RE-REVIEW

Safety Assessment of Alkyl Sulfosuccinate Salts as Used in Cosmetics

CIR EXPERT PANEL MEETING

JUNE 10-11, 2013

Memorandum

To: CIR Expert Panel Members and Liaisons
From: Monice M. Fiume MMF
Senior Scientific Analyst/Writer
Date: May 17, 2013
Subject: Safety Assessment of Alkyl Sulfosuccinate Salts as Used in Cosmetics (a Re-review)

Diethylhexyl sodium sulfosuccinate (previously named dioctyl sodium sulfosuccinate) was reviewed by the Cosmetic Ingredient Review (CIR) Expert Panel in 1994, and a safe concentration limit of 0.42% was established. A petition to re-open the report to review new clinical data was received, and in 1998, the Panel amended the report to conclude that this ingredient is safe as used in cosmetic formulations. In the discussion, the Panel stressed that care should be taken to avoid irritancy, especially in those products intended for prolonged contact with the skin. In that it has been 15 years since that report was published, the Panel is being asked to determine whether there is any reason to re-open the safety assessment on this ingredient, or, if the conclusion of safe as used is reaffirmed.

Since the 1998 report was issued, the number of reported uses in cosmetic formulations has increased from 35 to 62 uses. However, the concentration of use has not changed. The data that were available for the 1998 report (i.e., 1984 data) indicated that diethylhexyl sodium sulfosuccinate was used in a variety of product-types at concentrations of ≤5%; current information report that the maximum use concentration is 4.4% in eyebrow pencil formulations. These data and other published information not found in the original safety assessments are included in this re-review document.

The Panel is also being asked to consider whether the safety of 19 alkyl sulfosuccinate salts (diesters and monoesters; listed in the Introduction to the report) can be supported by the data on diethylhexyl sodium sulfosuccinate. All of the proposed "add-ons" are diesters and monoesters of 2-sulfosuccinic acid, all share a sulfo-substituted succinic acid core, all contain an ester linkage, and all are anionic surfactants. Only two of these ingredients are reported to be in use, and the use concentrations of those ingredients are similar to that of diethylhexyl sodium sulfosuccinate.

The original safety assessment on diethylhexyl sodium sulfosuccinate is included with this submittal, and information for that assessment is summarized as appropriate throughout the report, as indicated by *italicized text.*

Also included, so that you may check any details, are:

1. Final report on the safety assessment of alkyl PEG sulfosuccinates as used in cosmetics;
2. Information on ethylhexyl alcohol; excerpted from the amended safety assessment of alkyl ethylhexanoates as used in cosmetics;
3. Final report on the safety assessment of cetearyl alcohol, cetyl alcohol, isostearyl alcohol, myristyl alcohol, and behenyl alcohol;
4. Final report on the safety assessment of stearyl alcohol, oleyl alcohol, and octyl dodecanol; and
5. Final report on the safety assessment of Cocos nucifera (coconut) oil and related ingredients.

(con't)

The following unpublished data were received and are included with this submittal:

