
Amended Safety Assessment of Dialkyl Dimer Dilinoleates as Used in Cosmetics

Status: Re-Review for Panel Review
Release Date: May 11, 2018
Panel Meeting Date: June 4-5, 2018

The 2018 Cosmetic Ingredient Review Expert Panel members are: Chairman, 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 Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Priya A. Cherian, Scientific Analyst/Writer.

Memorandum

To: CIR Expert Panel Members and Liaisons
From: Priya Cherian, Scientific Analyst/Writer
Date: May 11, 2018
Subject: Amended Safety Assessment of Dialkyl Dimer Dilinoleates

Enclosed is the Amended Safety Assessment of Dialkyl Dimer Dilinoleates as Used in Cosmetics. (It is identified as *dilin062018rep* in the pdf document.) This is a re-review that is being initiated in accord with CIR's Procedures to reassess previously-reviewed conclusions after a period of 15 years.

In 2003, CIR published the Final Report on the Safety Assessment of Diisopropyl Dimer Dilinoleate, Diciteryl Dimer Dilinoleate, Diisostearyl Dimer Dilinoleate, Diethylhexyl [previously dioctyl] Dimer Dilinoleate, Dioctyldodecyl Dimer Dilinoleate and Ditridecyl Dimer Dilinoleate. Based on the available data, the Panel concluded that the dialkyl dimer dilinoleates named in that report are safe for use in cosmetics.

In addition to the ingredients that were included in the 2003 review, there are 2 possible "add-ons" that have not yet been looked at by CIR. Di-C16-18 Alkyl Dimer Dilinoleate and Di-C20-40 Alkyl Dimer Dilinoleate were added to this group due to structural and chemical similarities to the original dialkyl dimer dilinoleates. FDAVCRP use data for this group of ingredients have been added to this report. A concentration of use survey is underway. Both 2018 and 1998 VCRP data regarding frequency of use suggest Diisopropyl Dimer Dilinoleate and Diisostearyl Dimer Dilinoleate are the most widely used among the 8 ingredients included in the report. Diisopropyl Dimer Dilinoleate had 35 reported uses in 1998, and 145 reported uses in 2018. The majority of uses for this ingredient in both 1998 and 2018 were in the form of lipsticks.

A thorough search of the literature published since the report was issued in 2003 was completed, however, no new data were found. Summary information from the original report on the 6 previously included dialkyl dimer dilinoleates have been included in *italicized text* in the safety assessment, as appropriate. The 2003 report is included for your review so that detailed information is easily accessible.

The Panel should determine whether the original conclusion is still valid. If not, then the Panel should reopen the safety assessment to amend the conclusion. If the existing conclusion is still valid, then the Panel should determine if the report should be reopened to add the additional 2 ingredients.

The following are included in this package for your review:

- *dilin062018rep*: re-review document
- *dilin062018prev*: Final Report on the Amended Safety Assessment of Diisopropyl Dimer Dilinoleate, Diciteryl Dimer Dilinoleate, Diisostearyl Dimer Dilinoleate, Dioctyl Dimer Dilinoleate, Dioctyldodecyl Dimer Dilinoleate, and Ditridecyl Dimer Dilinoleate
- *dilin062018flow*: report flowchart
- *dilin062018FDA*: 2018 VCRP data
- *dilin062018prof*: data profile
- *dilin062018hist*: history
- *dilin062018strat*: search strategy
- *dilin062018min*: minutes from the previous deliberations of the 6 dialkyl dimer dilinoleates

History - Dialkyl Dimer Dilinoleates

Dialkyl Dimer Dilinoleates

1996: The Panel added Dicetearyl Dimer Dilinoleate, Diisostearyl Dimer Dilinoleate, Dioctyl Dimer Dilinoleate, Dioctyldodecyl Dimer Dilinoleate, and Ditridecyl Dimer Dilinoleate to the original report.

1997: The Panel concluded that the available data were insufficient to support the safety of these ingredients in cosmetic formulations.

2003: The panel published an amended safety assessment with a conclusion that the 6 dialkyl dimer dilinoleates listed in the report were safe as used in cosmetics.

June 2018: Re-Review

The re-review document was presented to the Panel.

Data Profile for the Amended Safety Assessment of Dialkyl Dimer Dilinoleates as Used in Cosmetics - June 4-5, 2018 - Priya Cherian																		
	Reported Use	Method of Manufacture	Impurities	Dermal Penetration	ADME	Animal Tox – Acute, Dermal	Animal Tox – Acute, Oral	Animal Tox, Acute, Inhalation	Animal Tox – Rptd Dose, Dermal	Animal Tox, Rptd Dose, Oral	Animal Tox – Rptd Dose, Inhalation	Repro/Dev Tox	Genotox	Carcinogenicity	Dermal Irritation	Dermal Sensitization	Phototoxicity	Ocular Irritation
Dicetearyl Dimer Dilinoleate	O	O	O				O								O	O		O
Diethylhexyl Dimer Dilinoleate	O	O																
Diisopropyl Dimer Dilinoleate	X,O	O	O				O								O	O	O	O
Diisostearyl Dimer Dilinoleate	X,O	O	O				O								O	O	O	O
Dioctyl dodecyl Dimer Dilinoleate		O	O			O	O								O	O		O
Ditridecyl Dimer Dilinoleate		O																
Di-C16-18 Alkyl Dimer Dilinoleate																		
Di-C20-40 Alkyl Dimer Dilinoleate																		
Dilinoleic Acid (read-across)										O			O					

*"X" indicates that new data were available in this category for the ingredient; "O" indicates that old data from the original assessment were available

[Dialkyl Dimer Dilinoleates (3/29/2018; 4/2/2018)]

Ingredient	CAS #	InfoBase	SciFinder	PubMed	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	HPVIS	NICNA S	NTIS	NTP	WHO	FAO	FEMA	Web
Diisopropyl Dimer Dilinoleate	205393-95-9	1/1	33/0	1/0	2/0	0	0	0	0	0	0	0	0	0	0	0	0	
Dicetearyl Dimer Dilinoleate	135320-20-1 501901-81-1	1/1	2/0	1/0	2/0	0	0	0	0	0	0	0	0	0	0	0	0	
Diisostearyl Dimer Dilinoleate	103213-19-0	1/1	3/0	1/0	3/0	0	0	0	0	0	0	0	0	0	0	0	0	
Dioctylododecyl Dimer Dilinoleate	129423-60-5	1/1	3/0	1/0	1/0	0	0	0	0	0	0	0	0	0	0	0	0	
Ditridecyl Dimer Dilinoleate		1/1	2/0	1/0	1/0	0	0	0	0	0	0	0	0	0	0	0	0	
Diethylhexyl Dimer Dilinoleate		1/1	3/0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Di-C16-18		1/1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
Di-C20-40		1/1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	

Search Strategy

[identify total # of hits /# hits that were useful or examined for usefulness]

Search terms used: “Diisopropyl Dimer Dilinoleate” “Diisopropyl Dimer Dilinoleate toxicity” “Dicetearyl Dimer Dilinoleate” “Diisostearyl Dimer Dilinoleate” “Dioctylododecyl Dimer Dilinoleate” “Ditridecyl Dimer Dilinoleate” “Diethylhexyl Dimer Dilinoleate” “Dicetearyl Dimer Dilinoleate toxicity” “Dilinoleate toxicity” “di-c16-18 dilinoleate” “di-c20-40 dilinoleate”

Minutes from the 60th CIR Expert Panel meeting: September 19-20, 1996
Diisopropyl Dimer Dilinoleate

Dr. Schroeter noted that an informal data request on this ingredient was issued at the June 3-4, 1996 Panel meeting, and that his Team had also recommended the addition of the following ingredients to the present report: Dicetearyl Dimer Dilinoleate, Diisostearyl Dimer Dilinoleate, Dioctyl Dimer Dilinoleate, Dioctyldodecyl Dimer Dilinoleate, and Ditridecyl Dimer Dilinoleate.

The Panel agreed that the ingredients mentioned above should also be included in the present report, and voted unanimously in favor of issuing an Insufficient Data Announcement with the following data requests:

- (1) Current concentration of use data
- (2) Chemistry data, including structure, method of manufacture, and impurities data
- (3) UV absorption data; if there is significant absorption in the UVB or UVA range, then phototoxicity data are needed
- (4) Skin penetration; if there is significant skin penetration, then both A 28-day dermal toxicity study to assess general skin and systemic toxicity and a reproductive and developmental toxicity study are needed
- (5) Skin sensitization data
- (6) Two genotoxicity studies, one in a mammalian system; if positive, then a two-year carcinogenesis study using NTP methods is needed

Minutes from the 62nd CIR Expert Panel meeting: April 3-4, 1997

Diisopropyl Dimer Dilinoleate, Dicetearyl Dimer Dilinoleate, Diisostearyl Dimer Dilinoleate, Dioctyl Dimer Dilinoleate, Dioctyldodecyl Dimer Dilinoleate, and Ditridecyl Dimer Dilinoleate

Dr. Schroeter noted that an Insufficient Data Announcement with the following data requests was issued at the September 1996 Panel meeting:

- (1) Current concentration of use data
- (2) Chemistry data, including structure, method of manufacture, and impurities data

- (3) UV absorption data; if there is significant absorption in the UVB or UVA range, then phototoxicity data are needed
- (4) Skin penetration; if there is significant skin penetration, then both a 28-day dermal toxicity study to assess general skin and systemic toxicity and a reproductive and developmental toxicity study are needed
- (5) Skin sensitization data
- (6) Two genotoxicity studies, one in a mammalian system; if positive, then a two-year carcinogenesis study using NTP methods is needed

With the exception of items (4) and (6), all of the data included in this request were received.

The Panel voted unanimously in favor of issuing a Tentative Report with an insufficient data conclusion on this group of ingredients. The data needed in order for the Panel to complete its safety assessment are listed in the discussion section of the report as follows:

- (1) 28-day dermal toxicity data; if significantly absorbed, then reproductive and developmental toxicity data are needed*
- (2) Two genotoxicity studies, one using a mammalian system; if positive, a 2-yr dermal carcinogenicity assay using NTP methods is needed*

*All tests are to be performed on Diisopropyl Dimer Dilinoleate.

Minutes from the 73rd CIR Expert Panel meeting: Tuesday December 21, 1999

Diisopropyl Dimer Dilinoleate, Diciteryl Dimer Dilinoleate, Diisostearyl Dimer Dilinoleate, Dioctyl Dimer Dilinoleate, Dioctyldodecyl Dimer Dilinoleate, and Ditridecyl Dimer Dilinoleate

Dr. Schroeter recalled that the Panel issued a Final Report with an insufficient data conclusion on this group of ingredients at the September 22-23, 1997 Panel meeting. The Panel determined that the following data are needed for completion of this safety assessment: (1) 28-day dermal toxicity data; if significantly absorbed, developmental toxicity data are needed; and (2) Two genotoxicity studies, one using a mammalian system; if positive, a 2-year dermal carcinogenicity assay performed using The National Toxicology Program methods is needed. Since the Panel meeting, data needed in order for the Panel to complete its safety assessment were received. References to the use of the DEREK expert system in predicting toxicity were also received.

The Panel agreed that all of the information relating to DEREK (Deductive Estimation of Risk from Existing Knowledge - a computer-based, expert system QSAR analysis) be removed from the report section on Carcinogenicity as well the report discussion because DEREK is not an acceptable scientific method.

The Panel voted unanimously in favor of issuing a Tentative Amended conclusion that the ingredients in the Diisopropyl Dimer Dilinoleate ingredient family are safe as used in cosmetic formulations.

After noting differences in the wording of CIR report conclusions, this review included, Dr. McEwen recommended that CIR conclusions begin with the following phrase: "Based on the information contained in this report". Dr. Bergfeld agreed that this comment should be accepted as an editorial change in all CIR reports. The Panel agreed.

Dr. Belsito recommended that the following statements be added to the report discussion: Based on current use concentration data, these ingredients could be used at concentrations as high as 53% in a lipstick, but test concentrations in sensitization studies included in this review are up to 27%. However, given the size of the molecule, its solubility in water, its lipophilic nature, and the absence of any significant case reports on allergenicity in the literature, the Panel is not concerned about the lack of sensitization data at higher concentrations (i.e., concentrations > 27%). The Panel agreed with Dr. Belsito's proposal.

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INTRODUCTION

In 2003, the Cosmetic Ingredient Review (CIR) published a final report on the safety assessment of Diisopropyl Dimer Dilinoleate, Dicetearyl Dimer Dilinoleate, Diisostearyl Dimer Dilinoleate, Diethylhexyl Dimer Dilinoleate (at the time named Dioctyl Dimer Dilinoleate), Dioctyldodecyl Dimer Dilinoleate and Ditridecyl Dimer Dilinoleate.¹ The Expert Panel came to the conclusion that these ingredients are safe as used in cosmetic products.

According to the web-based *International Cosmetic Ingredient Dictionary and Handbook (wINCI Dictionary)*, the ingredients named above are reported to function as skin-conditioning agents.² Definitions, idealized structures, and functions of these ingredients can be seen in Table 1.

Since it has been at least 15 years since the safety assessment on the above ingredients, the Panel is being asked to determine whether the conclusion should be reaffirmed, or if a re-review is necessary. Additionally, the following 2 ingredients are being proposed for inclusion in this assessment:

Di-C16-18 Alkyl Dimer Dilinoleate
Di-C20-40 Alkyl Dimer Dilinoleate

These 2 ingredients are dialkyl dimer dilinoleates, and therefore structurally similar to the ingredients reviewed in the 2003 safety assessment. Indeed, there is a direct structural overlap between Dicetearyl Dimer Dilinoleate (i.e. di-C16 alkyl dimer dilinoleate) and one of the constituents of Di-C16-18 Alkyl Dimer Dilinoleate (i.e. a mixture of di-C16 alkyl dimer dilinoleate, di-C18 alkyl dimer dilinoleate and C16/C18 alkyl dimer dilinoleate). In addition to being a skin-conditioning agent, Di-C20-40 Alkyl Dimer Dilinoleate also functions as a viscosity-increasing agent-nonaqueous.²

These dialkyl dimer dilinoleates are the diesters of their respective alcohols and dilinoleic acid. Table 2 presents all relevant alcohols previously reviewed by CIR, and a list of relevant alcohols that have not yet been reviewed by CIR can be found in Table 3.

Excerpts from the summary of the 2003 report are included throughout the text of this re-review document, as appropriate, and are *identified by italicized text*. The 2003 report contained information regarding relevant alcohols. The full reports on the alcohols can be accessed on the CIR website (<https://www.cir-safety.org/ingredients>); therefore, information regarding these alcohols will not be included in this report. Additionally, the Discussion from the original report is included to provide pertinent background information about the existing conclusion. The Summary of this re-review only includes new data.

CIR safety assessments include relevant published and unpublished data that are available for each endpoint that is evaluated. Published data are identified by conducting an exhaustive search of the world's literature. A listing of the search engines and websites that are used and the sources that are typically explored, as well as the endpoints that CIR typically evaluates, is provided on the CIR website (<http://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites>; <http://www.cir-safety.org/supplementaldoc/cir-report-format-outline>). Unpublished data are provided by the cosmetics industry, as well as by other interested parties. Although an extensive search was conducted of the literature published since the original review, no new data were found.

CHEMISTRY

Definition and Structure

All of the ingredients in this report, including the two proposed add-ons, are dialkyl dimer dilinoleates. Each ingredient is the diester formed from the reaction of straight-chained or branched alkyl alcohols and dilinoleic acid. Dilinoleic acid, in turn, is the result of the catalytic dimerization of linoleic acid. This resultant dimer is a mixture of acyclic, monocyclic, and bicyclic compounds (Figure 1). Even these examples serve only as idealized structures, as the degree of unsaturation in each case is variable.³

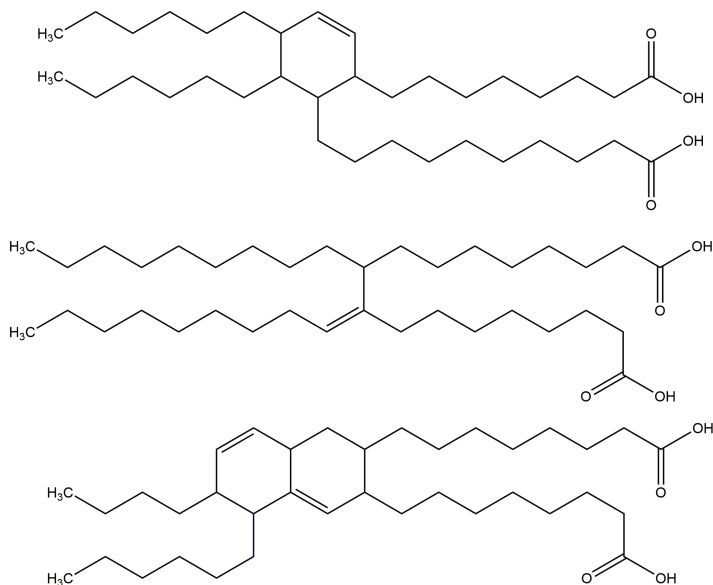


Figure 1. Examples of dilinoleic acid structures.

