4-^{14}C-*DL*-malic acid (sp. act. 93 μCi/mmol) administered orally or intraperitoneally (i.p.) to male albino Wistar Alderly Park SPF rats was excreted as carbon dioxide.[19]

Daily oral administration of 4 g/kg malic acid resulted in increased glucuronic acid excretion in the urine.[20] Upon oral administration of ^{14}C-*L*-malic acid to male albino Wistar Alderly Park SPF rats, most of the radioactivity was excreted as carbon dioxide.[19]

Upon i.p. administration of ^{14}C-*L*-malic acid to rats, most of the radioactivity was excreted as carbon dioxide.[19]

TOXICOLOGICAL STUDIES

Acute Toxicity

Dermal

DI-C12-13 ALKYL MALATE

The acute dermal LD_{50} of di-C12-13 alkyl malate for male and female Wistar rats (n = 5) was > 2000 mg/kg (2 mL/kg; 100%).[21] There were no clinical signs during the 7-day observation period and no pathology at necropsy.

Oral – Non-Human

DI-C12-13 ALKYL MALATE

The acute oral LD_{50} of di-C12-13 alkyl malate for Wistar rats (n = 5/sex) was > 5000 mg/kg in sesame seed oil.[22] There were no mortalities. During a 48-h observation period, 3 males exhibited intense fur erection and one male showed ante and post mortem a mycosis in one foreleg.

DIETHYLHEXYL MALATE

The reported LD_{50} for diethylhexyl malate is > 5g/kg for albino rats (strain not provided).[23]

MALIC ACID AND SODIUM MALATE

The oral LD_{50}s of malic acid for albino CD-1 outbred mice (n = 5/sex), albino Wistar rats (n = 5/sex), and Dutch-Belted rabbits (n = 5/sex) were approximately 2.66, 3.5, and 3 g/kg, respectively.[24-27] Malic acid was administered as a 25% aqueous solution. Signs of toxicity included ataxia, prostration, convulsions, retraction of the abdomen, respiratory distress, cyanosis and death.

The oral LD_{LO} of malic acid for rabbits was 5 g/kg.[28] The oral "lethal dose" of *L*-malic acid for rabbits was 5 g/kg, and for sodium malate in dogs was 1 g/kg.[29]

DIBUTYL MALATE

The oral LD_{50} of dibutyl malate was reported to be 3730 mg/kg for rats.[30]

Other Dose Administration

MALIC ACID

The acute LD_{50} of malic acid administered intravenously was 2.4 g/kg for rabbits, and the i.p. LD_{50} values for mice and rats were 50 to 100 and 100 to 200 mg/kg, respectively.[29]

In an experiment comparing different stereocenters, the i.p. administration to rats of 1 g/kg *L*-malic acid was not lethal, but the same dose of *D*-malic acid killed rats within 20-25 min.[31] Another experiment showed that 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 author did not have an explanation for the difference in toxicity between the two isomers.

The i.p. administration of 2 g/kg *DL*-malic acid was not lethal to rats.[32] The i.p. LD_{50} of malic acid for mice and rats ranged from 50-100 and 100-200 mg/kg, respectively.

Repeated Dose Toxicity

Dermal

DI-C12-13 ALKYL MALATE

Di-C12-13 alkyl malate (10 mL/kg; 1000 mg/kg/d) was dermally applied under occlusion daily to the shaved dorsal area of male and female New Zealand White rabbits (n = 5/sex) for 28 days.[33] Each bandage was removed after 6 h and the treatment area was not washed. There were no clinical signs observed during treatment and the two-week observation period. Necropsies, hematology, and clinical chemistry (including liver function) were unremarkable.

Oral – Non-Human

MALIC ACID AND SODIUM MALATE

In a chronic oral study, feeding malic acid (500, 5000, 50,000 ppm; 0.05%, 0.5%, 5.0%) to Charles River rats (n = 30/sex) for 104 weeks resulted in no compound related lesions (types not provided).[34] No significant changes or lesions were observed when dogs were fed malic acid (500, 5000, 50,000 ppm) for 104 weeks.[35]

DIBUTYL MALATE

In a repeated oral dose and reproductive toxicity/developmental toxicity screening assay using rats, dibutyl malate (300 mg/kg) produced renal tubular lesions and increased liver and kidney weights. The NOEL was 95 mg/kg.[30]

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

There were no reproductive or developmental studies discovered for the ingredients in this safety assessment.