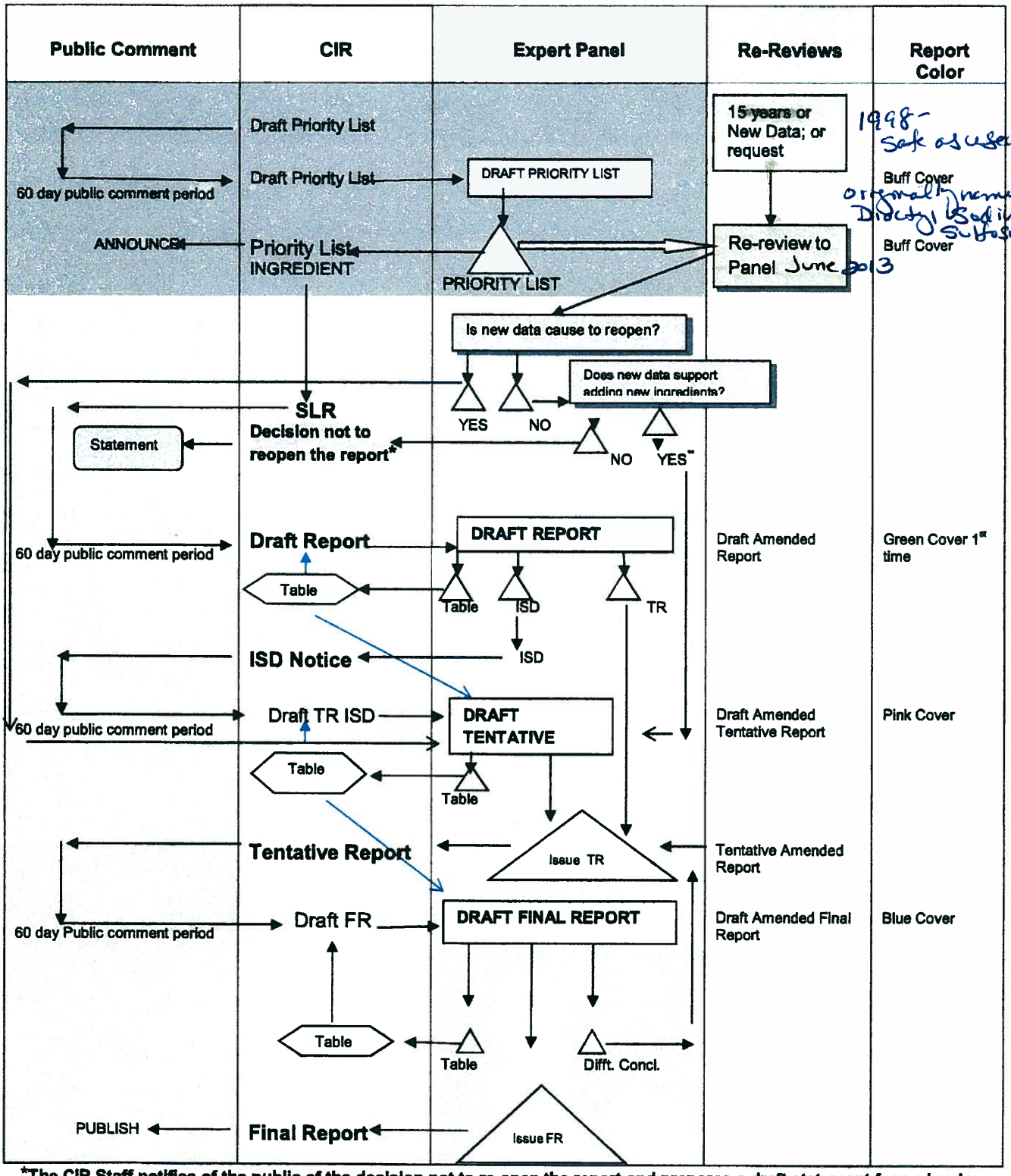
1. Personal Care Products Council. Concentration of use by FDA Product Category: Alkyl Sulfosuccinate Salts. (2012 survey data)

The following are possible outcomes of the Panel review of this document:

1. If the Panel finds that the existing data support the safety of the 19 additional alkyl sulfosuccinate salts, then the Panel should be prepared to re-open the safety assessment to add these ingredients, and issue a Tentative Amended Report, providing a rationale for the Discussion.
2. If the Panel finds the existing data do not support adding the additional ingredients, and finds that the data do not support the existing conclusion for diethylhexyl sodium sulfosuccinate, then Panel should be prepared to re-open the safety assessment to amend the report.
3. If the Panel finds the existing data do not support adding the additional ingredients, but finds that the data do support the existing conclusion for diethylhexyl sodium sulfosuccinate, then Panel should be prepared to not re-open the safety assessment, reaffirming the conclusion.

Alkyl Sulfosuccinate Salts June 2013

SAFETY ASSESSMENT FLOW CHART



*The CIR Staff notifies of the public of the decision not to re-open the report and prepares a draft statement for review by the Panel. After Panel review, the statement is issued to the Public.

**If Draft Amended Report (DAR) is available, the Panel may choose to review; if not, CIR staff prepares DAR for Panel Review.

△ Expert Panel Decision

Alkyl Sodium Sulfosuccinate Salts Re-Review History

1994/1998: Original and Amended Safety Assessment on Dioctyl Sodium Sulfosuccinate (now named, Diethylhexyl Sodium Sulfosuccinate

In 1994, the Expert Panel reviewed the safety of this diethylhexyl sodium sulfosuccinate in cosmetics, and a safe concentration limit of 0.42% was established.

A petition to re-open the report to review new clinical data was received, and in 1998, the Panel amended the report to conclude that this ingredient is safe as used in cosmetic formulations. In the discussion, the Panel stressed that care should be taken to avoid irritancy, especially in those products intended for prolonged contact with the skin.