Esterification of this mixture of acids, then results in a mixture of esters, the dialkyl dimer dilinoleates (Figure 2.)

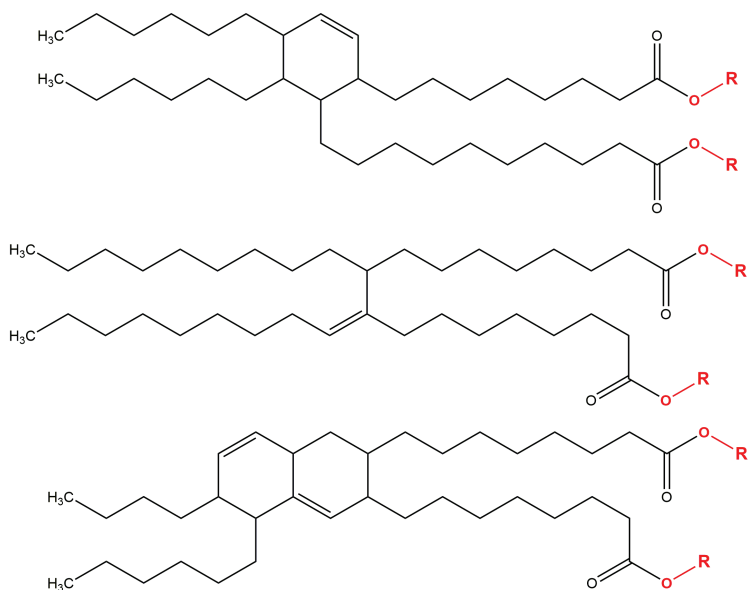


Figure 2. Examples of dialkyl dimer dilinoleates wherein O-R represents the alcohol residue.

For example, Diisopropyl Dimer Dilinoleate is the mixture of esters wherein O-R (Figure 2) is the residue of isopropyl alcohol (Figure 3).

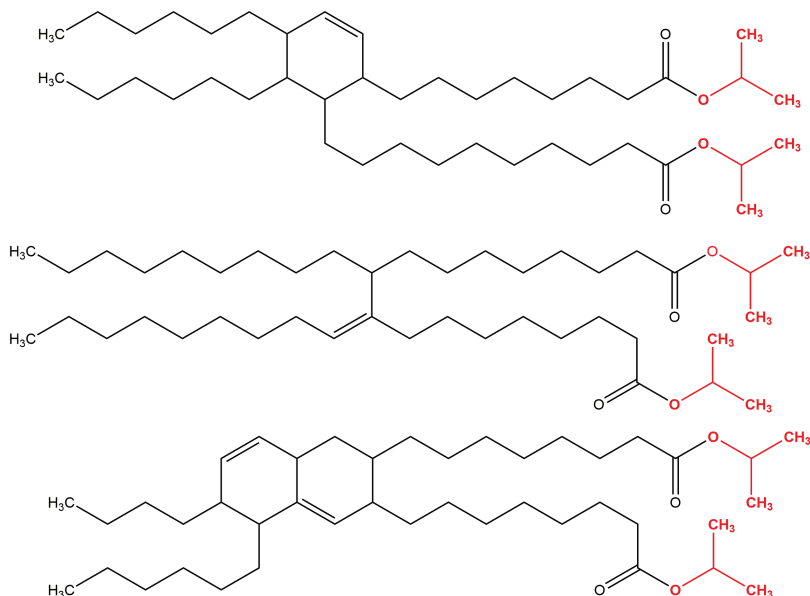


Figure 3. Diisopropyl Dimer Dilinoleate is the esterification product with isopropanol.

Physical and Chemical Properties

All ingredients are the diesters of their respective alcohols and dilinoleic acid.² Physical and chemical properties of Diisopropyl Dimer Dilinoleates are described in Table 4.

Method of Manufacture

The reviewed dialkyl dimer dilinoleates are manufactured by an esterification process using their respective alcohols and dilinoleic acid.¹

Impurities

Diisopropyl Dimer Dilinoleate

For Diisopropyl Dimer Dilinoleate, impurities were recorded as <.01% isopropyl alcohol and <0.5% dilinoleic acid (test method unavailable).¹

Diisostearyl Dimer Dilinoleate

Impurities of Diisostearyl Dimer Dilinoleate were <1% isostearyl alcohol and <0.5% dilinoleic acid.¹

Dicetearyl Dimer Dilinoleate

Impurities of Dicetearyl Dimer Dilinoleate were anticipated to be 0.1%-5.0% dilinoleic acid and cetearyl alcohol.¹

Dioctyldodecyl Dimer Dilinoleate

Dioctyldodecyl Dimer Dilinoleate impurities were anticipated to be 0.1%-5.0% dilinoleic acid and octyldodecanol.¹

Ultraviolet Absorption

Dicetearyl Dimer Dilinoleate

Dicetearyl Dimer Dilinoleate, 1% in 99% hexane, did not absorb in the ultraviolet A (UVA) or UVB range.¹ An absorbance peak of approximately 3.5 was observed at a wavelength of approximately 230 nm. A second peak was observed at approximately 270 nm, with an absorbance of approximately 0.7.

Dioctyldodecyl Dimer Dilinoleate

Dioctyldodecyl Dimer Dilinoleate, 10% in 90% hexane, did not absorb in the UVA or UVB range.¹ An absorbance peak of approximately 4.9 was observed at approximately 230 nm. A second peak was observed at approximately 270 nm, with an absorbance of approximately 4.2.

USE

Cosmetic

The safety of the cosmetic ingredients addressed in this assessment is evaluated based on data received from the Food and Drug Administration (FDA) and the cosmetics industry on the expected use of these ingredients in cosmetics. Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in the FDA Voluntary Cosmetic Registration Program (VCRP) database. Use concentration data are submitted by the cosmetic industry in response to a survey, conducted by the Personal Care Products Council (Council), of maximum reported use concentrations by product category.

Based on 2018 VCRP data, 2 out of the 8 ingredients included in this safety assessment are currently in use.⁴ The most frequently used ingredient according to 2018 VCRP data, Diisopropyl Dimer Dilinoleate, is reported to be used in 145 formulations. The majority of these uses are in leave-on formulations, primarily lipsticks (87 uses) and eye shadows (11 uses; Table 5). Diisostearyl Dimer Dilinoleate is reported to be used in 20 formulations, 19 of which are in leave-on products. A concentration of use survey is currently being conducted, and those data will be added once received; therefore it is not apparent whether concentration of use has changed.

The above ingredients, as well as Dicetearyl Dimer Dilinoleate and Diethylhexyl Dimer Dilinoleate, were previously recorded to be in use. According to 1998 VCRP data, Diisopropyl Dimer Dilinoleate had the greatest frequency of use, with 35 total formulations.¹ Of these formulations, 30 were leave-on products, and 5 were rinse-off products. The majority of the uses were lipstick formulations, with concentrations as high as 53%, and in foundations with concentrations as high as 7%.

Both historical and current use data are provided in Table 5. The dialkyl dimer dilinoleates not in use, according to 2018 VCRP data, are listed in Table 6.

All of the ingredients named in this report were found in the Cosmetics Directive of the European Union. None of the ingredients named in this report are not restricted from use in any way under the rules governing cosmetic products in the European Union.⁵

Non-Cosmetic

Non-cosmetic uses of dialkyl dimer dilinoleates were not identified in the published literature.

TOXICOKINETIC STUDIES

No toxicokinetics studies were submitted in the original report, no new data was found in published literature, and unpublished data were not submitted.

Absorption, Distribution, Metabolism, and Excretion (ADME)

Dilinoleic acid, a component of each relevant ingredient, was studied. A 13-week rat feeding study suggested that dilinoleic acid, or its metabolite(s), is widely distributed through the body when ingested.¹

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Oral

Diisopropyl Dimer Dilinoleate

Groups of five male and five female albino rats were used. The acute oral LD₅₀ of Diisopropyl Dimer Dilinoleate was > 5.0 g/kg.¹ The “limits of acute oral toxicity” of 50% of a lip gloss and a lipstick formulation, both containing 10% Diisopropyl Dimer Dilinoleate, in corn oil was > 15.9 g/kg.

Diisostearyl Dimer Dilinoleate

The LD₅₀ of Diisostearyl Dimer Dilinoleate was > 5.0 g/kg when testing groups of five male and five female albino rats.¹ A similar study suggested an oral LD₅₀ of > 5.0 ml/kg.

Diocetyldodecyl Dimer Dilinoleate

Five male and five female rats were doses with 5 g/kg Diocetyldodecyl Dimer Dilinoleate.¹ None of the animals died. The oral LD₅₀ for the rats was > 5.0 g/kg.

Dermal

Diocetyldodecyl Dimer Dilinoleate

Rats were used in an acute dermal toxicity test.¹ Test substance was applied to the dorsal area and trunk at concentrations of 5 g/kg bw. No gross tissue or organ abnormalities were found. The acute dermal LD₅₀ for Diocetyldodecyl Dimer Dilinoleate was determined to be > 5 g/kg.

Subchronic Toxicity

Dilinoleic Acid

In a 13-week study, rats were given a maximum of 5% (w/w) dilinoleic acid.¹ A no-observable-adverse-effect level (NOAEL) was not found because of macrophage aggregation seen in the mesenteric lymph node at the lowest dose level (0.1%).

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

No developmental/reproductive toxicity studies were submitted in the original report, no new data was found in published literature, and unpublished data were not submitted.

GENOTOXICITY

Genotoxicity studies were not found in the published literature, and unpublished data were not submitted. However, data were included in the original safety assessment on dilinoleic acid.

An Ames test using Salmonella typhimurium strains TA 1535, TA 1537, TA 100, and TA 98 to test the genotoxicity of dilinoleic acid yielded negative results.¹ Chromosome aberrations were studied in human lymphocytes with and without metabolic concentration at a maximum concentration of 300 µg/ml. No clastogenic effects were reported. Forward mutations were studied in mouse L5178Y lymphoma cells with and without metabolic treatment. Dilinoleic acid was considered negative in the mouse lymphoma cell assay.

CARCINOGENICITY STUDIES

Carcinogenicity studies were not found in the published literature, and unpublished data were not submitted.

OTHER RELEVANT STUDIES

Comedogenicity

Diisopropyl Dimer Dilinoleate

Rabbits were treated with 0.5 mL of a test article containing Diisopropyl Dimer Dilinoleate (concentration was not stated).¹ The researchers concluded that Diisopropyl Dimer Dilinoleate only caused very minor irritation and did not produce a comedogenic effect.

Diisostearyl Dimer Dilinoleate

Rabbits were treated with 0.5 mL of a test substance containing Diisostearyl Dimer Dilinoleate (concentration was not stated).¹ The researchers stated that Diisostearyl Dimer Dilinoleate caused only very minor irritation and was not comedogenic.

DERMAL IRRITATION AND SENSITIZATION

Irritation

Animal

Diisopropyl Dimer Dilinoleate

A dose of 0.5 mL Diisopropyl Dimer Dilinoleate was applied to 6 rabbits under an occlusive patch for 72 hours.¹ The primary irritation index (PII) was 0.10.

Dicetearyl Dimer Dilinoleate

The PII was 0.00 for New Zealand albino rabbits dosed with 0.5mL Dicetearyl Dimer Dilinoleate using the same procedure above.¹ Dicetearyl Dimer Dilinoleate was considered not to be a skin irritant.

Diisostearyl Dimer Dilinoleate

A 0.5 mL dose of Diisostearyl Dimer Dilinoleate led to a PII of 0.00 using the same procedure above.¹ In a separate study, 6 New Zealand White rabbits were exposed to 10% Diisostearyl Dimer Dilinoleate in corn oil. A dose of 0.5 mL was applied and scored at 24 hours and 72 hours after application. The PII was 0.75, and 10% w/w Diisostearyl Dimer Dilinoleate produced minimal irritation.¹

Diocetyldodecyl Dimer Dilinoleate

The PII was 0.00 for New Zealand rabbits dosed with 0.5 mL Diocetyldodecyl Dimer Dilinoleate applied dermally, and covered with an occlusive patch. Diocetyldodecyl Dimer Dilinoleate was not a primary skin irritant.¹

Human

Diisopropyl Dimer Dilinoleate

Multiple studies were performed involving lip products that contained Diisopropyl Dimer Dilinoleate at a maximum concentration of 18%.¹ Three of the subjects with sensitive skin reported “a mild burning of the lips” and two reported “mild to moderate tautness of the lips;” the reactions were mild in intensity and transient in nature.

A moisturizer formulating containing 5% Diisopropyl Dimer Dilinoleate was not a dermal irritant.¹ The authors also concluded that makeup-formulations containing 2% Diisopropyl Dimer Dilinoleate were not acnegenic, comedogenic, or irritating.

Diisostearyl Dimer Dilinoleate

Twenty subjects underwent a single-insult occlusive patch test (SIOPT) to test a concealer containing 10% Diisostearyl Dimer Dilinoleate.¹ The concealer, which was applied undiluted, had a PII of 0.084/4. In a different study, a 10% Diisostearyl Dimer Dilinoleate concealer was used for 5 days among 22 females, 15 of whom were lactic acid sensitive. Two subjects reported mild clinical changes, and one subject reported slight stinging.

Sensitization

Human

Diisopropyl Dimer Dilinoleate

A human repeat-insult patch test (HRIPT) was conducted using occlusive patches on 154 subjects to determine the sensitization potential of lipstick formulations containing 10%, 18% or 27% Diisopropyl Dimer Dilinoleate.¹ One subject had a single 1+ response upon challenge [at the 10% concentration,], but overall, allergic responses were not observed. No reactions were recorded for the 27% or 18% group upon challenge.

A study testing a liquid makeup formulation was performed using 0.1 mL of test substance containing Diisopropyl Dimer Dilinoleate, according to the same procedures above.¹ Of the 76 subjects completing this study, 16 had scores of 1 (mild reaction—faint/definitely pink) and two had scores of 1 and 2 (moderate reaction—definite redness) during inductions. Reactions were not observed upon challenge. In a modified Draize assay of a make-up formulation containing 3.5% Diisopropyl Dimer Dilinoleate, adverse reactions were not reported and the test substance was not a significant skin irritant or sensitizer.

Dicetearyl Dimer Dilinoleate

A test substance (0.1 g or ml) containing Dicetearyl Dimer Dilinoleate was applied to the back under an occlusive patch (3 days/week for 3 weeks) in an HRIPT study involving 60 subjects.¹ After 10-14 days of no treatment, a challenge patch was applied to a previously unexposed area. Adverse reactions were not noted during the induction or challenge phase.

Diisostearyl Dimer Dilinoleate

The sensitization potential of an undereye concealer containing 10% Diisostearyl Dimer Dilinoleate was evaluated in a maximization test.¹ A sensitization reaction was not observed at the 48- or 72-h readings.

Diocetyldodecyl Dimer Dilinoleate

An HRIPT was completed in 60 subjects with occlusive patches of a test material containing Dioctyldodecyl Dimer Dilinoleate (0.2 g or ml).¹ Adverse reactions were not noted during the induction or challenge phases.

Photosensitization/Phototoxicity

Diisopropyl Dimer Dilinoleate

Cosmetic formulation containing 2-27% Diisopropyl Dimer Dilinoleate were not photosensitizers.¹

Diisostearyl Dimer Dilinoleate

In a phototoxicity study, it was concluded that a concealer containing 10% Diisostearyl Dimer Dilinoleate had no photocontact-sensitizing potential.¹

OCULAR IRRITATION STUDIES

Diisopropyl Dimer Dilinoleate

Six rabbits had 0.1 mL of a test substance containing Diisopropyl Dimer Dilinoleate placed into the conjunctival sac of one eye.¹ Observations were made for seven days. No signs of irritation occurred.

A lip gloss and lipstick formulation containing 10% Diisopropyl Dimer Dilinoleate were placed into the conjunctival sac of rabbit eyes.¹ The lip gloss caused a maximum 1-h score of 4 for the conjunctivae, and the eyes were normal after one day. The lipstick caused a 1-h score of 2, and the eyes were normal after 3 days.