MALIC ACID

Malic acid did not cause developmental toxicity in albino CD-1 outbred mice (n = 25) up to 266 mg/kg (days 6 – 15 of gestation), rats (n = 25 – 29) up to 350 mg/kg (for 10 days during gestation), or Dutch-belted rabbits (n = 15 – 23) up to 300 mg/kg (days 6 – 18 of gestation).[36-38] In a multigenerational oral study of malic acid, there were no reproductive or developmental effects to albino rats up to 10,000 ppm in feed for the P1, P2, F1, and F2 generations.[39]

Malic acid (10.00 mg/egg in water) was injected into the air sac or yolk of white Leghorn chicken eggs (n = 20) at the 0 or 96 h of incubation.[40] There were no developmental effects observed when the chicks were examined after hatching.

DIBUTYL MALATE

In a repeated dose and reproductive toxicity/developmental toxicity screening assay for dibutyl malate (300 mg/kg), there were no adverse reproductive effects reported in rats.[30]

GENOTOXICITY

DIISOSTEARYL MALATE

In a reverse mutation assay using *Salmonella typhimurium* (TA98, TA100, TA1535, TA1537), diisostearyl malate (312.5, 625, 1250, 2500, 5000 µg/plate) was not mutagenic with or without metabolic activation.[41]

DI-C12-13 ALKYL MALATE

In an Ames test, di-C12-13 alkyl malate (1, 10, 100, 1000, 10,000 µg/plate) was not mutagenic to *S. typhimurium* (strains TA98, TA100, TA1535, TA1537, TA1538) with or without metabolic activation.[42] The results of the positive controls were as expected.

In a micronucleus assay using C57BL mice (n = 5/sex), di-C12-13 alkyl malate (250 mg/ml; 12500 mg/kg in sesame seed oil) administered intraperitoneally was not mutagentic.[43] Erythrocytes harvested from bone marrow were examined at 24, 48, and 72 h.

CARCINOGENICITY

There were no carcinogenicity studies discovered for the ingredients in this safety assessment.

MALIC ACID

In a chronic oral study, feeding malic acid (500, 5000, 50,000 ppm; 0.05%, 0.5%, 5.0%) to Charles River rats (n = 30/sex) for 104 weeks resulted in no compound related lesions (types not provided).[34] No significant changes or lesions were observed when dogs were fed malic acid (500, 5000, 50,000 ppm) for 104 weeks.[35]

IRRITATION AND SENSITIZATION

Irritation

Dermal – Non-Human

DI-C12-13 ALKYL MALATE

Di-C12-13 alkyl malate (10 mL/kg) was dermally applied under occlusion daily to the shaved dorsal area of male and female New Zealand White rabbits (n = 5) for 28 days.[33] No erythema or edema was observed.

Di-C12-13 alkyl malate (500 mg in 0.5 mL sesame seed oil) was not a dermal irritant when administered to the shaved skin (20 cm^2) of New Zealand White rabbits (n = 6) for 4 h.[44] No erythema or edema were observed at 1, 24, 48, and 72 h.

DIETHYLHEXYL MALATE

Diethylhexyl malate (100%; 0.5 ml) was applied to intact and abraded skin of New Zealand White rabbits (n = 6) under occlusion. The test sites were observed at 24 and 72 h. The primary irritation index (PII) was 1.18; diethylhexyl malate was determined not to be a primary irritant to rabbits.[45]

A primary dermal irritation test of diethylhexyl malate (100%) under occlusion for 24 h was conducted using New Zealand White rabbits (n = 6).[46] The PII was 3.53. The authors concluded that diethylhexyl malate was not a dermal irritant to rabbits.

MALIC ACID

Malic acid (500 mg/24 h) was moderately irritating to rabbit skin and was a strong irritant to guinea pigs.[27]

Dermal – Human

DI-C12-13 ALKYL MALATE

In a human patch test (n = 38), di-C12-13 alkyl malate (100%; 0.5 mL) was not irritating when administered to a 1 cm^2 area under occlusion for 48 h.[47] No erythema or edema was observed at 15 min and 24 h..

MALIC ACID

In a test determining the subjective skin irritation potential (n = 10), the average irritation scores over a 15-minute period were 39.4, 37.1, and 23.1 for malic acid (1 M in ethanol [SD40], ethoxydiglycol, butylene glycol) at pH 3, 5, and 7, respectively.[48]

In 2 human repeated insult patch tests (HRIPT) of products containing malic acid (0.022725% and 0.00375%), these products were predicted to be non to moderate irritants (Table 5).[49]

Ocular

DI-C12-13 ALKYL MALATE

Di-C12-13 alkyl malate (100%; 0.1 mL) was not irritating to the eyes of New Zealand White rabbits (n = 6).[50]

In a chorio-allantoic membrane (CAM) assay, di-C12-13 alkyl malate (200 µL) was not predicted to be an ocular irritant.[51]

DIETHYLHEXYL MALATE

Diethylhexyl malate (100%; 0.1 ml) was administered into 1 eye of New Zealand White rabbits (n = 6).[52] The eyes were unwashed for 24 h. At 24 and 72 h and 4 and 7 days, the Draize score was 0. At 48 h, the score was 0.3. The authors

determined that diethylhexyl malate was not an ocular irritant to rabbits.