June 10-11, 2013: Re-Review for Panel Consideration

The Panel considered whether there was any reason to re-open the safety assessment on diethylhexyl sodium sulfosuccinate (previously named dioctyl sodium sulfosuccinate), or, if the conclusion was reaffirmed. Additionally, the Panel considered whether the existing data supports the safety of 19 additional alkyl sulfosuccinate salts (diesters and monoesters; listed below), and if so, whether those salts should be included in the report

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Diesters
Ammonium Dinonyl Sulfosuccinate
Diamyl Sodium Sulfosuccinate
Dicapryl Sodium Sulfosuccinate
Diheptyl Sodium Sulfosuccinate
Dihexyl Sodium Sulfosuccinate
Diisobutyl Sodium Sulfosuccinate
Ditridecyl Sodium Sulfosuccinate

Monoesters
Ammonium Lauryl Sulfosuccinate
Diammonium Lauryl Sulfosuccinate
Dipotassium Lauryl Sulfosuccinate
Disodium Cetearyl Sulfosuccinate
Disodium Cetyl Sulfosuccinate
Disodium Coco-Sulfosuccinate
Disodium Isodecyl Sulfosuccinate
Disodium Isostearyl Sulfosuccinate
Disodium Lauryl Sulfosuccinate
Disodium Oleyl Sulfosuccinate
Disodium Stearyl Sulfosuccinate
Disodium Tridecylsulfosuccinate

Alkyl Sulfosuccinate Salts Data Profile* – June 2013 – Monice Fiume															
	Reported Use	Method of Manufacture	Impurities	Toxicokinetics	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 Irr/Sens	Ocular Irritation
Diesters															
Diethylhexyl Sodium Sulfosuccinate	X	X	X	X	X	X		X	X	X	X	X	X	X	X
Ammonium Dinonyl Sulfosuccinate															
Diamyl Sodium Sulfosuccinate															
Dicapryl Sodium Sulfosuccinate															
Diheptyl Sodium Sulfosuccinate															
Dihexyl Sodium Sulfosuccinate															
Diisobutyl Sodium Sulfosuccinate															
Ditridecyl Sodium Sulfosuccinate															
Monoesters															
Ammonium Lauryl Sulfosuccinate	X														
Diammonium Lauryl Sulfosuccinate															
Dipotassium Lauryl Sulfosuccinate															
Disodium Cetearyl Sulfosuccinate															
Disodium Cetyl Sulfosuccinate															
Disodium Coco-Sulfosuccinate															
Disodium Isodecyl Sulfosuccinate															
Disodium Isostearyl Sulfosuccinate															
Disodium Lauryl Sulfosuccinate	X														
Disodium Oleyl Sulfosuccinate															
Disodium Stearyl Sulfosuccinate															
Disodium Tridecylsulfosuccinate															

*"X" indicates that data were available in a category for the ingredient

Alkyl Sulfosuccinate Salts

PubMed (April 5, 2013)

(DIETHYLHEXYL OR DIOCTYL OR DIAMYL OR DICAPRYL OR DIPENTYL OR DIHEPTYL OR DIISOBUTYL OR DIHEXYL OR METHYLPROPYL OR DITRIDECYL) AND SODIUM AND SULFOSUCCINATE – 300 hits

SciFinder (April 23, 2013)
The remaining Alkyl Sulfosuccinate salts – 55 hits/2 relevant papers

Searched:
ChemPortal
FDA
EC CosIng database
Merck
NTIS

Safety Assessment of Alkyl Sulfosuccinate Salts as Used in Cosmetics

Status:	Re-Review for Panel Consideration
Release Date:	May 17, 2013
Panel Meeting Date:	June 10-11, 2013

The 2013 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 Director is F. Alan Andersen, Ph.D. This re-review document was prepared by Monice M. Fiume, Senior Scientific Analyst/Writer, and Bart A. Heldreth, Ph.D., Chemist.

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INTRODUCTION

Diethylhexyl sodium sulfosuccinate (previously named dioctyl sodium sulfosuccinate) was reviewed by the Cosmetic Ingredient Review (CIR) Expert Panel in 1994, and a safe concentration limit of 0.42% was established. A petition to open the report to review new clinical data was received, and in 1998, the Panel amended the report to conclude that this ingredient is safe as used in cosmetic formulations.[1] In the discussion, the Panel stressed that care should be taken to avoid irritancy, especially in those products intended for prolonged contact with the skin.

In that it has been 15 years since that report was published, the Panel is being asked to determine whether there is any reason to re-open the safety assessment on this ingredient, or, if the conclusion is reaffirmed.