Dicetearyl Dimer Dilinoleate

In a Draize test conducted using six New Zealand white rabbits, Dicetearyl Dimer Dilinoleate (concentration not specified) had a maximum mean total score (MMTS) of 0.00.¹

Diisostearyl Dimer Dilinoleate

The ocular irritation potential of Diisostearyl Dimer Dilinoleate (concentration not specified) was determined in a Draize test; the test substance did not cause irritation to rabbit eyes.¹ In a similar study, 0.1 mL of 10% w/w Diisostearyl Dimer Dilinoleate in corn oil was applied to the conjunctival sac of 6 New Zealand white rabbits. No irritation was observed.

Dioctyldodecyl Dimer Dilinoleate

One-tenth mL of Dioctyldodecyl Dimer Dilinoleate (concentration not specified) was placed in the conjunctival sac of 6 rabbits.¹ The MMTS was 0.00, and Dioctyldodecyl Dimer Dilinoleate was nonirritating.

SUMMARY

In 2003, the Panel published a safety assessment with the conclusion that 6 dialkyl dimer dilinoleates were safe as used. This assessment is a re-review of those original ingredients, as well as 2 additional dialkyl dimer dilinoleates. All ingredients reviewed are diesters of their respective alcohols and dilinoleic acid. Each ingredient functions as a skin conditioning agent, however, Di-C20-40 Alkyl Dimer Dilinoleate also functions as a viscosity increasing agent.

Two of the 8 ingredients included in this safety assessment are currently in use. Diisopropyl Dimer Dilinoleate has the highest frequency of use, with 145 total uses; the majority of these uses are in leave-on formulations, primarily in lipsticks (87 uses). Diisostearyl Dimer Dilinoleate has 20 reported uses. In the original safety assessment, the maximum concentration of use of Diisopropyl Dimer Dilinoleate was 53% in lipsticks, and the maximum concentration of use for Diisostearyl Dimer Dilinoleate was 12% in lipsticks. Current maximum concentrations of use for these ingredients will be forthcoming. A concentration of use survey is in progress, and these data will be included once the survey is complete. No new studies regarding toxicity were found in the published literature.

DISCUSSION FROM ORIGINAL SAFETY ASSESSMENT¹

The CIR Expert Panel issued a safety assessment of these ingredients in September, 1997, with the conclusion that the available data were insufficient to support the safety of use of these ingredients in cosmetic formulations. Noting that

these additional data are likely not needed if these ingredients do not penetrate the skin; the Panel identified the following data needs:

- 1. 28-day dermal toxicity data; if significantly absorbed, developmental toxicity data are needed; and*
- 2. two genotoxicity studies, one using a mammalian system; if positive, a 2-year dermal carcinogenicity assay performed using the National Toxicology Program methods is needed.*

Since that time, additional data were received on ingredients considered in this report and on dilinoleic acid. These latter data were considered relevant to the safety assessment of the dilinoleic acids. The Panel considered that the results of the Ames testing and the genotoxicity assays in mammalian systems did not demonstrate any mutagenic potential of dilinoleic acid. These data, combined with the absence of structural alerts to suggest a mutagenic or carcinogenic risk, support the safety of these ingredients. The potential skin penetration of these ingredients was evaluated using an estimate of the octanol/water partition coefficient based on the structure of Diisopropyl Dimer Dilinoleate. The result of this analysis was a log P value of over 17. Although it is unrealistic to expect that an actual experimental determination of log P would yield a value this high, the recognized insolubility of these dilinoleic acids in water and their lipophilic nature is consistent with the findings of the C_{logP} software. As a result, the Panel does not believe there would be any significant skin penetration of these ingredients, and, therefore, no risk of reproductive, developmental, or other systemic toxicity. This finding is consistent with the results of the acute dermal toxicity tests, which found no signs of overt toxicity, adverse pharmacologic effects, abnormal behavior, or organ/tissue damage. The Panel did note that the concentration of use of Diisopropyl Dimer Dilinoleate was reportedly as high as 53% in lipsticks, but that the highest concentration tested for irritation/sensitization is 27%. Given the size of these molecules, their relative insolubility in water, their lipophilic nature, and the absence of any significant case reports of allergic reactions, a use concentration of 53% is not likely to be associated with any adverse effects.

TABLES**Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment²**

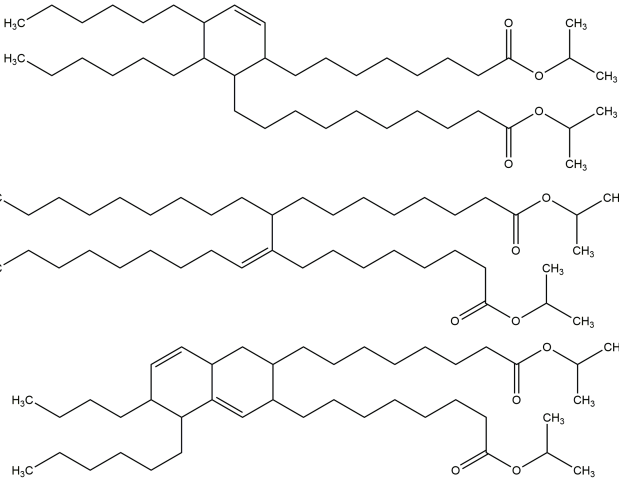
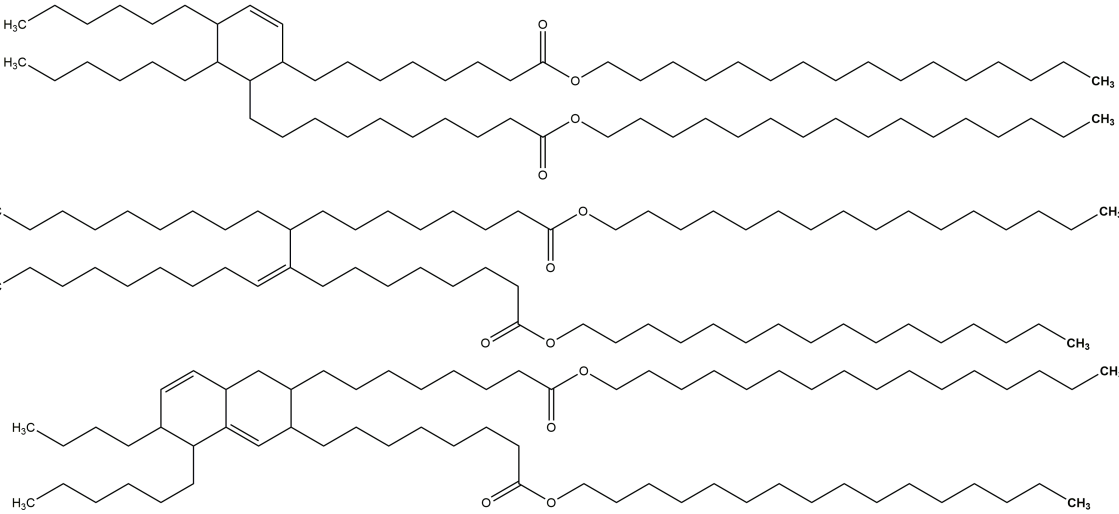
Name & CAS No.	Definition & Structure	Function(s)
Original Dialkyl Dimer Dilinoleates Diisopropyl Dimer Dilinoleate 205393-95-9	the diester of isopropyl alcohol and dilinoleic acid 	skin-conditioning agent – emollient
Dicetearyl Dimer Dilinoleate 135620-20-1	the diester of cetearyl alcohol and dilinoleic acid 	skin-conditioning agent— occlusive

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment²

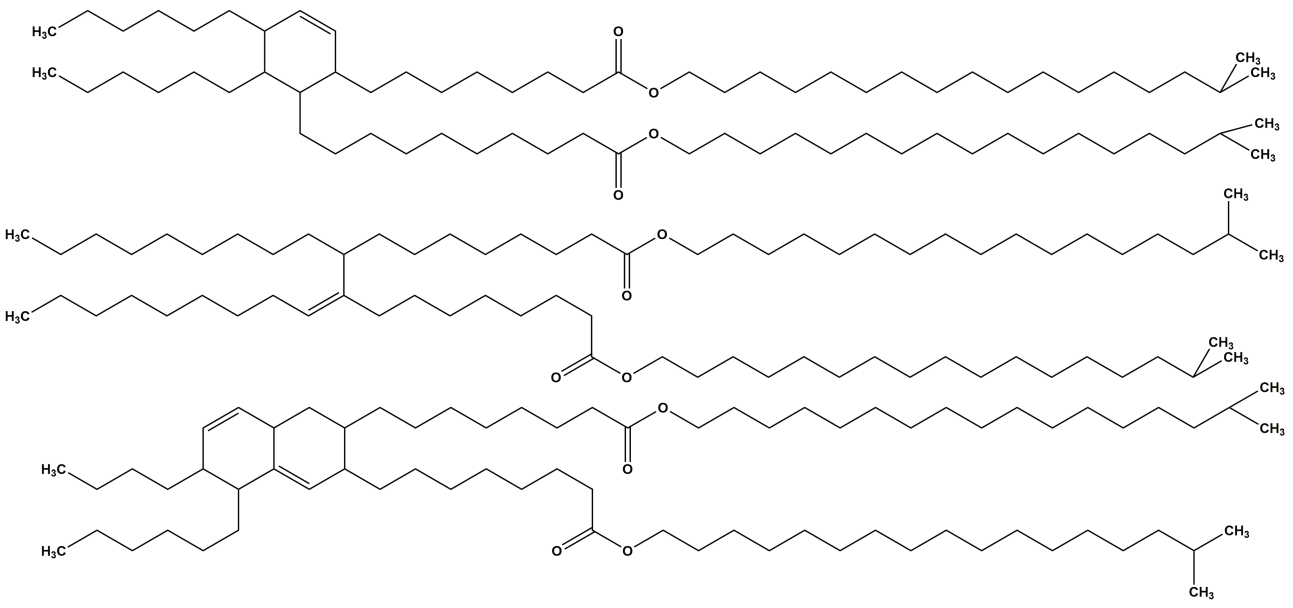
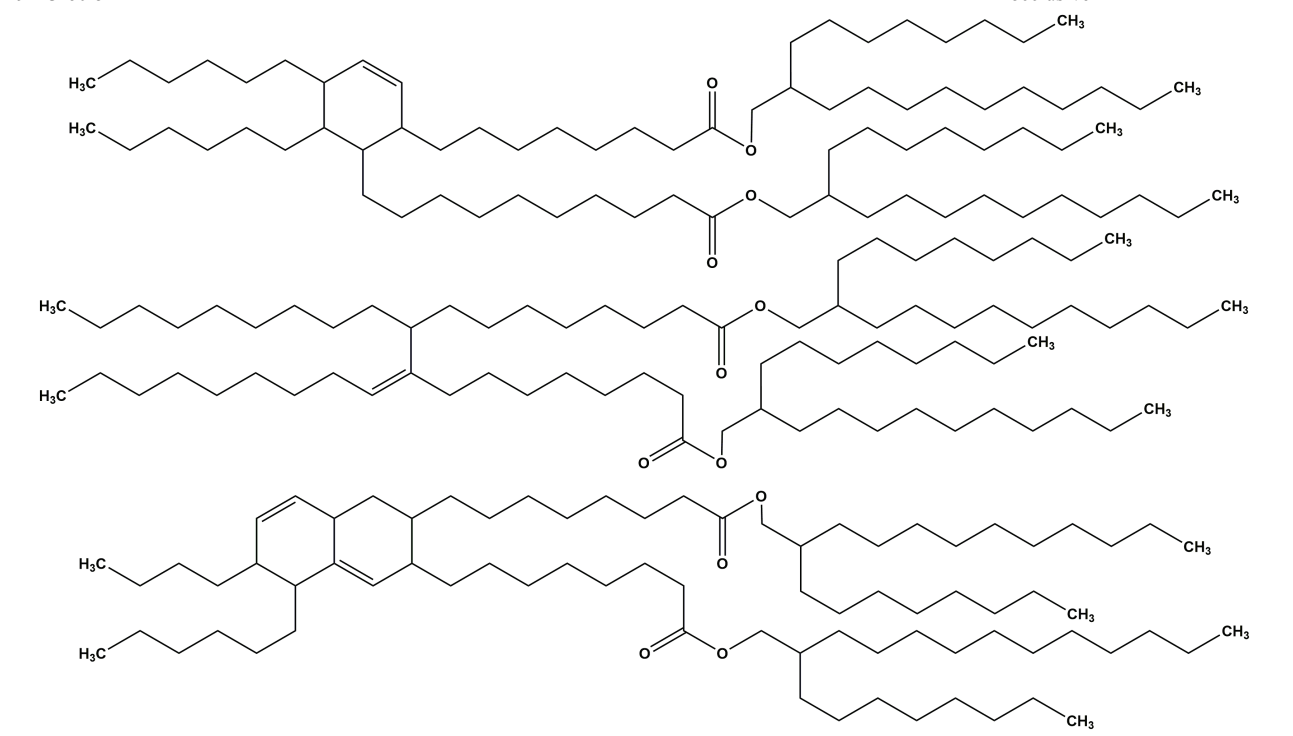
Name & CAS No.	Definition & Structure	Function(s)
Diisostearyl Dimer Dilinoleate 103213-19-0	the diester of isostearyl alcohol and dilinoleic acid	skin-conditioning agent-- occlusive
		
Dioctyldecyl Dimer Dilinoleate 129423-60-5	the diester of octyldecanol and dilinoleic acid	skin-conditioning agent-- occlusive
		

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment²

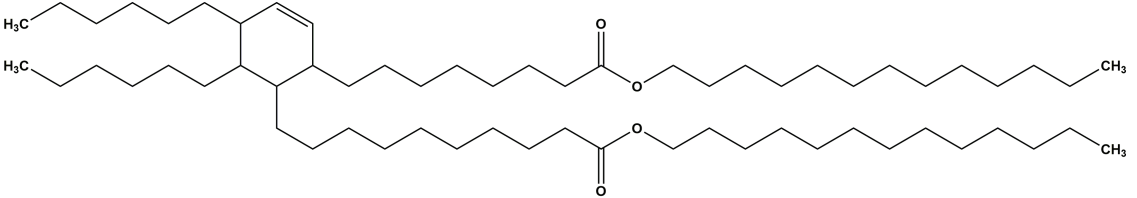
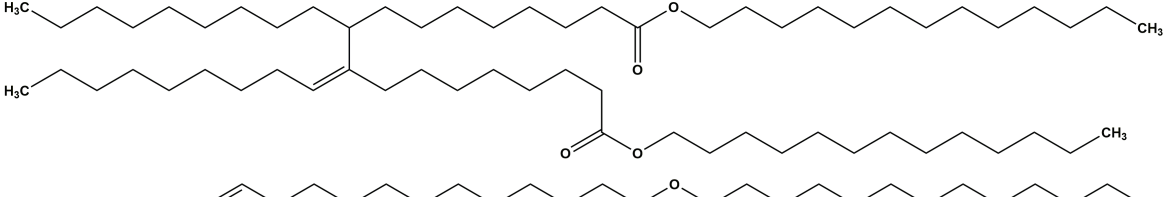
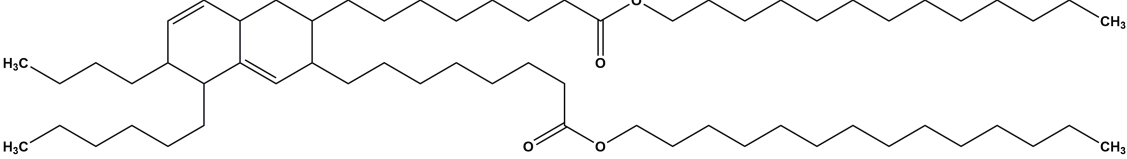
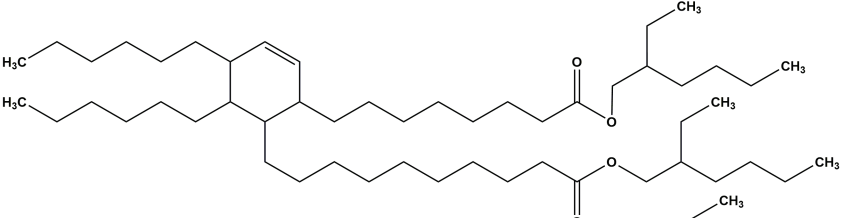
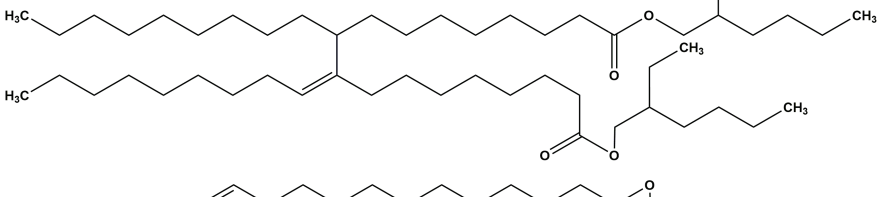
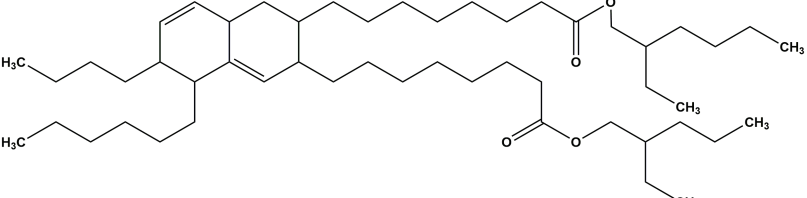
Name & CAS No.	Definition & Structure	Function(s)
Ditridecyl Dimer Dilinoleate	the diester of tridecyl alcohol and dilinoleic acid	skin-conditioning agent—occlusive
		