Diethylhexyl malate (100%; 0.1 ml) was administered into 1 eye of New Zealand White rabbits (unwashed, n = 6; washed after 4 sec, n = 3).[46] At 24 h, the Draize score for the unwashed eyes was 2.0 and 0.7 for the washed eyes. At 48 and 72 h, the Draize score was 0. The authors determined that diethylhexyl malate was practically non-irritating to rabbits.

MALIC ACID

Malic acid caused severe ocular irritation in rabbit eyes.[27]

In chorioallantoic membrane vascular assay (CAMVA) and bovine corneal opacity and permeability tests (BCOP) of products containing malic acid (2.2725%), these products were predicted to be ocular irritants (Table 4).[49]

Sensitization

Dermal – Non-Human

DI-C12-13 ALKYL MALATE

In a guinea pig sensitization assay (Buehler test) using female Hartley guinea pigs (n = 10), epicutaneous administration of di-C12-13 alkyl malate (100%) for three 6-h exposures 7 days apart under occlusion was not sensitizing.[53]

DIETHYLHEXYL MALATE

In a guinea pig sensitization test (Buehler test; n = 12) of diethylhexyl malate (100%) there was slight erythema on two sites after the sixth dose.[23] There was no sensitization observed at challenge.

Dermal – Human

DIISOSTEARYL MALATE

An HRIPT (n = 51) of diisostearyl malate (100%; 0.2 ml, 0.2 g) was performed.[54] No adverse effects were observed during induction or challenge.

MALIC ACID

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.[55] In an in vitro study assessing the effect of malic acid on cell renewal on human skin, an 18%, 10%, and 5% increase was observed at pH 3, 5, and 7, respectively.

In two HRIPTs of products containing malic acid (0.022725% and 0.00375%), sensitization was not induced. (Table 4).[49]

SUMMARY

Dialkyl malates are cosmetic ingredients that have a core of succinic acid (a four carbon, alkyl diacid), that is mono-substituted. All of these ingredients have at least one stereocenter and the stereoisomers are *D*- and *L*-forms and the racemic mixture, which is denoted D,L-. The INCI names are defined as ambiguous to these stereochemical details. While not a cosmetic ingredient, dibutyl malate is a dialkyl malate and data regarding this chemical were considered relevant and were included.

Dialkyl malates function mostly as skin-conditioning agents-emollients.

Malic acid can be produced by a process that uses maleic acid (a related but structurally different dicarboxylic acid), but the reaction products are generally purified until the amounts of fumaric and residual maleic acid are 7.5 and <500 ppm, respectively. It was considered likely that all of the diacid is consumed in the reaction and no malic acid is present in the final product. Because these ingredients are diesters, however, esterases in the skin may metabolize them to the monoester or possibly to the free acid and corresponding alcohol.

The total number of reported uses of diisostearyl malate was 574 (572 uses in leave-on products) and was reported to be used at 0.001% - 82%. Di-C12-13 alkyl malate was reported to be used in 29 products and was reported to be used at 1% - 36% in leave-on products. Diethylhexyl malate was reported to be used in 10 products and was reported to be used at 0.4% - 2% in leave-on products and 2% in rinse-off products.

There were no reported uses for: dibutyloctyl malate, diisoamyl malate, and dioctyldodecyl malate.

D- 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.

Radiolabeled malic acid orally and intraperitoneally administered to rats was excreted mostly as carbon dioxide.

The acute dermal LD_{50} of di-C12-13 alkyl malate for rats was > 2000 mg/kg.

The acute oral LD_{50} of di-C12-13 alkyl malate for rats was > 5000 mg/kg. The reported LD_{50} for diethylhexyl malate was > 5g/kg for rats.

The oral LD_{50} of malic acid for mice was 2.66 g/kg, 3.5 g/kg for rats, and 3 g/kg for rabbits. The oral lethal dose of malic acid was 5 g/kg in rabbits. The oral lethal dose of sodium malate was 1 g/kg in dogs. The i.v. LD_{50} of malic acid was 2.4 g/kg for rabbits, and the i.p. LD_{50} values for mice and rats were 50 to 100 and 100 to 200 mg/kg, respectively. The i.p. administration to rats of 1 g/kg *L*-malic acid was not lethal, but the same dose of *D*-malic acid killed rats within 20-25 min. The i.p. administration of 2 g/kg *DL*-malic acid was not lethal to rats.