In addition to diethylhexyl sodium sulfosuccinate, there are 19 additional alkyl sulfosuccinate salts (diesters and monoesters) listed in the *International Cosmetic Ingredient Dictionary and Handbook*.[2] All 20 ingredients are anionic surfactants. The Panel is being asked to consider whether these salts, listed below, are appropriate "add-ons" to the report on diethylhexyl sodium sulfosuccinate. To be considered appropriate add-ons, that means that the existing data from the 1998 CIR safety assessment on diethylhexyl sodium sulfosuccinate, and the additional data found since that time that are summarized in the re-review document, are adequate to support the safety of the additional 19 ingredients. If the Panel finds that it is appropriate to include these salts, then the Panel will open this re-review to add these ingredients.

Diesters	Monoesters
Ammonium Dinonyl Sulfosuccinate	Ammonium Lauryl Sulfosuccinate
Diamyl Sodium Sulfosuccinate	Diammonium Lauryl Sulfosuccinate
Dicapryl Sodium Sulfosuccinate	Dipotassium Lauryl Sulfosuccinate
Diheptyl Sodium Sulfosuccinate	Disodium Cetearyl Sulfosuccinate
Dihexyl Sodium Sulfosuccinate	Disodium Cetyl Sulfosuccinate
Diisobutyl Sodium Sulfosuccinate	Disodium Coco-Sulfosuccinate
Ditridecyl Sodium Sulfosuccinate	Disodium Isodecyl Sulfosuccinate
	Disodium Isostearyl Sulfosuccinate
	Disodium Lauryl Sulfosuccinate
	Disodium Oleyl Sulfosuccinate
	Disodium Stearyl Sulfosuccinate
	Disodium Tridecylsulfosuccinate

Published literature that has become available since the CIR safety assessment was issued in 1998 are presented in this review. Data from the 1998 report on diethylhexyl sodium sulfosuccinate are summarized, and are indicated by *italicized text*.

The Panel has recently reviewed the alkyl PEG sulfosuccinates. In 2012, the Panel concluded the alkyl PEG sulfosuccinates are safe in the present practices of use and concentration when formulated to be non-irritating.[3] Additionally, some of the component alcohols, i.e. cetearyl, cetyl, coconut, isostearyl, oleyl, and stearyl alcohols, have been found safe as used.[4-6] Ethylhexyl alcohol has not been reviewed by the CIR, but data on this alcohol are summarized in previous CIR reviews.[7,8]

CHEMISTRY

Definition and Structure

The ingredients proposed for this review are the salts of mono- and di-esters of 2-sulfosuccinic acid. The ingredients all share a sulfo-substituted, succinic acid, core; accordingly, these salts are sulfosuccinates. For example, diheptyl sodium sulfosuccinate, an example of a diester, consists of a seven-carbon alkyl chain (heptyl), connected to the sulfosuccinate core via an ester linkage, and followed by an ester linkage to an additional seven-carbon alkyl chain. (Figure 1.)

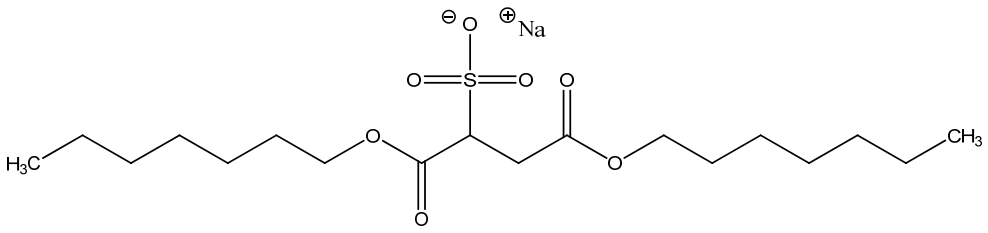


Figure 1. Diheptyl Sodium Sulfosuccinate

Sulfosuccinate monoesters (e.g., dipotassium lauryl sulfosuccinate) contain just one hydrophobic end that consists of a fatty chain (e.g., lauryl ester) and carboxylic acid salt. The level of hydrophobicity imparted by the fatty chains is dependent on the number (mono- or di-ester) and length of these chains. Due to the ester linkage, these sulfosuccinate ingredients are theoretically sensitive to hydrolysis, especially under acidic conditions.

The ingredients included in this assessment are defined in Table 1, and the structures are depicted foloowing the text of this document.

Physical and Chemical Properties

Little published physical and chemical properties data were found. The data that were available are provided in Table 2.

Method of Manufacture

Diethylhexyl Sodium Sulfonate

Maleic anhydride is reacted with 2-ethylhexanol to product bis(2-ethylhexyl)maleate, which is then combined with sodium bisulfite under conditions conducive to the formation of the sulfonate structure through rearrangement with an accompanying saturation of the olefinic bond.[1]

In the production of diethylhexyl sodium sulfosuccinate, malic acid and 2-ethylhexanol are reacted to form the diester, which is sulfonated using sodium metabisulfite.[9] The reaction takes place in a closed system that is opened only for the addition of the reactants.