		
		
Diethylhexyl Dimer Dilinoleate	the diester of 2-ethylhexyl alcohol and dilinoleic acid	skin-conditioning agent—occlusive
		
		
		

Table 1. Definitions, idealized structures, and functions of the ingredients in this safety assessment²

Name & CAS No.	Definition & Structure	Function(s)
ADD-ONS		
Di-C16-18 Alkyl Dimer Dilinoleate [501901-81-1]	the diester of C16-18 alcohols and dilinoleic acid	skin-conditioning agent-- occlusive
Di-C20-40 Alkyl Dimer Dilinoleate	the diester of C20-40 alcohols and dilinoleic acid	skin-conditioning agent— occlusive/viscosity increasing agent—nonaqueous

Table 2. Alcohols of Relevant Dialkyl Dimer Dilinoleates reviewed by CIR

Ingredient	Alcohol	Conclusion	Reference
Diisopropyl Dimer Dilinoleate	Isopropyl Alcohol	Safe as used	2012 ⁶
Diceteryl Dimer Dilinoleate	Ceteryl Alcohol	Safe as used; this conclusion was reaffirmed in 2008	1988 ⁷ ; 2008 ⁸
Diisostearyl Dimer Dilinoleate	Isostearyl Alcohol	Safe as used; this conclusion was reaffirmed in 2008	1988 ⁷ ; 2008 ⁸
Diocylododecyl Dimer Dilinoleate	Octyldodecanol	Safe as used; this conclusion was reaffirmed in 2006	1985 ⁹ ; 2006 ¹⁰

Table 3. Alcohols of Relevant Dialkyl Dimer Dilinoleates not yet reviewed by CIR

Ingredient	Alcohol
Diethylhexyl Dimer Dilinoleate	2-Ethylhexyl Alcohol
Tridecyl Dimer Dilinoleate	Tridecyl Alcohol
Di-C16-18 Alkyl Dimer Dilinoleate	C16-18 Alcohol
Di-C20-40 Alkyl Dimer Dilinoleate	C20-40 Alcohol

Table 4. Physical and chemical properties

Property	Description	Reference
Diisopropyl Dimer Dilinoleate		
physical characteristics	<i>non-oily, clear to slightly hazy yellow liquid with a mild, characteristic, fatty odor</i>	1
molecular weight (g/mol)	650	1
solubility	<i>Soluble in most organic solvents; insoluble in water and lower-molecular weight diols and triols</i>	1
boiling point (°C)	>200	1
freezing point (°C)	-11	1
refractive index (@ 25 °C)	1.4590-1.4650 1.4550-1.4655	1
specific gravity (@ 25 °C)	0.965 to 0.975	1
log P	17.79	1
Diisostearyl Dimer Dilinoleate		
physical characteristics	<i>clear to slightly hazy yellow liquid with a characteristic odor</i>	1
molecular weight (g/mol)	1078	1
solubility	<i>soluble in most organic solvents; insoluble in water and low-molecular-weight diols and triols</i>	1
freezing point (°C)	5	1
refractive index (@ 25 °C)	1.468-1.478	1
specific gravity (@ 25 °C)	0.895± 0.01	1
log P	32.44 (estimated)	11
Dicetearyl Dimer Dilinoleate		
physical characteristics	<i>yellow semi-solid with bland odor practically odorless buttery yellow solid</i>	1
molecular weight (g/mol)	1013.8	12
boiling point (°C)	500	1
solubility	<i>insoluble in water</i>	1
log P	30.62 (estimated)	11
moisture content	0.5%	1
microbial content	500 (opg) max; no pathogens	1
Dioctylododecyl Dimer Dilinoleate		
physical characteristics	<i>clear liquid with a bland odor</i>	1
molecular weight (g/mol)	1126.0	12
boiling point (°C)	450	1
solubility	<i>insoluble in water</i>	1
log P	34.40 (estimated)	11
specific gravity (@ 25°C)	1.15	1
moisture content	0.5%	1
Tridecyl Dimer Dilinoleate		
molecular weight (g/mol)	929.6	12
log P	27.67 (estimated)	11
Diethylhexyl Dimer Dilinoleate		
molecular weight (g/mol)	789.4	12
log P	22.62 (estimated)	11
ADD-ONS		
Di-C16-18 Alkyl Dimer Dilinoleate		
molecular weight (g/mol)	1014-1078	12
log P	30.62-32.44 (estimated)	11
Di-C20-40 Alkyl Dimer Dilinoleate		
molecular weight (g/mol)	1126.0-1687.1	12
log P	34.55-54.19 (estimated)	11

Table 5. Current and historical frequency and concentration of use of Dialkyl Dimer Dilinoleates according to duration and exposure

	# of Uses		Max Conc of Use (%)		# of Uses		Max Conc of Use (%)	
	Dicetearyl Dimer Dilinoleate				Diethylhexyl [Dioctyl] Dimer Dilinoleate			
	2018	1998	2018	1991 ¹	2018	1998 ¹	2018	1999 ¹
Totals*	NR	NR	**	7	NR	1	**	1-12
Duration of Use								
Leave-On	NR	NR	**	NR	NR	1	**	1-12
Rinse-Off	NR	NR	**	NR	NR	NR	**	NR
Diluted for (Bath) Use	NR	NR	**	NR	NR	NR	**	NR
Exposure Type								
Eye Area	NR	NR	**	NR	NR	NR	**	5-11
Incidental Ingestion	NR	NR	**	7	NR	NR	**	7-12
Incidental Inhalation-Spray	NR	NR	**	NR	NR	NR	**	NR
Incidental Inhalation-Powder	NR	NR	**	NR	NR	NR	**	1-7
Dermal Contact	NR	NR	**	NR	NR	1	**	1-11
Deodorant (underarm)	NR	NR	**	NR	NR	NR	**	NR
Hair - Non-Coloring	NR	NR	**	NR	NR	NR	**	NR
Hair-Coloring	NR	NR	**	NR	NR	NR	**	NR
Nail	NR	NR	**	NR	NR	NR	**	NR
Mucous Membrane	NR	NR	**	7	NR	NR	**	7-12
Baby Products	NR	NR	**	NR	NR	NR	**	NR
	Diisopropyl Dimer Dilinoleate				Diisostearyl Dimer Dilinoleate			
	2018 ⁴	1998 ¹	2018	1999 ¹	2018 ⁴	1998 ¹	2018	1999 ¹
Totals*	145	35	**	0.1-53	20	20	**	1-12
Duration of Use								
Leave-On	142	30	**	30	19	20	**	1-12
Rinse-Off	3	5	**	5	1	NR	**	NR
Diluted for (Bath) Use	NR	NR	**	NR	NR	NR	**	NR
Exposure Type								
Eye Area	12	2	**	0.1-3	7	11	**	5-11
Incidental Ingestion	87	12	**	4-53	5	2	**	7-12
Incidental Inhalation-Spray	13 ^a	4 ^a ; 4 ^b	**	9.25; 2-10 ^a ; 3-5 ^b	4 ^a	NR	**	NR
Incidental Inhalation-Powder	NR	4 ^b	**	3-5 ^b ; 30	NR	3	**	1-7
Dermal Contact	53	22	**	0.05-30	15	18	**	1-11
Deodorant (underarm)	NR	NR	**	20 ^a	NR	NR	**	NR
Hair - Non-Coloring	5	1	**	9.25-10	NR	NR	**	NR
Hair-Coloring	NR	NR	**	NR	NR	NR	**	NR
Nail	NR	NR	**	NR	NR	NR	**	NR
Mucous Membrane	88	12	**	4-53	6	2	**	7-12
Baby Products	NR	NR	**	NR	NR	NR	**	NR

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

^a Includes products that can be sprays, but it is not known whether the reported uses are sprays

^b Not specified whether this product is a spray or a powder or neither, but it is possible it may be a spray or a powder, so this information is captured for both categories of incidental inhalation

^c Includes products that can be powders, but it is not known whether the reported uses are powders

NR – no reported use

**The concentration of use survey for 2018 is currently in progress. This data will be added to the report once available.

Table 6. Dialkyl Dimer Dilinoleates not reported to be in use.

Ingredient
Diocylododecyl Dimer Dilinoleate
Diiridecyl Dimer Dilinoleate
Di-C16-18 Alkyl Dimer Dilinoleate
Di-C20-40 Alkyl Dimer Dilinoleate

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Final Report on the Amended Safety Assessment of Diisopropyl Dimer Dilinoleate, Dicetearyl Dimer Dilinoleate, Diisostearyl Dimer Dilinoleate, Dioctyl Dimer Dilinoleate, Dioctyldodecyl Dimer Dilinoleate, and Ditridecyl Dimer Dilinoleate¹

Diisopropyl Dimer Dilinoleate, Dicetearyl Dimer Dilinoleate, Diisostearyl Dimer Dilinoleate, Dioctyl Dimer Dilinoleate, Dioctyldodecyl Dimer Dilinoleate, and Ditridecyl Dimer Dilinoleate are diesters of their respective alcohols and dilinoleic acid. They function as skin-conditioning agents in a variety of cosmetic products at concentrations around 10%, but may be used at concentrations up to 53% in lipsticks. These ingredients do not absorb radiation in the ultraviolet (UV) UVA or UVB range and the only impurities expected are <0.5% dilinoleic acid, <0.1% isopropyl alcohol or <1% isostearyl alcohol, and/or small amounts of dilinoleic acid and cetearyl alcohol or octyldodecanol, depending on which diester is used. The potential skin penetration of these ingredients was evaluated using an estimate of the octanol/water partition coefficient ($\log P$ of 17.7) based on the structure of Diisopropyl Dimer Dilinoleate. This is consistent with the insolubility of these ingredients in water. Safety test data on dilinoleic acid (no adverse effects) were considered relevant because dilinoleic acid is a component of these diesters and a likely breakdown product. The acute oral and dermal LD₅₀ values for rats of Diisopropyl, Diisostearyl, and Dioctyldodecyl Dimer Dilinoleate were >5.0 g/kg. In a subchronic feeding study, macrophage aggregation was seen in the mesenteric lymph node at the lowest dose level (0.1% in the diet). These ingredients did not produce skin or ocular irritation in animal tests, nor were they comedogenic. Ames testing, clastogenesis in human lymphocytes in culture, and L5178Y mouse lymphoma cell forward mutations were all negative, indicating no dilinoleic acid genotoxicity. No carcinogenicity or reproductive/developmental toxicity data were available; however, structural alerts that would suggest a mutagenic or carcinogenic risk are absent. Significant reproductive/developmental toxicity or other systemic toxicity is not expected with these ingredients because they remain on the skin surface. In clinical studies, cosmetic formulations containing these ingredients did not produce skin irritation or sensitization, although one report of sensitization to dilinoleic acid appeared in the case literature. The Panel did note that the concentration of use of Diisopropyl Dimer Dilinoleate was reportedly as high as 53%

in lipsticks, but that the highest concentration tested for irritation/sensitization is 27%. Given the size of these molecules, their relative insolubility in water, their lipophilic nature, and the absence of any significant case reports of allergic reactions, a use concentration of 53% is not likely to be associated with any adverse effects. Accordingly, these diesters were considered safe as used in cosmetic products.

INTRODUCTION

Diisopropyl Dimer Dilinoleate, Dicetearyl Dimer Dilinoleate, Diisostearyl Dimer Dilinoleate, Dioctyl Dimer Dilinoleate, Dioctyldodecyl Dimer Dilinoleate, and Ditridecyl Dimer Dilinoleate are diesters of their respective alcohols (i.e., isopropyl, cetearyl, isostearyl, 2-ethylhexyl, octyldodecyl, and tridecyl, respectively) and dilinoleic acid (Pepe, Wenninger, and McEwen 2002). These ingredients function as skin conditioning agents.

In 1997, the Cosmetic Ingredient Review (CIR) Expert Panel concluded that the available data were insufficient to support the safety of these ingredients in cosmetic formulations. Since that time, additional data were provided on these ingredients and on dilinoleic acid, previously called dimer acid. The term dimer acid is used in several of the publications, but the correct current usage is dilinoleic acid and that terminology has been used in this safety assessment. Data on dilinoleic acid have been considered in reaching a new conclusion. This safety assessment also considers pertinent data from the safety assessments on **Isopropyl Linoleate** (Elder 1992), **Cetearyl and Isostearyl Alcohol** (Elder 1988), and **Octyl Dodecanol** (Elder 1985), which are included with data on the dimer dilinoleates. In these previous safety assessments, the Expert Panel had reached the conclusions that the data were insufficient to determine the safety of Isopropyl Linoleate (the additional data needed were irritation, sensitization, and genotoxicity data), that Cetearyl and Isostearyl Alcohol were safe as used (both at concentrations $\leq 25\%$), and that Octyl Dodecanol was safe as used (concentrations >50%).

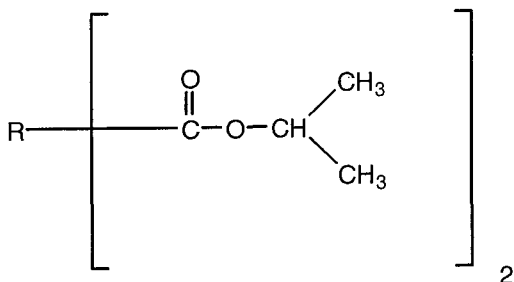
Received 24 March 2003; accepted 1 July 2003.

¹Reviewed by the Cosmetic Ingredient Review Expert Panel. This report was prepared by Monice Zondlo Fiume, former Scientific Analyst/Report Management Coordinator. Address correspondence to F. Alan Andersen, Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 310, Washington, DC 20036, USA.

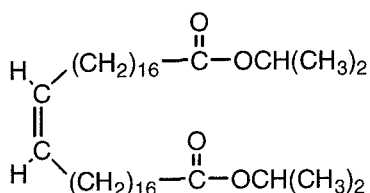
CHEMISTRY

Definition and Structure

Diisopropyl Dimer Dilinoleate (CAS no. 103213-20-3) is the diester of isopropyl alcohol and dilinoleic acid (q.v.) (Pepe, Wenninger, and McEwen 2002) and conforms to the following formula (Cosmetic, Toiletry, and Fragrance Association [CTFA] 1997) where R represents the dilinoleyl moiety:



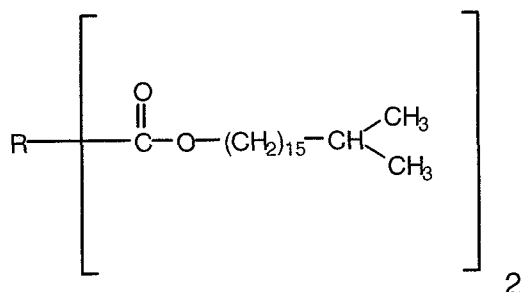
The structure may also be shown as (CTFA 1999a):



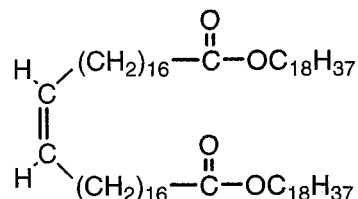
Diisopropyl Dimer Dilinoleate is also known as Diisopropyl Dilinoleate (CTFA 1996a); Diisopropyl Dimerate; Dilinoleic Acid, Diisopropyl Ester; Bis(1-Methylethyl)Dimerate; Dilinoleic Acid, Bis(1-Methylethyl) Ester (Pepe, Wenninger, and McEwen 2002); and Bis(2-Propanol) 9,12-Octadecadienoic Dilinoleic Acid (CTFA 1997).

Dicetearyl Dimer Dilinoleate (CAS number and structure unavailable) is the diester of cetearyl alcohol and dilinoleic acid (q.v.) (Pepe, Wenninger, and McEwen 2002) and has the empirical formula $C_{70}H_{132}O_4$ (Innovachem, Inc. 1996). Dicetearyl Dimer Dilinoleate is also known as Diketostearyl Dilinoleate (Brooks Industries Inc. 1996a).