There were no clinical signs observed during treatment and the two-week observation period when 10 mL/kg di-

C12-13 alkyl malate was dermally applied to rabbits for 28 days

In a chronic oral study, feeding malic acid up to 50,000 ppm to rats for 104 weeks 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 104-week study.

Malic acid did not cause developmental toxicity in mice up to 266 mg/kg, rats up to 350 mg/kg, or rabbits up to 300 mg/kg. In a multigenerational oral study of malic acid, there were no reproductive or developmental effects in rats up to 10,000 ppm in the P1, P2, F1, and F2 generations. Malic acid at 10.00 mg in water/egg injected into the air sac or yolk of chicken eggs at the 0 or 96 h of incubation caused no developmental effects the chicks.

In a reverse mutation assay using *S. typhimurium*, diisostearyl malate was not mutagenic with or without metabolic activation up to 5000 μg/plate. In an Ames test, di-C12-13 alkyl malate was not mutagenic to *S. typhimurium* with or without metabolic activation up to 10,000 μg/plate.

In a micronucleus assay using C57BL mice (n = 5/sex), di-C12-13 alkyl malate (250 mg/ml; 12500 mg/kg in sesame seed oil) administered intraperitoneally was not mutagenic.

Di-C12-13 alkyl malate at 100% was not a dermal irritant in rabbits treated daily for 28 days..

Malic acid (500 mg/24 h) was moderately irritating to rabbit skin and was a strong irritant to guinea pigs. 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 a human patch test, di-C12-13 alkyl malate was not irritating at 100%.

Di-C12-13 alkyl malate was not irritating to the eyes of rabbits at 100%. In a chorio-allantoic membrane (CAM) assay, di-C12-13 alkyl malate was not predicted to be an ocular irritant.

Malic acid caused severe ocular irritation in rabbit eyes at 500 mg.

Di-C12-13 alkyl malate and diethylhexyl malate were not sensitizing to guinea pigs at 100%.

No adverse effects were observed during induction or challenge in an HRIPT of diisostearyl malate at 100%.

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. In two HRIPTs of products containing malic acid up to 0.022725%, sensitization was not induced.

DISCUSSION

The similar chemical structures, physicochemical properties, functions and concentrations in cosmetics allowed grouping these ingredients together and extending the available toxicological data to support the safety of the entire group.

D-malic acid was considered GRAS except for use in baby food since babies cannot digest *D*-malic acid. It was considered likely that all of the malic acid reacted to alcohols to produce these dialkyl malates is consumed in the reaction and no malic acid is present in the final product. At most, malic acid may be an trace impurity in dialkyl malates. The Panel also considered the toxicity of maleic acid, a possible impurity of (and not to be confused with) malic acid. Because the amount of maleic acid in malic acid is low, it follows that use of dialkyl malates in cosmetics could not reach a level of toxicological concern for maleic acid. The Panel also noted that none of these ingredients are reported to be used in baby products.

The Panel noted that the previous conclusion of the malic acid/sodium malate safety assessment stated that there were insufficient data to reach a safety conclusion on the use of these ingredients as anything but pH adjusters and there was a need for dermal sensitization studies. An HRIPT of diisostearyl malate at 100% did not result in irritation during induction or sensitization at challenge, and guinea pig sensitization tests of diethylhexyl malate and di-C12-13 alkyl malate, both at 100%, also did not produce sensitization in these animals. The Panel concluded that even though malic acid/sodium malate may be irritating, these results support the view that the dialkyl malates are not irritating or sensitizing.

There was concern expressed that the possible metabolite octyldodecanol is a penetration enhancer and dermal irritant. However, the potential concentration of the alcohol that would be generated in skin would be very low.

The Panel discussed the issue of incidental inhalation exposure from cosmetic sprays and loose powders (i.e., perfumes, face powders, body and hand sprays, and foot powders and sprays). There were no inhalation toxicity data available. These ingredients are reportedly used at concentrations up to 10% in cosmetic products that may be aerosolized. The Panel noted that 95%-99% of particles/droplets would not be respirable to any appreciable amount. Furthermore, these ingredients are not likely to cause any direct toxic effects in the upper respiratory tract, based on the properties of the dialkyl malates and on data that shows that these ingredients are not irritants. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. The Panel considered other data available to characterize the potential for dialkyl malates to cause systemic toxicity, irritation, or sensitization. They noted the lack of systemic toxicity at high doses in acute and subchronic oral exposure studies; no irritation or sensitization in multiple tests of dermal and ocular exposure; and the absence of genotoxicity in two Ames assays and a micronucleus assay. A detailed discussion of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at http://www.cir-safety.org/cir-findings.