Dialkyl Sodium Sulfosuccinate

The dialkyl sodium sulfosuccinates are prepared by the action of the appropriate alcohols on maleic anhydride followed by the addition of sodium bisulfite.[10-12]

Impurities

Diethylhexyl Sodium Sulfosuccinate

The *Food Chemicals Codex* has the following acceptance criteria for diethylhexyl sodium sulfosuccinate: not less than (NLT) 98.5% $C_{20}H_{37}NaO_7S$; not more than (NMT) 2 mg/kg lead; NMT 0.2% bis(2-ethylhexyl)maleate; NMT 2.0% loss on drying; 15.5-16.2% residue on ignition.[13] The *United States Pharmacopeia* acceptance criteria are: NLT 99.0% and NMT 100.5% $C_{20}H_{37}NaO_7S$ calculated on the anhydrous basis; NMT 2.0% water; NMT 0.001% heavy metals; NMT 0.4% bis(2-ethylhexyl)maleate; and 15.5-16.5% residue on ignition, calculated on the anhydrous basis.[14]

USE

Cosmetic

The alkyl sulfosuccinate salts are all reported to function in cosmetics as surfactants.[2] (Table 1.) The Food and Drug Administration (FDA) collects information from manufacturers on the use of individual ingredients in cosmetics as a function of cosmetic product category in its Voluntary Cosmetic Registration Program (VCRP). VCRP data obtained from the FDA in 2013,[15] and data received in response to a survey of the maximum reported use concentration by category conducted by the Personal Care Products Council (Council),[16] indicate that three alkyl sulfosuccinate salts named in this report (diethylhexyl sodium sulfosuccinate; ammonium lauryl sulfosuccinate; disodium lauryl sulfosuccinate) are in use.

The current and historical frequency and concentration of use data for diethylhexyl sodium sulfosuccinate are provided in Table 3. The frequency of use increased, from use in 38 cosmetic formulations (1995 data)[1] to use in 62 cosmetic formulations in 2013.[15] The use concentration appears to not have changed. According to the survey conducted by the Council in 2012, the maximum concentration of use reported for diethylhexyl sodium sulfosuccinate is 4.4% in eyebrow pencil formulations;[16] the 1998 safety assessment stated that although concentration of use data were no longer reported to the FDA, 1984 data indicated that diethylhexyl sodium sulfosuccinate was used in a variety of product-types at concentrations of ≤5%.

Frequency[15] and concentration of use[16] data for ammonium lauryl sulfosuccinate and disodium lauryl sulfosuccinate are provided in Table 4. Ammonium lauryl sulfosuccinate is used in two shampoos at 1.6%. Disodium lauryl sulfosuccinate is used in 44 cosmetic formulations; it is used at up to 3% in leave-on and at up to 7% in rinse-off products.

Diethylhexyl sodium sulfosuccinate is used in hair spray formulations at a concentration of 0.15% in an aerosol and at 0.25% in pump spray formulations. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 μm, with propellant sprays yielding a greater fraction of droplets/particles <10 μm compared with pump sprays.[17,18] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and thoracic regions of the respiratory tract and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[19,20]

All of the alkyl sulfosuccinate salts named in this report are listed in the European Union inventory of cosmetic ingredients.[21]

Non-Cosmetic

Sodium 1,4-dialkyl sulfosuccinates are exempt from the requirement of a tolerance for residues when used as an inert ingredient in pesticide formulations for pre-harvest and post-harvest uses, as well as, for application to animals under 40 CFR

180.910 and 40 CFR 180.930, respectively. This regulation eliminates the need to establish a maximum permissible level for residues of the sodium 1,4-dialkyl sulfosuccinates.

Diethylhexyl Sodium Sulfosuccinate

Diethylhexyl sodium sulfosuccinate is generally recognized as safe and effective as a laxative drug product for over-the-counter use. (58 FR 46589, Sept 2, 1993).