Diisostearyl Dimer Dilinoleate (CAS no. 103213-19-0; Scher Chemicals, Inc. 1991; CTFA 1997) is the diester of isostearyl alcohol and dilinoleic acid (Pepe, Wenninger, and McEwen 2002) that conforms to the following structure, again where R represents the dilinoleyl moiety:



The structure also may be drawn as (CTFA 1999a):



Diisostearyl Dimer Dilinoleate is also known as Diisostearyl Dilinoleate (CTFA 1996a); Diisostearyl Dimerate; Dilinoleic Acid, Diisostearyl Ester (Pepe, Wenninger, and McEwen 2002); and Bis[16-Methyl-1-Heptadecanol]9,12-Octadecadienoic Dilinoleic Acid Ester (Scher Chemicals, Inc. 1991; CTFA 1997).

Diocetyl Dimer Dilinoleate (CAS number and structure unavailable) is the diester of 2-ethylhexyl alcohol and dilinoleic acid (q.v.) and has the empirical formula $C_{52}H_{96}O_4$ (Pepe, Wenninger, and McEwen 2002). Diocetyl Dimer Dilinoleate is also known as Diocetyl Dilinoleate (CTFA 1996a); Diocetyl Dimerate; Bis(2-Ethylhexyl)Dimerate; and Dilinoleic Acid, 2-Ethylhexyl Ester (Pepe, Wenninger, and McEwen 2002).

Diocetyldodecyl Dimer Dilinoleate (CAS no. 129423-60-5) is the diester of octyldodecanol and dilinoleic acid (q.v.) and has the empirical formula $C_{76}H_{144}O_4$. A structure was not available. Diocetyldodecyl Dimer Dilinoleate is also known as Di-2-Octyldodecyl Dimerate; 9,12-Octadecadienoic Acid, 2-Octyldodecyl Ester, Dimer; and 2-Octyldodecyl 9,12-Octadecadienoate Dimer (Pepe, Wenninger, and McEwen 2002).

Ditridecyl Dimer Dilinoleate (CAS number and structure unavailable) is the diester of tridecyl alcohol (q.v.) and dilinoleic acid (q.v.) and has the empirical formula $C_{62}H_{116}O_4$. Ditridecyl Dimer Dilinoleate is also known as Ditridecyl Dimerate; Dilinoleic Acid, Ditridecyl Ester; and Dilinoleic Acid, Ditridecyl Ester (Pepe, Wenninger, and McEwen 2002).

Physical and Chemical Properties

The physical and chemical properties of Diisopropyl, Diisostearyl, Dicetearyl, and Diocetyldodecyl Dimer Dilinoleate are described in Table 1.

Manufacture and Production

Diisopropyl Dimer Dilinoleate is manufactured by an esterification process using isopropyl alcohol and dilinoleic acid (CTFA 1997). Acid catalysts are used in the reaction and then neutralized and removed.

Dicetearyl Dimer Dilinoleate is prepared by direct esterification of one mole of dilinoleic acid with two moles of cetearyl alcohol (Innovachem, Inc. 1996).

Diisostearyl Dimer Dilinoleate is manufactured by an esterification process using isostearyl alcohol and dilinoleic acid (CTFA 1997). Acid catalysts are used in the reaction and then neutralized and removed.

TABLE 1
Physical and chemical properties

Properties	Description	Reference
Diisopropyl Dimer Dilinoleate		
Physical characteristics	Non-oily, clear to slightly hazy yellow liquid with a mild, characteristic, fatty odor	Nikitakis and McEwen 1990
	Clear to slightly hazy liquid with a slight odor	Scher Chemicals, Inc. 1996a
Molecular weight	650	Scher Chemicals, Inc. 1996a
% free fatty acid as Dilinoleic Acid	1.5	Scher Chemicals, Inc. 1996a
Boiling point	>200°C	Scher Chemicals, Inc. 1996b
Freezing point	-11.0°C (max)	Scher Chemicals, Inc. 1996a
Solubility	Soluble in most organic solvents; insoluble in water and lower-molecular-weight diols and triols	Nikitakis and McEwen 1990; Scher Chemicals, Inc. 1996a
Octanol/water partition coefficient calculation	Calculated log P value of 17.790	CTFA, 1999a
Refractive index (25°C)	1.4590-1.4650 1.4550-1.4655	Nikitakis and McEwen 1990 Scher Chemicals, Inc. 1996a
Specific gravity (25°C)	0.890-0.910	Nikitakis and McEwen 1990; Scher Chemicals, Inc. 1996a
Acid value	3.0 (max)	Nikitakis and McEwen 1990; Scher Chemicals, Inc. 1996a
Flash point, open cup	>170°C	Scher Chemicals, Inc. 1996a
Saponification value	160-180 160-185	Nikitakis and McEwen 1990 Scher Chemicals, Inc. 1996a
Iodine value	15.0 (max)	Nikitakis and McEwen 1990; Scher Chemicals, Inc. 1996a
Diisostearyl Dimer Dilinoleate		
Physical characteristics	Clear to slightly hazy yellow liquid with a characteristic odor	Scher Chemicals, Inc. 1991
Molecular weight	1078	Scher Chemicals, Inc. 1991
Ester content	96%	Scher Chemicals, Inc. 1991
Freezing point	5.0°C max	Scher Chemicals, Inc. 1991
Solubility	Soluble in most organic solvents; insoluble in water and low-molecular-weight diols and triols	Scher Chemicals, Inc. 1991
Refractive index (25°C)	1.468-1.478	Scher Chemicals, Inc. 1991
Specific gravity (25°C)	0.895 ± 0.01	Scher Chemicals, Inc. 1991
Acid value	5.0 (max)	Scher Chemicals, Inc. 1991
Flash point, open cup	170°C (max)	Scher Chemicals, Inc. 1991
Saponification value	90-110	Scher Chemicals, Inc. 1991
Iodine value	15 (max)	Scher Chemicals, Inc. 1991
Dicetearyl Dimer Dilinoleate		
Physical characteristics	Yellow semi-solid with a bland odor Practically odorless buttery yellow solid	Brooks Industries Inc. 1996a Brooks Industries Inc. 1996b
Boiling point	932°F	Brooks Industries Inc. 1996a
Solubility	Insoluble in water	Brooks Industries Inc. 1996a
Specific gravity	0.95	Brooks Industries Inc. 1996a
Acid value	5.0 (max)	Brooks Industries Inc. 1996b
Flash point, open cup	500°F	Brooks Industries Inc. 1996a
Saponification value	85-125	Brooks Industries Inc. 1996b
Moisture content	0.5%	Brooks Industries Inc. 1996b
Microbial content	500 opg max; no pathogens	Brooks Industries Inc. 1996b

(Continued on next page)

TABLE 1
Physical and chemical properties (*Continued*)

Properties	Description	Reference
Diocetyldodecyl Dimer Dilinoleate		
Physical characteristics	Clear liquid with a bland odor	Brooks Industries Inc. 1996c
Boiling point	842°F	Brooks Industries Inc. 1996c
Solubility	Insoluble in water	Brooks Industries Inc. 1996c
Specific gravity	1.15	Brooks Industries Inc. 1996c
Acid value	5.0 (max)	Brooks Industries Inc. 1996d
Flash point, open cup	500°F	Brooks Industries Inc. 1996c
Saponification value	90–110	Brooks Industries Inc. 1996d
Moisture content	0.5%	Brooks Industries Inc. 1996d

Diocetyldodecyl Dimer Dilinoleate is prepared by direct esterification of one mole of dilinoleic acid with two moles of octyldodecanol (Innovachem, Inc. 1996).

Analytical Method

Published data on analytical methods used to determine the ingredients included in this review were not found. Relevant information on related chemicals from previous safety assessments was available and is provided below.

Isopropyl Linoleate has been analyzed via infrared spectroscopy and gas chromatography (Elder 1992).

Cetearyl and Isostearyl Alcohol are fatty alcohols that have been identified using gas-liquid chromatography (GLC), liquid chromatography, thin-layer chromatography (TLC), gas chromatography (GC), and mass spectrometry (Elder 1988).

Octyl Dodecanol is a fatty alcohol that also has been identified using GLC, TLC, differential scanning calorimetry, and GC (Elder 1985).

Ultraviolet Absorbance

Dicetearyl Dimer Dilinoleate, 1% in 99% hexane, did not absorb in the ultraviolet A (UVA) or UVB range (CTFA 1996b). An absorbance peak of approximately 3.5 was observed at a wavelength of approximately 230 nm. A second peak was observed at approximately 270 nm, with an absorbance of approximately 0.7.

Diocetyldodecyl Dimer Dilinoleate, 10% in 90% hexane, did not absorb in the UVA or UVB range (CTFA 1996b). An absorbance peak of approximately 4.9 was observed at approximately 230 nm. A second peak was observed at approximately 266 nm, with an absorbance of approximately 4.2.

Impurities

Diisopropyl Dimer Dilinoleate impurities are <0.1% isopropyl alcohol and <0.5% dilinoleic acid (CTFA 1997).

Dicetearyl Dimer Dilinoleate impurities were anticipated to be small amounts (0.1% to 5.0%) of dilinoleic acid and cetearyl alcohol (Innovachem, Inc. 1996).

Diisostearyl Dimer Dilinoleate impurities are <1% isostearyl alcohol and <0.5% dilinoleic acid (CTFA 1997).

Diocetyldodecyl Dimer Dilinoleate impurities were anticipated to be small amounts (0.1% to 5.0%) of dilinoleic acid and octyldodecanol (Innovachem, Inc. 1996).

USE

Cosmetic

Diisopropyl Dimer Dilinoleate is reported to function as a skin-conditioning agent—emollient and Dicetearyl Dimer Dilinoleate, Diisostearyl Dimer Dilinoleate, Dioctyl Dimer Dilinoleate, Diocetyldodecyl Dimer Dilinoleate, and Ditridecyl Dimer Dilinoleate are reported to function as skin-conditioning agents—occlusive (Pepe, Wenninger, and McEwen 2002).

Information on use of ingredients in cosmetic formulations is available from the Food and Drug Administration (FDA) as part of a voluntary industry reporting program (FDA 1998) as follows: 35 cosmetic formulations, Diisostearyl Dimer Dilinoleate was used in 20 cosmetic formulations, and Dioctyl Dimer Dilinoleate was used in 1 cosmetic formulation.

The specific product types in which these ingredients are used are presented in the first two columns of Table 2. The number in parentheses in the first column represents how many of this type of product were reported to FDA (e.g., 501 eye shadow products) and the second column tells how many of those products contained the ingredient in question. Thus, of 501 eye shadow products, 1 contained Diisopropyl Dimer Dilinoleate.

Dicetearyl Dimer Dilinoleate, Diocetyldodecyl Dimer Dilinoleate, and Ditridecyl Dimer Dilinoleate were not reported to be used in 1998.

In addition, industry provides information directly to CIR on the current concentration of use (CTFA 1999b). In some cases, a current concentration of use is provided even when there is no current use reported to FDA. It should be presumed that an industry report of a current concentration of use means the ingredient is in use. These data are included in the third column of Table 2. Brooks Industries (1996e) reported that Dicetearyl and Diocetyldodecyl Dimer Dilinoleate are used in commercial

TABLE 2
Frequency of use and concentration of use of cosmetic ingredients as a function of product category

Product category (Number of formulations reported to FDA 1998) ^a	Number of formulations containing ingredient (FDA 1998) ^a	Current concentration of use (CTFA 1999b) ^b (%)	Historical concentration of use (FDA 1984) ^a (%)
Diisopropyl Dimer Dilinoleate			
Eye lotion (18)	—	0.1–0.3	—
Eye shadow (501)	1	3	—
Mascara (167)	—	2	—
Other eye makeup preparations (116)	1	—	—
Hair spray (261)	—	9.25	—
Tonics, dressings, and other hair-grooming aids (512)	1	10	—
Blushers (all types) (229)	1	0.5–19	—
Face powders (250)	—	30	—
Foundations (283)	4	3–7	—
Lipstick (758)	12	4–53	1–10
Makeup bases (132)	—	3.5	0.1–1
Other makeup preparations (122)	1	11	—
Deodorants (underarm) (250)	—	20	—
Skin cleansing preparations (630)	5	0.1–5	>0–0.1
Face and neck preparations (excluding shaving preparations) (251)	2	5	0.1–1
Body and hand preparations (excluding shaving preparations) (776)	2	3	—
Moisturizing preparations (743)	1	2	>0–0.1
Night preparations (185)	2	2	—
Paste masks (mud packs) (255)	—	0.1	—
Other skin care preparations (683)	2	—	—
1997 total for Diisopropyl Dimer Dilinoleate	35	0.1–53	
Dicetearyl Dimer Dilinoleate			
Lipstick (758)	—	7	—
1997 total for Dicetearyl Dimer Dilinoleate	—	7	
Diisostearyl Dimer Dilinoleate			
Eye shadow (501)	8	5	—
Eyeliner (514)	—	7–11	—
Eye lotion (18)	1	10	—
Other eye makeup preparations (116)	2	10	—
Blushers (all types) (229)	1	—	—
Face powders (250)	—	7	—
Foundations (283)	2	10	—
Lipstick (758)	2	7–12	—
Other makeup preparations (122)	1	8.3	—
Body and hand preparations (excluding shaving preparations) (776)	3	1	—
1997 total for Diisostearyl Dimer Dilinoleate	20	1–12	
Diocetyl Dimer Dilinoleate			
Moisturizing preparations (743)	1	—	—
Lipstick (758)	—	12.1	—
1997 total for Diocetyl Dimer Dilinoleate	1	12.1	

^aInformation reported to FDA by those companies that participated in a voluntary reporting program.

^bInformation submitted to CTFA by companies in response to a request from the trade association.

formulations at concentrations of 1% to 10%, but no product category was indicated, so these data are not in Table 2.

In addition to the current concentration of use data described above, there may be historical data from 1984 when FDA collected information on concentration as part of the voluntary reporting program (FDA 1984). If available, these historical data are also included in Table 2.

According to the Ministry of Health, Labor and Welfare (MHLW) in Japan, Diisopropyl, Dicetearyl, Diisostearyl, Dioctyl, Dioctyldodecyl, and Ditridecyl Dimer Dilinoleate are not restricted in any manner in cosmetic formulations (MHLW 2001).

Diisopropyl, Dicetearyl, Diisostearyl, Dioctyl, Dioctyldodecyl, and Ditridecyl Dimer Dilinoleate are not listed 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 the restrictions and conditions laid down) of the Cosmetics Directive of the European Union (European Economic Community 1995).

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

Data from dermal penetration tests were not available. Nor were data available on their octanol/water partition coefficients. Software which calculates $\log P$, however, is available (Leo 1993) and was used to calculate the value for Diisopropyl Dimer Dilinoleate, the smallest molecular weight compound in the group (CTFA 1999a).

The particular software used was ClogP[®] supplied by BioByte Corporation (<http://www.biobyte.com>). The resulting $\log P$ value of 17.790 was acknowledged to be “unrealistic in nature,” but was consistent with the insolubility in water of these ingredients.

One component of these ingredients, dilinoleic acid has been studied. Systemic effects seen in a 13-week rat feeding study suggest that dilinoleic acid, or its metabolite(s), is widely distributed throughout the body when ingested (Spurgeon and Hepburn 1993).

ANIMAL TOXICOLOGY

Acute Oral Toxicity

Diisopropyl Dimer Dilinoleate

Groups of five male and five female albino rats were used to determine the LD₅₀ of Diisopropyl Dimer Dilinoleate (Consumer Product Testing Co. 1978). The acute oral LD₅₀ of Diisopropyl Dimer Dilinoleate was >5.0 g/kg.

The “limits of acute oral toxicity” of 50% of a lipgloss and a lipstick formulation, both containing 10% Diisopropyl Dimer Dilinoleate, in corn oil was >15.9 g/kg (Revlon 1983a, 1983b).

Dicetearyl Dimer Dilinoleate

Groups of five male and five female Wistar albino rats were dosed with 5 g/kg Dicetyl Dimer Dilinoleate (AMA Laborato-

ries, Inc. 1991). None of the animals died. The oral LD₅₀ for rats was >5.0 g/kg and the authors considered that Dicetyl Dimer Dilinoleate was nontoxic by this route of delivery.

Diisostearyl Dimer Dilinoleate

Groups of five male and five female albino rats were used to determine the LD₅₀ of Diisostearyl Dimer Dilinoleate (Consumer Product Testing Co. 1979). The acute oral LD₅₀ of Diisostearyl Dimer Dilinoleate was >5.0 g/kg.