CONCLUSION

The CIR Expert Panel concluded that the following ingredients are safe for use in cosmetics in the present practices of use and concentration in this safety assessment:

- diisostearyl malate
- dibutyloctyl malate*
- di-C12-13 alkyl malate
- diethylhexyl malate
- diisoamyl malate*
- dioctyldodecyl malate*

*Not reported in current use. Were ingredients in this group to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in this group.

TABLES AND FIGURES

Table 1. The CAS numbers, definitions and functions of the ingredients in this safety assessment The first definition is provided by the International Cosmetic Ingredient Dictionary and Handbook; the definition in italics was developed by the CIR staff.[56]

Ingredient CAS No.	Definition	Function
Monohydroxysuccinates, free acid, and salt		
Diisostearyl Malate 67763-18-2 81230-05-9	Diisostearyl malate is the diester of isostearyl alcohol and malic acid; d*iisostearyl malate is a four carbon, hydroxy-diacid, esterified at each acid with a branched, eighteen carbon alkyl chain*.	Skin-conditioning agent – emollient
Dibutyloctyl Malate 399551-19-0	Dibutyloctyl malate is defined structurally*; the diester of 2-butyloctanol and malic acid; dibutyloctyl malate is a four carbon, hydroxy-diacid, esterified at each acid with a branched, twelve carbon alkyl chain (an eight carbon chain substituted at the two position with a four carbon alkyl chain).*	Plasticizer; skin-conditioning agent - emollient; solvent
Di-C12-13 Alkyl Malate	Di-C12-13 alkyl malate is the diester of C12-13 alcohols and malic acid; *Di-C12-13 alkyl malate is a mixture of diesters of C12 and C13 alcohols with malic acid; Di-C12-13 alkyl malate is a four carbon, hydroxy-diacid, esterified at each acid with either a twelve or thirteen carbon alkyl chain.*	Skin-conditioning agent – emollient
Diethylhexyl Malate 56235-92-8	Diethylhexyl malate is the diester of malic acid and 2-ethylhexanol; *diethylhexyl malate is the diester of malic acid and 2-ethylhexanol; diethylhexyl malate is a four carbon, hydroxy-diacid, esterified at each acid with a branched, eight carbon alkyl chain (a six carbon chain substituted at the two position with a two carbon alkyl chain).*	Skin-conditioning agent – emollient
Diisoamyl Malate [1587-19-5] (per CAS)	Diisoamyl malate is defined structurally; *diisoamyl malate is the diester of isoamyl alcohol and malic acid; diisoamyl malate is a four carbon, hydroxy-diacid, esterified at each acid with a branched, five carbon alkyl chain.*	Plasticizer; skin-conditioning agent - emollient; slip modifier; solvent
Dioctyldodecyl Malate	Dioctyldodecyl malate is defined structurally; *dioctyldodecyl malate is the diester of octyldodecyl alcohol and malic acid; dioctyldodecyl malate is a four carbon, hydroxy-diacid, esterified at each acid with a branched, twenty carbon alkyl chain (a twelve carbon chain substituted at the two position with an eight carbon alkyl chain).*	Skin-conditioning agent – miscellaneous

Table 2. Physical and chemical properties of alkyl malates.

Property	Value	Reference
Diisostearyl malate		
Physical Form	Liquid	[57]
Color	Clear colorless to slightly yellow	[57]
Odor	Slight, typical	[57]
Molecular Weight g/mol	639.04	calculated [58]
Molecular Volume m^3/kmol	0.6944 ± 3.0 x 10^{-4}	calculated [58]
Density/Specific Gravity @ 20ºC	0.920 ± 0.06 g/cm^3	calculated [58]
Vapor pressure mmHg@ 25ºC	3.4E^{-22}	calculated [58]
Boiling Point ºC	676.3 ± 35.0ºC	calculated [58]
Water Solubility	Insoluble	[59]
Dibutyloctyl malate		
Molecular Weight g/mol	470.73	calculated [58]
Molecular Volume m^3/kmol	0.4963+/-3.0 x 10^{-4}	calculated [58]
Density/Specific Gravity @ 20ºC	0.948+/-0.06	calculated [58]
Vapor pressure mmHg@ 25ºC	2.84E^{-14}	calculated [58]
Boiling Point ºC	547.6+/-30.0	calculated [58]
Water Solubility g/L @ 25ºC & pH 7	1.0^{-5}	calculated [58]

Table 2. Physical and chemical properties of alkyl malates.