Diethylhexyl sodium sulfosuccinate is included in the Listing Of Color Additives Exempt From Certification; it is used as a diluent in color additive mixtures for food use exempt from certification, and has a limitation of <9 ppm. (21CFR 73.1) It is approved as the direct food additive "cocoa with dioctyl sodium sulfosuccinate for manufacturing," whereby the amount of diethylhexyl sodium sulfosuccinate does not exceed 75 parts per million of the finished beverage (21CFR 172.520). Diethylhexyl sodium sulfosuccinate is also allowed as a multi-purpose food additive when it meets the specifications of the *Food Chemicals Codex* (21CFR172.810). With use as an emulsifier, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) has established an acceptable daily intake (ADI) of 0-0.1 mg/kg bw.[22]

Diethylhexyl sodium sulfosuccinate is approved for the following used as an indirect food additive: in adhesives (21CFR175.105); in resinous and polymeric coatings (21CFR175.300), in resinous and polymeric coatings for polyolefin films (21 CFR 175.320); as a component of paper and paperboard in contact with aqueous and fatty foods (21 CFR 176.170); in defoaming agents used in the manufacture of paper and paperboards (21 CFR 176.210); in cellophane (21 CFR 177.1200); in polymers in textile and textile fibers (21 CFR 177.2800); in sanitizing solutions for use on food-contact articles (21 CFR 178.1010); and in emulsifiers and/or surface-active agents in adjuvants, production aids, and sanitizers (21 CFR 178.3400).

Disodium Isodecyl Sulfosuccinate

Disodium isodecyl sulfosuccinate is approved as an indirect food additive in adhesives (21 CFR 175.105) and in emulsifiers and/or surface-active agents in adjuvants, production aids, and sanitizers (21 CFR 178.3400).

Diamyl, Dihexyl, and Diisobutyl Sodium Sulfosuccinate

Diamyl, dihexyl, and diisobutyl sodium sulfosuccinate are used as wetting agents, and diamyl sodium sulfosuccinate is used as an emulsifier in emulsion polymerization.[10-12]

TOXICOKINETICS

Absorption, Distribution, Metabolism, and Excretion

The metabolism and excretion of diethylhexyl sodium sulfosuccinate was determined in rats in several studies; limited details were available. Albino rats were given a single oral dose of 50 mg/kg bw [^{35}S]diethylhexyl sodium sulfosuccinate in an alcohol and water (1:1) solution.[23] More than 85% of the diethylhexyl sodium sulfosuccinate was excreted within 24-48 h after dosing, and all was excreted within 96-120 h. The majority of the radioactivity, 66%, was excreted in the feces. Only 25-35% of the dose was excreted in the urine, and that was within 24-48 h after dosing. At 96-168 h after dosing, only trace amounts of radioactivity were found in the tissues.

However, in other studies, the feces were not the primary route of excretion. In a study in which two rats were given a single oral dose of 5 or 10 mg diethylhexyl sodium sulfosuccinate in water, and two rats were given a single intravenous (i.v.) dose of 10 mg diethylhexyl sodium sulfosuccinate, the animals dosed orally with 5 and 10 mg excreted 18.6% and 15.5% of the total dose and the animals dosed i.v. excreted 12.3-15.5% of the dose in the urine in 24 h.[23] The rats dosed orally excreted 0.9 and 8.7% of the dose in the feces in this time period; however, the animals that were dosed intravenously did not excrete any of the dose in the feces. The 24-48 h urine samples were analyzed for 2-ethylhexanol, and no detectable levels were found.

In another study in which a male rat was dosed by gavage with 10 mg/kg bw [^{14}C]diethylhexyl sodium sulfosuccinate, 64.1% of the radioactivity was excreted in the urine and 37.4% in the feces in the first 24 h, and then only approximately 1% in the urine and 0.9% in the feces in the next 24 h.[23] The researchers stated that diethylhexyl sodium sulfosuccinate must undergo extensive metabolism in the rat because no unchanged diethylhexyl sodium sulfosuccinate was found in the urine, and only a small amount was present in the feces.

Metabolism and excretion was also determined in rabbits and dogs; as with the rat studies, limited details were available. One female rabbit and one male Beagle dog were each given a single oral dose, and one of each species was given a single i.v. dose of 4 mg [^{14}C]diethylhexyl sodium sulfosuccinate.[23] In the rabbits, within 24 h, 87% and 69.7% was excreted in the urine following oral and i.v. dosing, respectively, and similar patterns of metabolites were found with both routes of administration.

In the dogs, similar excretion patterns and metabolic profiles were observed for both routes of dosing. Approximately 21% of the radioactivity was excreted in the urine in the first 24 h. The majority of the radioactivity, approximately 70%, was excreted in the feces at 24-48 h post-dosing. Blood samples were analyzed for 2-ethylhexanol compounds; with i.v. administration, the blood levels fell rapidly during the first hour, and none was found after 8 h. Similarly, following oral administration, small amounts of 2-ethylhexanol was found in the blood after 1 h, and none was found after 8 h.