In another study using five male and five female albino rats, the oral LD₅₀ of Diisostearyl Dimer Dilinoleate was >5.0 ml/kg (Wells Laboratories, Inc. 1990a).

Dioctyldodecyl Dimer Dilinoleate

Five male and five female rats were dosed with 5 g/kg Dioctyldodecyl Dimer Dilinoleate (AMA Laboratories, Inc. 1990a). None of the animals died. The oral LD₅₀ for rats was >5.0 g/kg and the authors considered that Dioctyldodecyl Dimer Dilinoleate was nontoxic by this route of delivery.

Isopropyl Linoleate

The acute oral LD₅₀ of 10% Isopropyl Linoleate in corn oil was >64 cc/kg (Elder 1992).

Cetearyl and Isostearyl Alcohol

The oral LD₅₀ using rats of 25% and 27% Isostearyl Alcohol in lipstick and 100% Isostearyl Alcohol was >15 g/kg (Elder 1988).

Octyl Dodecanol

Signs of toxicity were not observed in a percutaneous toxicity study using undiluted Octyl Dodecanol (Elder 1985). A single oral dose of 5 g/kg undiluted Octyl Dodecanol to five rats did not produce signs of toxicity. A lipstick containing 10.2% Octyl Dodecanol was diluted to 50% and orally administered to rats at a dose of 25 g/kg; no deaths occurred.

Acute Dermal Toxicity

An acute dermal toxicity test of Dioctyldodecyl Dimer Dilinoleate using male and female rats was conducted by Product Safety Labs (1999). Ten animals (equal numbers of each sex) were clipped on the dorsal area and the trunk. The test substance was applied evenly over an area of 2 × 3 inches, covered with a gauze pad, and wrapped with tape. The concentration delivered was determined based on each animal’s weight and adjusted to be 5 g/kg of body weight. After 24 h, the tape and pads were removed and the area wiped with corn oil, ethanol, and water with clean towels to remove residual test substance. Animals were observed 1 to 3 h after application and at least once daily for 14 days. All 10 animals survived, gained weight, and appeared active and healthy. All animals were sacrificed on day 14 and gross necropsies were performed. No gross tissue or organ abnormalities were found. The acute dermal LD₅₀ of Dioctyldodecyl Dimer Dilinoleate was determined to be >5 g/kg.

TABLE 3

Statistically significant clinical chemistry changes in plasma from male (M) and/or female (F) rats exposed to Dilinoleic Acid (Spurgeon and Hepburn 1993)

Parameter	Exposure level (w/w) in diet		
	0.1%	1.0%	5.0%
Electrolytes			
Decreased calcium	F	F	M/F
Enzymes			
Increased alkaline phosphatase		M/F	M/F
Decreased 5'-nucleosidase	M		M/F
Increased alanine aminotransferase			M/F
Increased aspartame aminotransferase	F		F
Metabolites			
Increased bilirubin		M	M
Decreased total cholesterol		M/F	M/F
Decreased triglycerides		M	M/F
Decreased glucose		F	
Proteins			
Decreased total protein			M/F
Decreased albumin			M/F
Decreased beta globulin fraction		M	M
Increased albumin/globulin ratio		M	M

Subchronic Toxicity

Although data on the short-term or chronic toxicity of the ingredients included in this report were not available, subchronic toxicity data on dilinoleic acid were found.

Dilinoleic Acid

Spurgeon and Hepburn (1993) conducted a 13-week feeding study using 20 male and 20 female CD strain rats. Animals were fed either 5%, 1%, or 0.1% (w/w) dilinoleic acid ad libitum in a basic purified diet. All animals were checked at least twice each work day and once each weekend day. Animals were weighed weekly. Food and water intake for each cage of five animals was recorded twice per week and weekly values calculated. An ophthalmoscopic examination was performed prior to the start of the study and at the end. At the end of the study, all animals were sacrificed, detailed necropsies were performed, hematologic and clinical chemistry tests were done and tissues were taken for histological analysis.

All of the animals survived the treatment and no treatment related adverse reactions were noted. Likewise, there were no treatment-related weight changes. Food intake was significantly lower in males and females of the 5% dilinoleic acid group over the first 4 weeks of the study. In females of this group, food conversion frequency was significantly higher than controls. There were statistically significant variations in weekly water intake, but there was no clear treatment related effect and the accumulated water intake did not differ between treatment and control groups. No treatment-related ocular effects were noted. There

was a small, but statistically significant increase in the mean cell hemoglobin levels in male rats in the 5% group and an increase in clotting time in female rats in the 1% group and in both sexes in the 5% group. These changes were not considered to be clinically significant. Changes in plasma electrolyte levels, enzymes, metabolites, and proteins are shown in Table 3. Statistically significant kidney, spleen, and liver weight changes are shown in Table 4.

TABLE 4

Statistically significant organ weight changes in male and/or female rats exposed to Dilinoleic Acid (Spurgeon and Hepburn 1993)

Organ	Exposure level (w/w) in diet		
	0.1%	1.0%	5.0%
Spleen	No change	Weight decrease in males	Weight decrease in males
Spleen ^a	No change	Weight decrease in males ^a	Weight decrease in males ^a
Kidney	No change	No change	Weight decrease in females
Liver	Weight decrease in females	Weight decrease in males	Weight decrease in males
Liver ^a	Weight decrease in females ^a	Weight decrease in both sexes ^a	Weight decrease in both sexes ^a

^aRelative to body weight.

Necropsy findings included enlargement of mesenteric lymph nodes, yellow coloration of caecal contents, and uterine fluid distension. Treatment-related effects were noted on histological examination of the mesenteric lymph nodes, the spleen, the liver, and the adrenal and thyroid glands at the 1% and 5% exposure levels. Effects on the mesenteric lymph nodes were also noted at the 0.1% exposure level. Specifically, macrophage aggregation in the mesenteric lymph nodes did appear to be dose related and correlated with the enlargement seen at necropsy. Pigmented macrophages were seen in more spleen tissue samples and there were more pigmented macrophages per sample as a function of exposures. There was no evidence of any degenerative effect associated with these pigmented macrophages. Liver bile duct proliferation and sclerosis (with minimal mixed inflammatory cell infiltration) were seen. Periportal cytoplasmic vacuolation was decreased in the two higher-exposure groups.

Cortical vacuolation in the adrenal gland was observed in female rats in the two higher-exposure groups and cytoplasmic rarefaction was decreased in the highest-exposure group, but there was no degenerative change. Slight follicular epithelial hypertrophy in the thyroid gland was noted in female rats in the highest-exposure group. This sex-related effect was considered unusual. Examination of the uteri suggested that the changes noted at autopsy were not treatment related. Retinal folding/atrophy was higher in rats fed dilinoleic acid, but the effect was not exposure related.

Overall, the authors indicated that it was difficult to correlate the gross findings with the clinical chemistry findings and/or with the histopathological findings. The possible correlation of bile duct changes with alkaline phosphatase activity increases was suggested, but it was noted that the physical changes were very minor. A link between serum calcium and protein decreases was not consistent across sexes and exposure levels. Either a block in lipid absorption or an alteration in lipid metabolism was postulated as an explanation for the cholesterol and triglyceride changes, with the latter possibly related in turn to the periportal hepatocyte vacuolation seen on histological examination, but no definitive conclusion was reached. Because of the many changes that were seen at different levels of examination and the macrophage aggregation seen in the mesenteric lymph node at the lowest dose level, the authors did not identify a no-effect level (Spurgeon and Hepburn 1993).

Dermal Irritation

Diisopropyl Dimer Dilinoleate

The dermal irritation potential of Diisopropyl Dimer Dilinoleate was determined using three male and three female rabbits (species not specified) by applying 0.5 ml of the test substance under an occlusive patch to an abraded and intact site (sites not specified) on each animal (Consumer Product Testing Co. 1978). Observations were made after 24 and 72 h. The primary irritation index (PII) was 0.10.

Dicetyl Dimer Dilinoleate

The dermal irritation potential of Dicetyl Dimer Dilinoleate was evaluated using six New Zealand albino rabbits following the procedure described above (AMA Laboratories, Inc. 1990b). The PII was 0.00 and Dicetyl Dimer Dilinoleate was considered not to be a skin irritant.

Diisostearyl Dimer Dilinoleate

The dermal irritation potential of Diisostearyl Dimer Dilinoleate was determined using six New Zealand white rabbits following the procedure previously described (Consumer Product Testing Co. 1979). The sites were evaluated 24 and 72 h after application. The PII was 0.0 and the researchers concluded that Diisostearyl Dimer Dilinoleate was considered not to be a dermal irritant.

The dermal irritation potential of 10% *w/w* Diisostearyl Dimer Dilinoleate in corn oil was determined using six New Zealand white rabbits by applying 0.5 ml of the test article to an intact and an abraded site (Wells Laboratories, Inc. 1990b). The test sites were scored 24 and 72 h after application. The PII was 0.75, and 10% *w/w* Diisostearyl Dimer Dilinoleate produced minimal irritation.

Dioctyl dodecyl Dimer Dilinoleate

The dermal irritation potential of Dioctyl dodecyl Dimer Dilinoleate was evaluated using six New Zealand albino rabbits following the procedure previously described (AMA Laboratories, Inc. 1990c). The PII was 0.00 and Dioctyl dodecyl Dimer Dilinoleate was not a primary skin irritant.

Isopropyl Linoleate

Undiluted Isopropyl Linoleate was a slight irritant to rabbit skin and a 10% aqueous suspension was a nonirritant; using purer samples, both were slight irritants (Elder 1992). Ten percent Isopropyl Linoleate in corn oil was very poorly tolerated by rabbit skin and a 10% aqueous suspension was relatively well tolerated. Using purer samples, there was a slight intolerance to undiluted Isopropyl Linoleate and the 10% Isopropyl Linoleate suspension was again relatively well tolerated.

Ceteryl and Isostearyl Alcohol

A cream containing 3% Ceteryl Alcohol applied using an occlusive patch was mildly irritating to the skin of rabbits (Elder 1988). Lipstick formulations containing 25% and 27% Isostearyl Alcohol applied to rabbits using an occlusive patch produced primarily barely perceptible erythema and an antiperspirant formulation containing 5% Isostearyl Alcohol applied using occlusive patches was mildly irritating to rabbit skin.

Octyl Dodecanol

Using rabbits, undiluted Octyl Dodecanol produced skin irritation indices of 0/4, 0.5/4, and 1.13/4 in three tests and a 30% aqueous solution produced a skin irritation index of 0/4 (Elder 1985). In other studies, 0.1 g of undiluted Octyl Dodecanol

was severely irritating to rabbit skin and moderately irritating to guinea pig and rat skin, whereas 0.05 g was nonirritating to pig and human skin. A single application of a product containing 4% Octyl Dodecanol using an occlusive patch produced no to mild irritation and a product containing 10.2% Octyl Dodecanol that was applied to the skin of rabbits for 3 to 4 days produced minimal to mild irritation.

Dermal Sensitization

Published data on the sensitization potential in animals of the ingredients included in this report were not found, but data were available on Cetearyl and Isostearyl Alcohol.

Cetearyl and Isostearyl Alcohol

In two studies using 5% Isostearyl Alcohol and one study in which the effective Isostearyl Alcohol concentration was 0.2%, sensitization was not induced (Elder 1988).

Comedogenicity

Diisopropyl Dimer Dilinoleate

The Consumer Product Testing Co. (1984a) determined the comedogenic potential of Diisopropyl Dimer Dilinoleate using three rabbits (species and sex not specified) by applying 0.5 ml of the test article (as received) to the right ear of each animal 5 days per week for 4 weeks; the left ear was used as an untreated control. The ears were observed daily. Increasing hyperkeratosis and erythema were observed for all test ears. Microscopic examination reported minimal locally extensive acanthosis in the epidermis of two test ears and a mild focal epidermal inclusion cyst in the dermis of one control ear. The researchers stated that Diisopropyl Dimer Dilinoleate caused only very minor irritation and did not produce a comedogenic effect.

Diisostearyl Dimer Dilinoleate

The Consumer Product Testing Co. (1984b) assessed the comedogenic potential of Diisostearyl Dimer Dilinoleate using three rabbits (species and sex not specified) following the procedure described above. The ears were observed daily. Increasing hyperkeratosis and erythema were observed in all test ears. Microscopic examination reported mild locally extensive acanthosis and minimal locally extensive hyperkeratosis in the epidermis of one test ear, minimal multifocal heterophilic inflammation in the dermis of one test ear, and mild multifocal hyperkeratosis in the hair follicles of one test ear. The researchers stated that Diisostearyl Dimer Dilinoleate caused only very minor irritation and was not comedogenic.

Ocular Irritation

Diisopropyl Dimer Dilinoleate

The ocular irritation potential of Diisopropyl Dimer Dilinoleate was determined using six male and female rabbits by placing 0.1 ml of the test substance into the conjunctival sac; the

eyes were not rinsed (Consumer Product Testing Co. 1978). Observations were made for 7 days. Diisopropyl Dimer Dilinoleate was not an ocular irritant.

In an ocular irritation study using rabbits, both a lipgloss and a lipstick formulation containing 10% Diisopropyl Dimer Dilinoleate were instilled undiluted into the conjunctival sac and the eyes were not rinsed (Revlon 1983a). For the lipgloss, a maximum 1-h score of 4 was observed for the conjunctivae and the eyes were normal after 1 day. For the lipstick, a maximum 1-h score of 2 was observed for the conjunctivae and the eyes were normal after 3 days.

Dicetearyl Dimer Dilinoleate

The ocular irritation potential of Dicetyl Dimer Dilinoleate was determined using six New Zealand white rabbits by placing 0.1 ml of the test substance into the conjunctival sac; the eyes were not rinsed (AMA Laboratories, Inc. 1990d). The untreated contralateral eye served as a control. Irritation was scored 24, 48, and 72 h after application according to the method of Draize. The maximum mean total score (MMTS) was 0.00, and Dicetyl Dimer Dilinoleate was considered nonirritating.

Diisostearyl Dimer Dilinoleate

The ocular irritation potential of Diisostearyl Dimer Dilinoleate was determined using six New Zealand white rabbits by placing 0.1 ml of the test substance (as received) into the conjunctival sac; the eyes were not rinsed (Consumer Product Testing Co. 1979). The untreated contralateral eye served as a control. Observations were made 24, 48, and 72 h after application and after 4 and 7 days if irritation persisted. Irritation was not observed and the researchers concluded that Diisostearyl Dimer Dilinoleate was not an ocular irritant.

In a similar study, 0.1 ml of 10% w/w Diisostearyl Dimer Dilinoleate in corn oil was applied to the conjunctival sac of six New Zealand white rabbits, and the eyes were not rinsed (Wells Laboratories, Inc. 1990c). Irritation was not observed, and Diisostearyl Dimer Dilinoleate was nonirritating.

An Eytex UMA assay was performed using 15 to 100 μ l of a foundation containing 2% Diisostearyl Dimer Dilinoleate (CTFA 1995). Doses of 15 to 50 μ l had an irritancy classification of minimal/mild and a dose of 100 μ l had an irritancy classification of minimal.

Diocetyldodecyl Dimer Dilinoleate

The ocular irritation potential of Diocetyldodecyl Dimer Dilinoleate was determined using six New Zealand white rabbits by placing 0.1 ml of the test substance into the conjunctival sac; the eyes were not rinsed (AMA Laboratories, Inc. 1990e). The untreated contralateral eye served as a control. Irritation was scored 24, 48, and 72 h after application according to the method of Draize. The MMTS was 0.00, and Diocetyldodecyl Dimer Dilinoleate was nonirritating.

Isopropyl Linoleate

Undiluted Isopropyl Linoleate and a 10% aqueous suspension of Isopropyl Linoleate were slight ocular irritants and 10% Isopropyl Linoleate in corn oil did not produce any ocular irritation in rabbit eyes (Elder 1992).

Cetearyl and Isostearyl Alcohol

A cream containing 3% Cetearyl Alcohol was nonirritating to rabbit eyes (Elder 1988). A pump spray antiperspirant containing 5% Isostearyl Alcohol was a moderate ocular irritant to rabbits eyes and one containing 10% induced transient corneal, conjunctival, and iridial irritation. Two lipstick formulations containing 25% Isostearyl Alcohol were minimally irritating and a lipstick formulation containing 27% Isostearyl Alcohol was a mild irritant to rabbit eyes.

Octyl Dodecanol

Formulations containing 3% to 10.2% Octyl Dodecanol produced no or minimal, transient irritation in rabbits eyes (Elder 1985). Undiluted Octyl Dodecanol produced irritation scores in rabbit eyes of 4/110 on day 1 and 0/110 by day 4 in one study, and scores of 1/110 on days 1 and 2 and 0/110 by day 3 in another study.