Property	Value	Reference
Di-C12-13 alkyl malate		
Log Kow @ 40 °C	>6.4	[60]
Diethylhexyl malate		
Molecular Weight g/mol	358.51	calculated [58]
Molecular Volume m^3/kmol	364.2+/-3.0 cm^3	calculated [58]
Density/Specific Gravity @ 20°C	0.984+/-0.06 g/cm^3	calculated [58]
Vapor pressure mmHg@ 25°C	6.31 x 10^{-10}	calculated [58]
Boiling Point °C	448.4+/-25.0	calculated [58]
Diisoamyl malate		
Molecular Weight g/mol	274.35	calculated [58]
Molecular Volume m^3/kmol	265.2+/-3.0 cm^3	calculated [58]
Density/Specific Gravity @ 20°C	1.006 g/cm^3	calculated [61]
Vapor pressure mmHg@ 25°C	9.08E^{-07}	calculated [58]
Boiling Point °C	152-157	calculated [61]
Dioctyldodecyl malate		
Molecular Weight g/mol	134.09	calculated [58]
Density/Specific Gravity @ 20°C	1.641+/-0.06	calculated [58]
Vapor pressure mmHg@ 25°C	7.19E^{-05}	calculated [58]
Boiling Point °C	306.4+/-27.0	calculated [58]

Table 3. Frequency of use and concentration according to duration and exposure.[9,10]

Use type	Uses	Concentration (%)	Uses	Concentration (%)	Uses	Concentration (%)
	Diisostearyl Malate		**Di-C12-13 Alkyl Malate**		**Diethylhexyl Malate**	
Total/range	**694**	**0.001-82**	**27**	**1-36**	**12**	**0.4-2**
Duration of use						
Leave-on	690	0.2-82[1,2]	24	1-36	11	0.4-2
Rinse-off	4	0.001-29	3	NR	1	2
Diluted for (bath) use	NR	NR	NR	NR		
Exposure type						
Eye area	87	0.2-36	1	NR	NR	NR
Incidental ingestion	345	5-82	NR	NR	NR	NR
Incidental inhalation-sprays	4	3-10	NR	1	NR	NR
Incidental inhalation-powders	28	0.4-12	NR	NR	NR	NR
Dermal	346	0.2-49[1,2]	26	1-36	9	0.4-2
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair-noncoloring	3	0.001-15	1	3	3	2
Hair-coloring	NR	3	NR	NR	NR	NR
Nail	NR	0.4-49	NR	NR	NR	NR
Mucous Membrane	345	5-82	1	NR	NR	NR
Baby	NR	NR	NR	NR	NR	NR

NR = None reported
[1] 3% in a body oil listed under "other fragrance preparation".
[2] 10% in a lip cream.

Table 4. Dermal irritation, sensitization and ocular irritation studies of products containing malic acid.[49]

Irritation				
Test Material	**Concentration of malic acid in product/actual concentration of malic acid tested/pH**	**n**	**Procedure**	**Results**
Hair styler	1%/0.022725%/3.6	101	Modified HRIPT. Induction 21 days, rest 10-24 days, challenge 4 days using semi-occlusive patch.	Predicted not to be a significant skin irritant. Standardized cumulative irritation = 1181.5, negative control (undosed patch) = 45.6, positive control (1% SLS) = 2052.8.
Hair shampoo	0.5%/0.000375%/3.0	98	Modified HRIPT. Induction 21 days, rest 10-24 days, challenge 4 days using occlusive patches.	Predicted to be a moderate skin irritant. Standardized cumulative irritation = 965.1, negative control (distilled water) = 33, positive control (0.1% SLS) = 1307.76.
Sensitization				
Hair styler[1]	1%/0.022725%/3.6	101	Modified HRIPT. Induction 21 days, rest 10-24 days, challenge 4 days using semi-occlusive patch.	Solution did not induce allergic contact dermatitis in any subject.
Hair shampoo[2]	0.5%/0.000375%/3.0	98	Modified HRIPT. Induction 21 days, rest 10-24 days, challenge 4 days using occlusive patches.	Solution did not induce allergic contact dermatitis in any subject.
Ocular irritation				
Test material	**Concentration/ pH**	**CMVA results (RC_{50} (95% CI)**	**BCOP Results (In vitro score/opacity score/permeability score)**	**Prediction**
Hair styler	2.2757%/3.6	>50% (NA)	74.3/69.9/0.296	Severe ocular irritant
Hair shampoo	2.275%/3.0	1.6 (0.62-3.9)	9.09/5.4/0.246	Ocular irritant

[1] Same study as irritation study above.
[2] Same study as irritation study above.

