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 Dilinoleate[1]

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 LD_{50} 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 ≤25%), and that Octyl Dodecanol was safe as used (concentrations >50%).

Received 24 March 2003; accepted 1 July 2003.

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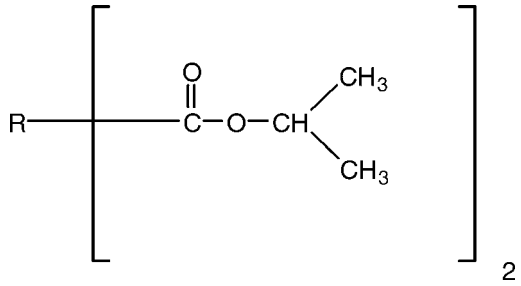
International Journal of Toxicology, 22(Suppl. 2):45–61, 2003

ISSN: 1091-5818 print / 1092-874X online
DOI: 10.1080/10915810390239469

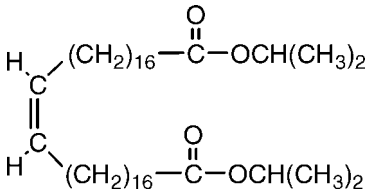
CHEMISTRY

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:



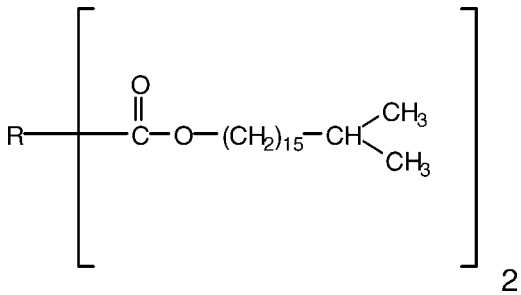
The structure may also be shown as (CTFA 1999a):



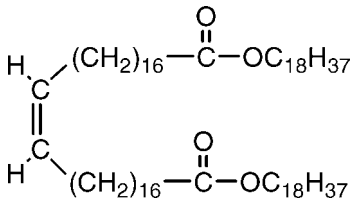
Diisopropyl Dimer Dilinoleate is also known as Diisopropyl Dilinoleate (CTFA 1996a); Diisopropyl Dimerate; Dilinoleic Acid, Diisopropyl Ester; Bis(1-Methylethyl)Dimerate; Dilinoleic Acid, Bis(1-Methylethyl) Ester (Pepe, Wenninger, and McEwen 2002); and Bis(2-Propanol) 9,12-Octadecadienoic Dilinoleic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

Dioctyl 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). Dioctyl Dimer Dilinoleate is also known as Dioctyl Dilinoleate (CTFA 1996a); Dioctyl Dimerate; Bis(2-Ethylhexyl)Dimerate; and Dilinoleic Acid, 2-Ethylhexyl Ester (Pepe, Wenninger, and McEwen 2002).

Dioctyldodecyl 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. Dioctyldodecyl 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 Dioctyldodecyl 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	$>200^{\circ}$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	Nikitakis and McEwen 1990
	1.4550–1.4655	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	$>170^{\circ}$C	Scher Chemicals, Inc. 1996a
Saponification value	160–180	Nikitakis and McEwen 1990
	160–185	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	Brooks Industries Inc. 1996a
	Practically odorless buttery yellow solid	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
	Dioctyldodecyl 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

Dioctyldodecyl 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.

Dioctyldodecyl 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).

Dioctyldodecyl 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, Dioctyldodecyl 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, Dioctyldodecyl 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 Dioctyldodecyl 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	
	Dioctyl Dimer Dilinoleate		
Moisturizing preparations (743)	1	—	—
Lipstick (758)	—	12.1	—
1997 total for Dioctyl Dimer Dilinoleate	1	12.1	

[a]Information reported to FDA by those companies that participated in a voluntary reporting program.
[b]Information 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 LD_{50} of Diisopropyl Dimer Dilinoleate (Consumer Product Testing Co. 1978). The acute oral LD_{50} 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 Laboratories, Inc. 1991). None of the animals died. The oral LD_{50} 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 LD_{50} of Diisostearyl Dimer Dilinoleate (Consumer Product Testing Co. 1979). The acute oral LD_{50} of Diisostearyl Dimer Dilinoleate was >5.0 g/kg.

In another study using five male and five female albino rats, the oral LD_{50} 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 LD_{50} 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 LD_{50} of 10% Isopropyl Linoleate in corn oil was >64 cc/kg (Elder 1992).

Cetearyl and Isostearyl Alcohol

The oral LD_{50} 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 LD_{50} 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)

	Exposure level (w/w) in diet		
Parameter	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)

	Exposure level (w/w) in diet		
Organ	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]

[a]Relative 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.

Dicetearyl 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.

Dioctyldodecyl Dimer Dilinoleate

The dermal irritation potential of Dioctyldodecyl 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 Dioctyldodecyl 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.

Cetearyl and Isostearyl Alcohol

A cream containing 3% Cetearyl 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 μl of a foundation containing 2% Diisostearyl Dimer Dilinoleate (CTFA 1995). Doses of 15 to 50 μl had an irritancy classification of minimal/mild and a dose of 100 μl had an irritancy classification of minimal.

Dioctyldodecyl Dimer Dilinoleate

The ocular irritation potential of Dioctyldodecyl 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 Dioctyldodecyl 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-μl 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 μg/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 μg/ml of dilinoleic acid in the absence of metabolic activation. This increase was not 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 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]

[a] Significantly different from control ($p < 0.001$).

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]

[a] Significantly different from control ($p < 0.001$).
[b] Significantly 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 semiocclusive 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 irritatant.

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."

Dioctyldodecyl Dimer Dilinoleate

An RIPT was completed using 60 subjects, 11 males and 49 females, to determine the sensitization potential of Dioctyldodecyl 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. Dioctyldodecyl 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/cm^2, was applied under an occlusive patch for 24 h, after which time the patch was removed and the site irradiated with 3 minimal erythemal 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/cm^2 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/cm^2 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/cm^2/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/cm^2/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/cm^2/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 ($\pm$/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 undereye 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/cm^2 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 a 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 LD_{50} 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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