GENOTOXICITY*Dilinoleic Acid*

Huntington Research Centre Ltd. (1993a) studied chromosome aberrations in human lymphocytes in culture as a function of exposure to dilinoleic acid, with and without metabolic activation by Aroclor 1254-induced S9 rat liver fraction. Cultures were established for 48 h, at which time 50- μ l aliquots of dilinoleic acid were added to give final concentrations of 300, 150, 75, 37.5, 18.8, 9.4, 4.7, 2.3, 1.2, and 0.6 μ g/ml. Ethylmethanesulfonate and cyclophosphamide were used as positive controls. A reduction in the mitotic index (to 65%) was noted in the highest dose without metabolic activation. Metaphase analysis of human lymphocytes exposed to dilinoleic acid found no evidence of an increase in chromosome aberrations at any dose level. A repeat of the study failed to reproduce the effect seen on mitotic index. Positive controls yielded the expected significant increases in chromosome aberrations. The conclusion was that dilinoleic acid produces no clastogenic effect in this test system.

The Huntington Research Center Ltd. (1993b) also assayed forward mutations in mouse L5178Y lymphoma cells after exposure to dilinoleic acid, again with and without metabolic activation by aroclor-induced S9 rat liver fraction. Ethylmethanesulfonate (EMS) and 20-methylcholanthrene (20-MC) were used as positive controls. Cell survival and the number of thymidine kinase deficient colonies were determined after exposure to concentrations of dilinoleic acid as shown in Tables 5 and 6.

A small, but statistically significant increase in the mutation frequency was found in cells exposed to 250 μ g/ml of dilinoleic acid in the absence of metabolic activation. This increase was not

TABLE 5

Mutation frequency in mouse L5178Y lymphoma cells exposed to Dilinoleic Acid in the presence of metabolic activation

Dilinoleic Acid concentration	Mean number of mutants per 10 ⁶ survivors
First experiment	
0	133
50	119
100	102
150	101
225	133
20-MC	465 ^a
Second experiment	
0	105
10	96
150	95
225	103
250	87
EMS	972 ^a

^aSignificantly different from control ($p < 0.001$).

considered to indicate a real genotoxicity risk. All other exposures to dilinoleic acid were negative. Positive controls yielded the expected large and highly statistically significant increases in mutation frequency. Overall, dilinoleic acid was considered negative in the mouse L5178Y lymphoma cell assay (Huntington Research Centre Ltd. 1993b).

TABLE 6

Mutation frequency in mouse L5178Y lymphoma cells exposed to Dilinoleic Acid in the absence of metabolic activation

Dilinoleic Acid concentration	Mean number of mutants per 10 ⁶ survivors
First experiment	
0	80
50	55
100	88
150	54
225	95
EMS	672 ^a
Second experiment	
0	67
10	84
150	92
225	95
250	116 ^b
EMS	980 ^a

^aSignificantly different from control ($p < 0.001$).

^bSignificantly different from control ($p < 0.05$).

Widebank et al. (1993) performed an Ames reverse mutation assay using *Salmonella typhimurium* strains TA1535, TA1537, TA100, and TA98 exposed to dilinoleic acid in the presence and absence of metabolic activation by an S9 liver fraction from Aroclor 1254-induced rats. Positive controls were treated with 2-aminoanthracene with metabolic activation, and 2-nitrofluorene, sodium azide, and 9-aminoacridine without metabolic activation. The highest dose (5 mg/plate) used in a survival assay was found to be nonlethal, so this dose was used in the mutation assay, along with other lower doses. S9 fraction concentrations of 10% and 30% were used with strains TA1535, TA1537, and TA98, but only 10% was used with TA100. Assays were done in duplicate. The assays were repeated three additional times on strains TA1537 and TA98.

No significant increases in reverse mutations were seen for strains TA1535 and TA100 with or without metabolic activation. In the first assay of TA1537 with metabolic activation (S9 fraction at 30%), there was a significant increase in reverse mutations at 5 mg/plate, and in one repeat assay, there was a significant increase at 2 mg/plate with 30% S9. In the first assay of TA98 with metabolic activation (S9 fraction at 10% and 30%), there was a significant increase in reverse mutations at several test concentrations. These results were not seen in the other assay originally done or in any other of the repeat studies. Positive controls gave the expected clearly significant increases in revertants.

Because dilinoleic acid at these concentrations tends to form a precipitate at the dose levels used in these studies, the authors report difficulty in discriminating between revertant colonies and the precipitate. This is offered as a possible explanation for the positive results that were seen. Regardless, the conclusion was that the positive results were not reproducible and that dilinoleic acid was negative in the Ames test (Widebank, Wolfreys, and Henderson 1993).

CARCINOGENICITY

Published data on the carcinogenic potential of the ingredients included in this review were not found.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Published data on the reproductive and developmental toxicity of the ingredients included in this review were not found.

CLINICAL ASSESSMENT OF SAFETY

Dermal Irritation

Diisopropyl Dimer Dilinoleate

The irritation potential of a lipgloss containing 10% Diisopropyl Dimer Dilinoleate was evaluated using 100 subjects in an occlusive skin patch test (Revlon 1983a). The test material was applied for 48 h, and the test site was scored upon patch removal and 24 h after removal. Significant skin reactions were not observed. The authors stated that the lipgloss containing 10% Diisopropyl Dimer Dilinoleate was not a primary irritant.

The irritation potential of a lipstick formulation containing 10% Diisopropyl Dimer Dilinoleate was evaluated using 100 subjects following the procedure described above (Revlon 1983b). The authors stated that the lipstick containing 10% Diisopropyl Dimer Dilinoleate was not a primary irritant.

The Harrison Research Laboratories, Inc. (HRL) performed a 45-day use test to assess the irritation and acnegenic potential of liquid make-up formulations containing 2% Diisopropyl Dimer Dilinoleate (HRL, Inc. 1992). Potential subjects were screened for participation in the study based on the acne condition of their skin; half of the subjects selected had mild to moderate acne and half had normal skin or minimal acne. The study was completed using 54 female subjects, the majority of who were black. Prior to testing, a 24-h semioclusive patch test was performed on the arm of each subject. The make-up formulations were to be applied by the subjects twice daily for 45 days. The skin of each subject was evaluated for irritation and acne on days 0, 4, 7, 11, 14, 21, 28, 35, and 45. One subject had dryness on days 14, 21, 28, and 35. The acne scores of 1 subject decreased two grades, of 15 subjects decreased one grade, and of 1 subject increased one grade. The authors concluded that the make-up formulations containing 2% Diisopropyl Dimer Dilinoleate were not acnegenic, comedogenic, or irritating.

The irritation potential of a moisturizer formulation containing 5% Diisopropyl Dimer Dilinoleate was evaluated using 110 subjects (Consumer Product Testing Co. 1995). The test material, 0.2 ml, was applied to the skin of the upper back between the scapulae under an occlusive patch for 48 h. Reactions were not observed at the test site after 48 or 72 h, so the moisturizer formulation containing 5% Diisopropyl Dimer Dilinoleate was not a dermal irritant.

A 28-day use test was performed to assess the irritation potential of lipstick formulations containing 18% Diisopropyl Dimer Dilinoleate (HRL, Inc. 1996). The test was completed by 81 female subjects, with 51 categorized as having normal skin and 31 categorized as having sensitive skin. Each subject was patch tested on the arm with the test formulation prior to use. The subjects were to use only the test lipstick, apply it a minimum of five times per day, and wear it a minimum of 8 h. Dermatological examinations were made on days 0, 7, 12, 21, and 28. One subject had transient dryness/scaling. Test article-related erythema, edema, or subjective irritation were not observed. The authors concluded that lipstick formulations containing 18% Diisopropyl Dimer Dilinoleate were not dermal irritants in subjects with normal or sensitive skin.

Hershey Medical Center (1996) also performed a 28-day use test to assess the irritation potential of lipstick formulations containing 8.2% or 13% Diisopropyl Dimer Dilinoleate. The test was completed by 50 female subjects, with 25 self-assessed as having normal skin and 25 self-assessed as having sensitive skin. Dermatological examinations were made on days 0, 7, 14, 21, and 28. Signs of irritation were not reported by the subjects with normal skin. Three of the subjects with sensitive skin reported "a mild burning of the lips" and two reported "mild to moderate

tautness of the lips"; the reactions were mild in intensity and transient in nature. Lipstick formulations containing 8.2% and 13% Diisopropyl Dimer Dilinoleate did not produce irritant or allergic contact dermatitis.

In their Material Safety Data Sheet (MSDS), Scher Chemicals, Inc. (1996b) stated that prolonged contact with Diisopropyl Dimer Dilinoleate could cause skin irritation.

Diisostearyl Dimer Dilinoleate

A single-insult occlusive patch test (SIOPT) was performed using 20 subjects to determine the irritation potential of a concealer containing 10% Diisostearyl Dimer Dilinoleate (CTFA 1991a). The concealer, which was applied undiluted, had a PII of 0.08/4.

A 5-day use test of a concealer containing 10% Diisostearyl Dimer Dilinoleate was performed using 22 female subjects, 15 of whom were lactic acid sensitive (CTFA 1991b). Application of the concealer produced mild clinical changes in two subjects and very slight stinging in one subject. The authors concluded that the concealer was acceptable for use.

Cetearyl and Isostearyl Alcohol

Three lipstick formulations containing 25%, 27%, and 28% Isostearyl Alcohol and 25% Isostearyl Alcohol in petrolatum produced no irritation to the volar forearm of subjects, whereas an antiperspirant containing 5% Isostearyl Alcohol applied under an occlusive patch on the back produced severe irritation (Elder 1988).

Octyl Dodecanol

A moisturizing cream containing 4% Octyl Dodecanol produced no or minimal irritation in subjects and undiluted Octyl Dodecanol produced mild irritation in 1/40 subjects in a SIOPT (Elder 1985). An eye pencil formulation containing 3% Octyl Dodecanol was essentially nonirritating to slightly irritating after patch testing for 21 days. Technical grade Octyl Dodecanol applied to the back under an occlusive patch did not produce irritation.

Dermal Sensitization

Diisopropyl Dimer Dilinoleate

A repeat-insult patch test (RIPT) was conducted using 154 subjects (19 males and 135 females) to determine the sensitization potential of a lipstick containing 10% Diisopropyl Dimer Dilinoleate (CTFA 1986a). The test material was applied to the upper back under an occlusive patch 3 days per week for 3 weeks. After a 2-week nontreatment period, two consecutive 48-h challenge patches were applied to the upper back on the side opposite induction patch placement. The test sites were evaluated at 48 and 96 h. One subject had a single 1+ response upon challenge; but overall, allergic responses were not observed. The authors concluded that a lipstick formulation containing 10% Diisopropyl Dimer Dilinoleate was not a clinically significant irritant or sensitizer.

TKL Research, Inc. (1992a) performed an RIPT using 76 subjects to determine the sensitization potential of a liquid make-up formulation containing 2% Diisopropyl Dimer Dilinoleate. A screening test was first performed using 10 subjects to whom 0.1 ml of the test material was applied to the patch and allowed to air dry for 15 min prior to application. Occlusive patches were applied to the infrascapular area of the back on a Friday, Monday, and Wednesday, and they were removed after 24 h. The test site was evaluated on Monday, Wednesday, Thursday, and Friday. Two subjects had mild reactions, described as faint/definite pink, on days 3 to 5 or days 3 and 4, respectively.

In the main portion of the study, occlusive patches containing 0.1 ml of test material were applied for 24 h to the infrascapular region of the back 3 days per week for 3 weeks, for a total of nine induction applications. The test sites were evaluated prior to patch reapplication. Following a 2-week nontreatment period, a challenge patch was applied for 24 h to a previously unpatched site. The challenge site was evaluated 24 and 48 h after patch removal. Of the 76 subjects completing the study, 16 had scores of 1 (mild reaction—faint/definitely pink) and two had scores of 1 and 2 (moderate reaction—definite redness) during induction. Reactions were not observed upon challenge. The researchers concluded there was no evidence of sensitization (TKL Research, Inc. 1992a).

A modified Draize assay was completed using 198 subjects, 50 males and 148 females, to determine the sensitization potential of a make-up formulation containing 3.5% Diisopropyl Dimer Dilinoleate (International Research Services, Inc. 1994). The test material, approximately 0.025 g, was applied to the back of each subject under a semi-occlusive patch 3 days per week for a total of 10 applications. The first patch was applied for 48 h and the remaining patches were applied for 24 h. Each site was scored after 48 h (or after 72 h on weekends). Following a 12-day nontreatment period, a 48-h challenge patch was applied to a previously unpatched site. The challenge site was scored upon patch removal and 96 h after application. Adverse reactions were not reported and a make-up formulation containing 3.5% Diisopropyl Dimer Dilinoleate was not a significant skin irritant or sensitizer.

Another RIPT was completed using 121 subjects, 30 males and 91 females, to determine the sensitization potential of a lipstick containing 27% Diisopropyl Dimer Dilinoleate (Hill Top Research, Inc. 1995). The test material, 0.1 g per patch, was applied to the upper arm under an occlusive patch 3 days per week for 3 weeks. After a 12 to 20-day nontreatment period, challenge patches were applied to the original and previously untested sites. The test sites were evaluated at 48 and 72 or 96 h after challenge patch application. During induction, two subjects had a response to the test material. A lipstick formulation containing 27% Diisopropyl Dimer Dilinoleate was not a sensitizer.

An RIPT was completed using 110 subjects according to the methods described above to determine the sensitization potential of a lipstick that contained 18% Diisopropyl Dimer Dilinoleate

(Hill Top Research, Inc. 1996). A lipstick formulation containing 18% Diisopropyl Dimer Dilinoleate was not a sensitizer.

Dicetearyl Dimer Dilinoleate

An RIPT was completed using 60 subjects, 11 males and 49 females, to determine the sensitization potential of Dicetearyl Dimer Dilinoleate (AMA Laboratories, Inc. 1996). The test material, 0.1 g or ml, was applied to the infrascapular region of the back under an occlusive patch 3 days per week for 3 weeks. The patches were removed 24 h after application, and the sites were evaluated prior to repatching. After a 10- to 14-day nontreatment period, a challenge patch was applied to a previously unexposed area of the back. The challenge site was evaluated 24 and 48 h after patch application. Adverse reactions were not noted during the induction or challenge phases. Dicetearyl Dimer Dilinoleate was not a primary irritant or sensitizer.

Diisostearyl Dimer Dilinoleate

A maximization test was performed using 27 subjects, 13 men and 14 women, to determine the sensitization potential of an undereye concealer containing 10% Diisostearyl Dimer Dilinoleate (Ivy Laboratories 1991). Because the concealer was not irritating in a pretest, sodium lauryl sulfate (SLS) pretreatment was used during induction. The concealer, 0.1 g, was applied to an SLS-pretreated site on the upper outer arm under an occlusive patch for 48 to 72 h; SLS pretreatment was used throughout the study unless irritation to the test material was observed. After a 10-day nontreatment period, a challenge was performed with a single 48-h application of the concealer to a previously unpatched site on the opposite arm. A sensitization reaction was not observed at the 48- or 72-h readings and the concealer containing 10% Diisostearyl Dimer Dilinoleate "is not likely to cause contact sensitivity reactions under normal use conditions."

Diocetyldodecyl Dimer Dilinoleate

An RIPT was completed using 60 subjects, 11 males and 49 females, to determine the sensitization potential of Diocetyldodecyl Dimer Dilinoleate (AMA Laboratories, Inc. 1996). The test material, 0.2 g or ml, was applied to the infrascapular region of the back under an occlusive patch 3 days per week for 3 weeks. The patches were removed 24 h after application, and the sites were evaluated prior to repatching. After a 10- to 14-day nontreatment period, a challenge patch was applied to a previously unexposed area of the back. The challenge site was evaluated 24 and 48 h after patch application. Adverse reactions were not noted during the induction or challenge phases. Diocetyldodecyl Dimer Dilinoleate was not a primary irritant or sensitizer.

Dilinoleic Acid

Wall (1984) reported a case of a woman who mixed epoxy resins and a flexibilizing hardener containing dilinoleic acid by pouring from a drum into a small can and then applying the mixture by brush. Within a week an irritation developed on exposed areas of her arms and face. When patch tested to 0.5%

dilinoleic acid in petrolatum, the result was positive. Patch tests on 15 control individuals were negative. The author speculated that it was unlikely that a molecule as large as dilinoleic acid was allergenic and suggested that the allergen was probably in smaller molecular fractions.