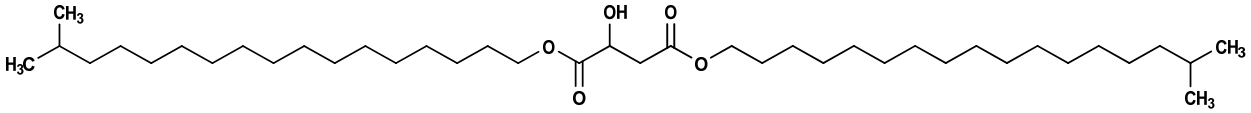
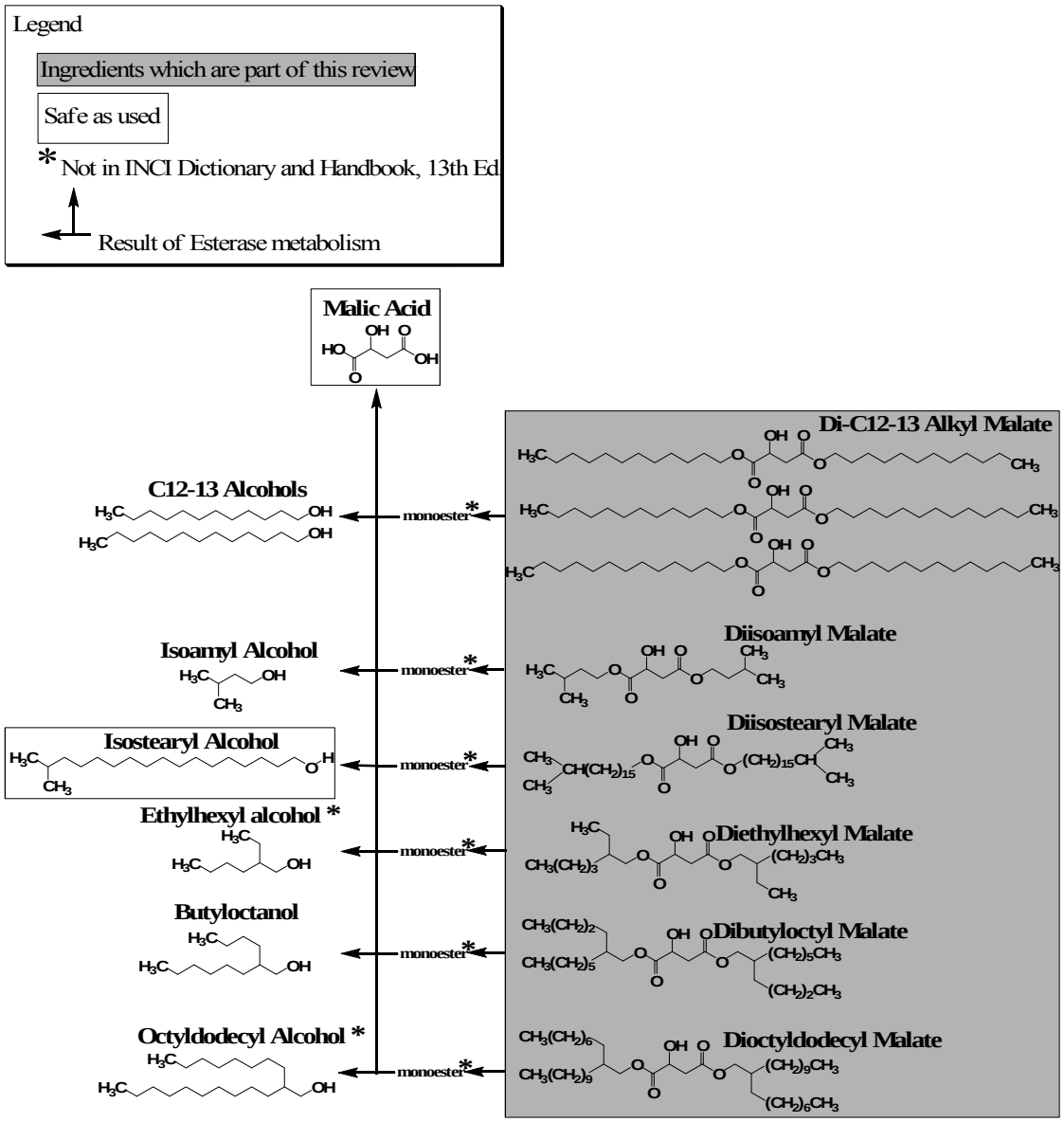


Figure 1. Diisostearyl malate.

Figure 2. Map of the ester ingredients in this assessment, and possible associated esterase metabolites.



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APPENDIX – POSSIBLE ESTERASE METABOLITE SUMMARY DATA OF ALCOHOLS

BUTYL OCTANOL – metabolite of dibutyloctyl malate

No data was found on this alcohol.