Penetration Enhancement

Surfactants can enhance the permeation rate of various compounds, inducing a concentration-dependent biphasic action with respect to altering skin permeability.[24] Surfactant molecules must diffuse through the lipid region of the stratum corneum in order to interact with the deeper protein-rich areas. Anionic can solubilize the less-soluble protein, or they can remain on the skin due to formation of chemical compounds with skin keratin, and they can interact strongly with both keratin and lipids. If exposure time is short, permeation through the stratum corneum by anionic materials is generally poor; however, permeation increases with a longer exposure time.

The effect of a diethylhexyl sodium sulfosuccinate microemulsion on the distribution of the polyphenols curcumin and resveratrol between the epidermis and dermis was examined in excised guinea pig and Yucatan micropig (YMP) skin.[25] The microemulsion consisted of 150 mM saline solution, isopropyl palmitate, diethylhexyl sodium sulfosuccinate, and ethanol, with a weight ratio of 20.2:31.3:33.3:15.2, and the mean particle size was 16.6 ± 1.8 nm. Franz-type diffusion cells were used, and 0.5 ml (guinea pig skin) or 1 ml (YMP skin) of the vehicle containing each polyphenol was added to the donor compartment as saturated concentration; the available diffusion area was approximately 0.62 cm^2. Vehicles consisting of a Tween 80 microemulsion or isopropyl myristate were also evaluated. Treatment time was 20 h for guinea pig skin and 40 h for YMP skin. The accumulation of the polyphenols in guinea pig and YMP skin was statistically significantly increased using diethylhexyl sodium sulfosuccinate microemulsion as the vehicle, as compared to that found with the Tween 80 microemulsion or isopropyl myristate. Approximately 1.7% curcumin and 2.2% resveratrol added to donor compartments were incorporated into the skin by the diethylhexyl sodium sulfosuccinate microemulsion. Skin accumulation of curcumin in the diethylhexyl sodium sulfosuccinate microemulsion was approximately 1.9 µmol/g skin in guinea pig skin and approximately 0.24 µmol/g skin in YMP skin; in the isopropyl myristate vehicle, almost no curcumin accumulated in either skin-type. Skin accumulation of resveratrol in the microemulsion was approximately 12 µmol/g skin in guinea pig skin and approximately 3 µmol/g skin in YMP skin; in the isopropyl myristate vehicle, approximately 1 µmol/g skin accumulated in guinea pig skin and 0.1 µmol/g accumulated in YMP skin. In determining the distribution in guinea pig and YMP skin, it was found that diethylhexyl sodium sulfosuccinate, curcumin, and resveratrol penetrated deep in the skin. In YMP skin, the distribution ratio of the polyphenols between the dermis and epidermis decreased with increased molecular weight.

TOXICOLOGICAL STUDIES

Single Dose (Acute) Toxicity

Dermal

The dermal LD_{50} of undiluted diethylhexyl sodium sulfosuccinate in rabbits was >10 g/kg.[9] Occlusive patches of 10 g/kg of the test material were applied to the clipped, unabraded, skin of five male New Zealand white rabbits. Skin fissuring, desquamation, and coriaceousness were observed.

Oral

The oral LD_{50} in rats of a product containing 84% diethylhexyl sodium sulfosuccinate was 3.69 g/kg, and the LD_{50} of a commercially available diethylhexyl sodium sulfosuccinate, administered as a 10% aq. solution or as an emulsion, was 1.9 g/kg in female rats. In mice, the oral LD_{50} for a commercial product containing an unspecified amount of diethylhexyl sodium sulfosuccinate as the active ingredient was 4.8 g/kg, and the i.v. LD_{50} for the product was 0.06 g/kg.[1]

The oral LD_{50} of diethylhexyl sodium sulfosuccinate was 2.64 g/kg bw in male albino ARS/ICR mice[26] and approximately 0.65 g/kg bw in guinea pigs.[27]

Repeated Dose Toxicity

Dermal

Four ml/kg of a test article containing an effective dose of 0.00126% diethylhexyl sodium sulfosuccinate in formulation was applied to the backs of rats, 5 days/wk, for 67 wks. (It is not stated whether the applications were covered.) No remarkable toxic effects were noted. However, minimal to moderate skin irritation was observed sporadically throughout the study.[1]

Oral

Repeated dose oral toxicity studies were performed in the 1940s on diethylhexyl sodium sulfosuccinate in rats, dogs, and monkeys. No remarkable toxic effects were found in rats fed ≤1.25 g/kg bw for 24 wks, in dogs fed 0.10 or 0.25 g/kg bw of a commercial surfactant containing diethylhexyl sodium sulfosuccinate as the active ingredient for 24 wks, or in monkeys fed 0.125 g/kg of the same preparation for 24 wks. However, in a study in which male rats were fed 2, 4, or 8% diethylhexyl sodium sulfosuccinate for 4 mos, the researchers found these doses to be very toxic. Reduced body weight gains were reported in rats fed ≤1% diethylhexyl sodium sulfosuccinate for 2 yrs.[1]

A group of 20 male and 20 female albino rats were fed a diet containing 1% diethylhexyl sodium sulfosuccinate (100% pure) for 90 days, and controls were given untreated feed.[9] All animals survived until study termination. There were no clinical signs of toxicity, and no dosing-related macroscopic or microscopic findings. Differences in body weights or organ weights compared to controls were not statistically significant.