Cetearyl and Isostearyl Alcohol

A cream formulation containing 3% Cetearyl Alcohol did not induce sensitization in 25 subjects after one 48-h challenge. Isostearyl Alcohol, 25% v/v in 95% isopropyl alcohol, caused some erythema during induction but did not induce sensitization. Antiperspirant formulations containing 5% Isostearyl Alcohol induced a sensitization reaction in 5/60, 4/148, and 6/148 subjects after one 24-h challenge and in 75, 65, 83, and 69 of 148 subjects after the first, second, third, and fourth 24-h challenge, respectively (Elder 1988).

Octyl Dodecanol

RIPTs of a product containing 3% Octyl Dodecanol produced isolated mild irritation in 2/210 subjects with no reactions at challenge and of a lipstick formulation containing 10.2% Octyl Dodecanol produced no irritation or sensitization. In a study examining allergic skin reactions to ointment bases, 6 of 1664 subjects reacted to 30% Octyl Dodecanol in petrolatum (Elder 1985).

Phototoxicity/Photoallergenicity

Diisopropyl Dimer Dilinoleate

A study was performed using 26 female subjects to determine the photoallergic potential of a lipstick containing 10% Diisopropyl Dimer Dilinoleate (CTFA 1986b). The test material, approximately 0.1 ml/cm², was applied under an occlusive patch for 24 h, after which time the patch was removed and the site irradiated with 3 minimal erythral dose (MED) using a xenon arc solar simulator (150 W). This process was repeated twice weekly for a total of six exposures. Ten days after the last induction exposure, a challenge patch was applied for 24 h to a previously untreated site, after which time the site was irradiated for 3 min using a Schott WG345 filter over the solar simulator. The challenge sites were graded 15 min and 24, 48, and 72 h after irradiation. Controls were performed following the same procedure in which the test material was applied but the site was not irradiated and in which an unpatched site was irradiated. Photoallergic responses were not observed and the authors concluded there was no photoallergy to a lipstick containing 10% Diisopropyl Dimer Dilinoleate.

TKL Research, Inc. (1992b) conducted a study using 12 female subjects to determine the phototoxic potential of a liquid make-up formulation containing 2% Diisopropyl Dimer Dilinoleate. The MED for each subject was determined prior to testing using a xenon Arc Solar Simulator (150 W), the output of which was measured daily. Occlusive patches containing 0.1 g of the test material, which were allowed to dry for 15 min, were applied to two sites on the infrascapular area of the back.

The patches were removed 24 h after application, and one test site was irradiated with 16 J/cm² of UVA using a filtered light source followed by 0.5 MED of UVB; the other test site was not irradiated. An untreated site was also irradiated in the same manner as the treated site and served as an irradiated control.

All sites were evaluated following patch removal and 24 and 48 h after irradiation. One subject required retesting due to questionable reactions; scores of 2 (moderate reaction—definite redness) and 1 (mild reaction—faint, definitely pink) were observed at the irradiated test site 24 and 48 h after irradiation, respectively, as compared to scores of 1 and 0, respectively, at the irradiated control site. Upon retest, normal reactions were observed. Irritation was not observed at the nonirradiated test sites of any of the subjects. The researchers concluded there was no evidence of phototoxicity (TKL Research, Inc. 1992b).

TKL Research, Inc. (1992c) performed a study using 26 subjects (1 male and 25 females) to determine the ability of a liquid make-up formulation containing 2% Diisopropyl Dimer Dilinoleate to induce a photoallergic reaction, i.e., photoallergic contact dermatitis. Each subject's MED was determined prior to testing using a xenon Arc Solar Simulator (150 W), the output of which was measured daily. Occlusive patches containing 0.1 ml of the test material, which were allowed to dry for 15 min, were applied to two sites on the lumbar area of the back twice a week for 3 weeks, for a total of six applications. The patches were removed 24 h after application, and one test site was irradiated with 2 MED using the full lamp spectrum. An untreated site was irradiated in the same manner as the treated site and served as an irradiated control.

All sites were evaluated following patch removal and 24 and 48 or 72 h after irradiation. Following a 16-day nontreatment period, two challenge patches were applied for 24 h to previously unpatched sites. Upon patch removal, one site was irradiated with 4 J/cm² of UVA and 0.5 MED of UVB. An adjoining, unpatched site was irradiated in the same manner and served as the irradiated control. Four subjects had reactions of 1 at the irradiated test site with scores of 0 at the irradiated control site. Reactions were not observed at the nonirradiated test sites of any of the subjects. The researchers concluded that there was "no evidence of photosensitization" with a liquid make-up formulation containing 2% Diisopropyl Dimer Dilinoleate (TKL Research, Inc. 1992c).

HRL, Inc. (1995a) conducted a study using 10 subjects (2 males and 8 females) with skin types I to III to determine the ability of a lipstick formulation containing 27% Diisopropyl Dimer Dilinoleate to induce a phototoxic response. Duplicate occlusive patches containing 0.1 g of test material were applied to the volar forearms of each subject for 24 h. Following patch removal, the test sites were scored, and the test site on one arm was irradiated for 15 min with UVA; the light source was four F40BL fluorescent tubes that deliver a dose of approximately 0.22 J/cm²/min at a distance of 15 ± 2 cm and the total dose was 3.3 J. An untreated site was irradiated and served as an irradiated control. The test sites were scored immediately after

irradiation and 24 and 48 h later. Reactions were not observed at the irradiated or non-irradiated test sites or at the irradiated control site and the authors concluded that the lipstick formulation containing 27% Diisopropyl Dimer Dilinoleate did not induce a phototoxic response.

HRL, Inc. (1995b) conducted a study using 27 subjects, 3 males and 24 females, with skin types I to III to determine the ability of a lipstick formulation containing 27% Diisopropyl Dimer Dilinoleate to induce a photoallergic response. The source of UVA irradiation was four F40BL fluorescent tubes that deliver a dose of approximately 0.22 J/cm²/min at a distance of 15 ± 2 cm. The source of UVB irradiation was the Solarium 300 (Sperti Sunlamp Division) that delivered a dose of approximately 1.2 mJ/cm²/s at a distance of 22 ± 2 cm. Duplicate occlusive patches containing 0.1 g of test material were applied for 24 h to the radial aspect of the volar forearms twice weekly for 3 weeks. Upon patch removal, the test sites were scored and the test area of one arm was irradiated with UVA for 15 min, for a total dose of 3.3 J, and with UVB at 2 MEDs or for a maximum of 120 s. An untreated site was also irradiated and served as the irradiated control. The sites were scored immediately after irradiation.

Following an approximately 2 week nontreatment period, challenge patches were applied for 24 h to previously unpatched sites on the ulnar side of the volar forearms. Upon patch removal, the sites were scored, the one forearm was irradiated with UVA only, and the irradiated sites were scored again. Both test sites were scored 48 and 72 h after patching. During induction, five subjects had "low-level (±/1) reactions" at the irradiated test material site, but reactions were not observed at the nonirradiated test site. Five subjects also had low-level reactions at the irradiated control site. Reactions were not observed upon challenge. The authors concluded that the lipstick formulation containing 27% Diisopropyl Dimer Dilinoleate did not induce a photoallergic or contact sensitization response (HRL, Inc. 1995b).

Diisostearyl Dimer Dilinoleate

Ivy Laboratories (1994) performed a photocontact allergenicity test using 28 female Caucasian subjects to determine the photosensitization potential of an under-eye concealer containing 10% Diisostearyl Dimer Dilinoleate. Eighty milligrams of the concealer were applied to the lower back of each subject for 24 h under an occlusive patch. The patches were then removed and the sites were exposed to 3 MEDs using a 150 W compact xenon arc source that had a UV-reflecting dichromic mirror and a 1-mm-thick Schott WG-320 filter (producing wavelengths of 290 to 400 nm). (The MED was determined in a pretest.) The patches were reapplied 48 h after the sites were irradiated.

This procedure was performed twice a week for 3 weeks. Ten to 14 days after the last induction exposure, a challenge was performed by applying 80 mg of the concealer to two previously untreated sites under occlusive patches for 24 h, removing one of the patches, and irradiating the site with 4 J/cm² of UVA. The second site was not irradiated and served as a control.

Sensitization reactions were not observed at either challenge site after 48 or 72 h, and the authors concluded that the concealer containing 10% Diisostearyl Dimer Dilinoleate had no photocontact-sensitizing potential (Ivy Laboratories 1994).

Octyl Dodecanol

A lipstick formulation containing 10.2% Octyl Dodecanol was not phototoxic or photoallergenic in a repeated insult photosensitization study (Elder 1985).

Ocular Irritation

Diisopropyl Dimer Dilinoleate

In their MSDS, Scher Chemicals, Inc. (1996b) stated that Diisopropyl Dimer Dilinoleate causes irritation and pain upon contact with the eye.

SUMMARY

Diisopropyl Dimer Dilinoleate, Dicetearyl Dimer Dilinoleate, Diisostearyl Dimer Dilinoleate, Dioctyl Dimer Dilinoleate, Dioctyldodecyl Dimer Dilinoleate, and Ditridecyl Dimer Dilinoleate are diesters of their respective alcohols and dilinoleic acid and function as skin conditioning agents. In 1998, it was reported to the FDA that Diisopropyl Dimer Dilinoleate, Diisostearyl Dimer Dilinoleate, and Dioctyl Dimer Dilinoleate were used in 35, 20, and one cosmetic formulation(s), respectively. Although Dicetearyl Dimer Dilinoleate was not reported to FDA as being used, industry did report a current concentration of use. The other ingredients included in this review were not reported to FDA as being used. Current concentrations of use for most product types was available, up to a high of Diisopropyl Dimer Dilinoleate in lipsticks of 53%. Most use concentrations are at 10% or less.

Dicetearyl and Dioctyldodecyl Dimer Dilinoleate did not absorb in the UVA or UVB range. The only impurities expected in Diisopropyl and Diisostearyl Dimer Dilinoleate are <0.5% dilinoleic acid and <0.1% isopropyl alcohol or <1% isostearyl alcohol, respectively, and in Dicetearyl and Dioctyldodecyl Dimer Dilinoleate are small amounts of dilinoleic acid and cetearyl alcohol or octyldodecanol, respectively. These ingredients are not soluble in water and this is reflected in a predicted octanol/water partition coefficient higher than would be expected naturally, and reportedly not likely to penetrate the skin.

The acute oral and dermal LD₅₀ for rats of Diisopropyl, Diisostearyl, and Dioctyldodecyl Dimer Dilinoleate was >5.0 g/kg. A no-observable-adverse-effect level (NOAEL) was not found in a subchronic feeding study because of macrophage aggregation seen in the mesenteric lymph node at the lowest dose level (0.1% in the diet).

Using rabbits, the PII of Diisopropyl, Diisostearyl, and Dioctyldodecyl Dimer Dilinoleate was 0.10, ≤0.75, and 0.00, respectively. These ingredients were not considered primary irritants to rabbit skin. Diisopropyl and Diisostearyl Dimer Dilinoleate were not comedogenic to the ears of rabbits and caused

very minor epidermal irritation. Diisopropyl, Diisostearyl, and Dioctyldodecyl Dimer Dilinoleate were not irritating to rabbit eyes.

Ames, clastogenesis, and L5178Y mouse lymphoma cell forward mutation testing were all negative, indicating no genotoxicity of these ingredients. No carcinogenicity, or reproductive and developmental toxicity data were available.

In clinical studies, cosmetic formulations containing 5% to 10% Diisopropyl Dimer Dilinoleate were not primary irritants and formulations containing 2% to 18% Diisopropyl Dimer Dilinoleate did not cause irritation or sensitization in 28- and 45-day use tests. One report of sensitization to dilinoleic acid appeared in the case literature. A cosmetic formulation containing 10% Diisostearyl Dimer Dilinoleate had a PII of 0.08/4 and, in a 5-day use test, was considered acceptable for use. Cosmetic formulations containing 2% to 27% Diisopropyl Dimer Dilinoleate and 10% Diisostearyl Dimer Dilinoleate were not sensitizers or photosensitizers. Dicetearyl and Dioctyldodecyl Dimer Dilinoleate were not sensitizers.

DISCUSSION

The CIR Expert Panel issued a safety assessment of these ingredients in September, 1997, with the conclusion that the available data were insufficient to support the safety of use of these ingredients in cosmetic formulations. Noting that these additional data are likely not needed if these ingredients do not penetrate the skin, the Panel identified the following data needs:

1. 28-day dermal toxicity data; if significantly absorbed, developmental toxicity data are needed; and
2. two genotoxicity studies, one using a mammalian system; if positive, a 2-year dermal carcinogenicity assay performed using the National Toxicology Program methods is needed.

Since that time, additional data were received on ingredients considered in this report and on dilinoleic acid. These latter data were considered relevant to the safety assessment of the dilinoleic acids.

The Panel considered that the results of the Ames testing and the genotoxicity assays in mammalian systems did not demonstrate any mutagenic potential of dilinoleic acid. These data, combined with the absence of structural alerts to suggest a mutagenic or carcinogenic risk, support the safety of these ingredients.

The potential skin penetration of these ingredients was evaluated using an estimate of the octanol/water partition coefficient based on the structure of Diisopropyl Dimer Dilinoleate. The result of this analysis was a log P value of over 17. Although it is unrealistic to expect that an actual experimental determination of log P would yield a value this high, the recognized insolubility of these dilinoleic acids in water and their lipophilic nature is consistent with the findings of the ClogP software. As a result, the Panel does not believe there would be any significant skin penetration of these ingredients, and, therefore, no risk of reproductive, developmental, or other systemic toxicity. This finding

is consistent with the results of the acute dermal toxicity tests, which found no signs of overt toxicity, adverse pharmacologic effects, abnormal behavior, or organ/tissue damage.

The Panel did note that the concentration of use of Diisopropyl Dimer Dilinoleate was reportedly as high as 53% in lipsticks, but that the highest concentration tested for irritation/sensitization is 27%. Given the size of these molecules, their relative insolubility in water, their lipophilic nature, and the absence of any significant case reports of allergic reactions, a use concentration of 53% is not likely to be associated with any adverse effects.

CONCLUSION

Based on the information contained in this safety assessment, the CIR Expert Panel concludes that Diisopropyl Dimer Dilinoleate, Dicetearyl Dimer Dilinoleate, Diisostearyl Dimer Dilinoleate, Dioctyl Dimer Dilinoleate, Dioctyldodecyl Dimer Dilinoleate, and Ditridecyl Dimer Dilinoleate are safe as used in cosmetic products.

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2018 FDA VCRP Frequency of Use Data

03C - Eye Shadow	977012604	DIISOPROPYL DIMER DILINOLEATE	11
03G - Other Eye Makeup Preparations	977012604	DIISOPROPYL DIMER DILINOLEATE	1
05G - Tonics, Dressings, and Other Hair Grooming Aids	977012604	DIISOPROPYL DIMER DILINOLEATE	4
05I - Other Hair Preparations	977012604	DIISOPROPYL DIMER DILINOLEATE	1
07A - Blushers (all types)	977012604	DIISOPROPYL DIMER DILINOLEATE	2
07C - Foundations	977012604	DIISOPROPYL DIMER DILINOLEATE	6
07E - Lipstick	977012604	DIISOPROPYL DIMER DILINOLEATE	87
07G - Rouges	977012604	DIISOPROPYL DIMER DILINOLEATE	1
07I - Other Makeup Preparations	977012604	DIISOPROPYL DIMER DILINOLEATE	10
10E - Other Personal Cleanliness Products	977012604	DIISOPROPYL DIMER DILINOLEATE	1
12A - Cleansing	977012604	DIISOPROPYL DIMER DILINOLEATE	2
12C - Face and Neck (exc shave)	977012604	DIISOPROPYL DIMER DILINOLEATE	4
12D - Body and Hand (exc shave)	977012604	DIISOPROPYL DIMER DILINOLEATE	3
12F - Moisturizing	977012604	DIISOPROPYL DIMER DILINOLEATE	7
12G - Night	977012604	DIISOPROPYL DIMER DILINOLEATE	2
12J - Other Skin Care Preps	977012604	DIISOPROPYL DIMER DILINOLEATE	3
03A - Eyebrow Pencil	977047441	DIISOSTEARYL DIMER DILINOLEATE	2
03B - Eyeliner	977047441	DIISOSTEARYL DIMER DILINOLEATE	4
03C - Eye Shadow	977047441	DIISOSTEARYL DIMER DILINOLEATE	1
07C - Foundations	977047441	DIISOSTEARYL DIMER DILINOLEATE	2
07E - Lipstick	977047441	DIISOSTEARYL DIMER DILINOLEATE	5
07I - Other Makeup Preparations	977047441	DIISOSTEARYL DIMER DILINOLEATE	1
10E - Other Personal Cleanliness Products	977047441	DIISOSTEARYL DIMER DILINOLEATE	1
12F - Moisturizing	977047441	DIISOSTEARYL DIMER DILINOLEATE	4