C12-13 ALCOHOL – metabolite of di-C12-13 alkyl malate

Acute Toxicity

The LD_{50} of dodecanol (C12) for rats was reported to be 12,800 mg/kg.[62]

The LD_{50} of isotridecanol (C13) for rats was reported to be 17,000 mg/kg.[62]

Ocular Irritation

Dodecanol was reported to have an ocular irritation score of 2 (out of 10) in a quantitative structure-activity relation (QSAR) analysis.[63]

ISOAMYL ALCOHOL – metabolite of diisoamyl malate

Cytotoxicity

Isoamyl alcohol had an IC_{50} of 28 mM for human lung carcinoma epithelial cells A549.[64] In a Comet assay, isoamyl alcohol was not toxic to A549 cells and V79 Chinese hamster cells at 46 mM and human peripheral blood cells at 23 mM.

Chemical Properties

Isoamyl alcohol is reported to have a log pK_p of -2.00 cm/h and a log K_{ow} of 1.16.[65-67]

Dermal Irritation

Isoamyl alcohol (up to 100% in acetone;olive oil 4:1) was negative in a LLNA.[68]

Genotoxicity

Isamyl alcohol was not clastogenic with or without metabolic activation to V79 Chinese hamster cells in a micronucleus test (5 and 9 mM) and a hypoxanthine-guanine-phosphoribosyl transferase gene mutation test (HPRT; 107 mM).[64] The authors concluded that isoamyl alcohol has no genotoxic potential in these in vitro conditions.

ISOSTEARYL ALCOHOL – metabolite of diisostearyl malate

Chemical Properties

Physicochemical properties of isostearyl alcohol were estimated by EPISuite to be: molecular weight, 639; log K_{ow}, 15.6; and water solubility, 1.5×10^{-11} mg/ml.[30]

Toxicity

The LD_{50} of isostearyl alcohol was reported to be > 2000 mg/kg in rats.[30]

Clinical Irritation and Sensitization

The skin irritation potential of isostearyl alcohol was evaluated in 19 male and female subjects (18-65 years old) at a concentration of 25.0% in petrolatum.[69] The test substance did not induce skin irritation in any of the subjects (Primary Irritation Index = 0.05). In 3 similar studies, 3 different lipstick products containing 25.0, 27.0, and 28.0% isostearyl alcohol, respectively, were tested according to the same protocol. The 3 products did not induce skin irritation. The irritation and sensitization potential of isostearyl alcohol (25% v/v in 95.0% isopropyl alcohol) was evaluated in 12 male subjects (21-60 years old). Challenge applications were made to original and adjacent sites 2 weeks after removal of the last induction patch. Three of 12 subjects had slight erythema during induction, and there was no evidence of sensitization.

The sensitization potential of a pump spray antiperspirant containing 5.0% isostearyl alcohol was evaluated using 148 male and female subjects.[69] The product was applied via an occlusive patch to the upper arm for a total of 9 induction applications (3 times/week for 3 weeks). Each patch remained for 24 h, and sites were scored immediately before subsequent applications. During the challenge phase, a patch was applied to the induction site and to a new site on the opposite arm of each subject. Reactions were scored 48 and 96 h after application. Ten of the 12 subjects with reactions suggestive of sensitization were re-challenged with the product 2 months later. Patches remained for 24 h, and sites were scored at 48 and 96 h post-application. Six subjects had reactions during the re-challenge. Four of the 6 subjects were then tested with 5.0% isostearyl alcohol in solution with ethanol 6 weeks after scoring of the first rechallenge; all had positive responses. Negative responses were reported when the product (without isostearyl alcohol) and 100.0% ethanol each were tested. In a second study, the same product was applied to 60 male and female subjects (same protocol). Five of the subjects had positive responses after the first challenge. One of the 5 was re-challenged with 5.0% isostearyl alcohol in ethanol solution, and a positive reaction was observed.

OCTYLDODECANOL – metabolite of dioctyldodecyl malate

Dermal Penetration Enhancement

Octyldodecanol (0.5, 1.00 mg/inch^2) increased the dermal penetration of formoterol fumarate.[70] Octyldoddecanol was not irritating to rabbit skin alone but increased the irritation of formoterol fumarate from a score of 0.21 (control) to 1.38. No irritation was observed in guinea pigs, rats, and miniature swine.

Octyldodecanol (5.0% w/w) increased human dermal penetration of octylmethoxycinnamate in an in vitro test.[71]

Case Reports

A 37-year-old man presented with swelling of the genitalia after the use of a cream to treat "thrush.[72] Symptoms were treated with prednisolone and antihistamines. Patch testing revealed a 3+ reaction to 13.5% octyldodecanol in liquid paraffin at 48 and 96 h. The authors note that his particular reaction is very rare.

A 62-year-old man presented with irritation, erythema and edema after using an anti-itch cream.[73] Patch testing revealed a + reaction to octyldodecanol at 3% in petrolatum.