Twelve rats/group were fed a diet containing 0, 0.5, 1.04, or 1.5% diethylhexyl sodium sulfosuccinate for 26 wks.[28] Body weight gains of females of the 1.04 and 1.5% dose groups were decreased during wk 3. Two control animals and 4 animals of the 1.5% group died during the study; two of the four animals of the 1.5% group had hemorrhagic gastroenteritis. No other effects were noted. The no-observable adverse effect level (NOAEL) was 0.5%, and the lowest-observable adverse effect level was 1.04%.

Groups of four male and four female Beagle dogs were dosed orally with tablets containing 30 mg/kg bw diethylhexyl sodium sulfosuccinate, 10 mg/kg bw diethylhexyl sodium sulfosuccinate + 5 mg/kg bw 1,8-dihydroanthroaquinone (DHA), or 30 mg/kg bw diethylhexyl sodium sulfosuccinate + 15 mg/kg bw DHA, daily, for 1 yr.[26] A control group was given a placebo tablet. Urinalysis was performed, and hematological and clinical chemistry parameters were measured at various intervals. No signs of toxicity were observed in any of the groups. Diethylhexyl sodium sulfosuccinate, alone and in combination with DHA, did not have any adverse effects on urinalysis, hematological or clinical parameters, or body weights, and it did not induce any gross or microscopic lesions. The NOAEL was >30 mg/kg bw.

Inhalation

Rats exposed to an aerosol of a product containing an effective diethylhexyl sodium sulfosuccinate concentration of 0.21% at an exposure concentration of 4.2 mg/m^3, 4 h/day, 5 days/wk, for 13 wks, had significant changes in hematology and clinical chemistry parameters as compared to controls. Mongrel dogs were exposed for 30-45 min to a 1% solution of a commercial detergent containing diethylhexyl sodium sulfosuccinate in equal volumes of 95% ethanol and isotonic saline, at a final concentration of 15 mg/kg of the test material, and then killed 30 min, 2 h, or 4 h after exposure. Gross, but not microscopic changes in pulmonary structure and changes in pulmonary function were observed; the researchers suggested that the test article was capable of displacing the normal alveolar surfactant into the airway and resulted in increased alveolar surface tension and instability.[1]

Fluorescent latex particles, 0.63 µm diameter, were administered in aerosol form to 30 rabbits.[29] Six rabbits were killed immediately after administration of the fluorescent particles (baseline group); 12 rabbits were given a diethylhexyl sodium sulfosuccinate aerosol prepared as a 2% solution in equal volumes of ethanol and physiological saline (detergent group) and 12 were given vehicle aerosol (control group). The detergent and control aerosols were administered as 200 pressure-controlled breaths at a frequency of 40/min, resulting in deposition of approximately 10 µl of fluid in the lungs; aerosol administration was repeated after 90 min. Groups of six animals from the detergent and control groups were then exposed to large tidal volume ventilation (LTVV) or conventional ventilation for 3 h. The total number of particles in the alveoli and ducts were similar for all groups, except for a statistically significant decrease in the control LTVV group. All test groups had reduced number of single particles in the alveoli as compared to the baseline group. The number of clustered particles was statistically significantly increased in the alveoli + ducts in the detergent-LTVV group, as compared to the baseline group.

Rabbits were administered [^{99m}Tc]diethylene triamine pentaacetate (^{99m}Tc-DTPA) using a nebulizer, and the effect of diethylhexyl sodium sulfosuccinate on the absorption of this compound from the lungs was examined.[30] The alveolo-capillary transfer of ^{99m}Tc-DTPA was measured for 30 min, and the rabbits were then nebulized with 0.2% solution of diethylhexyl sodium sulfosuccinate for 5 min. Thirty min later, the rabbits were nebulized with a 2% diethylhexyl sodium sulfosuccinate solution for 5 min. Diethylhexyl sodium sulfosuccinate greatly enhanced the alveolar absorption of ^{99m}Tc-DTPA.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

In a three-generation study, rats were fed 0, 0.1, 0.5, or 1.0% diethylhexyl sodium sulfosuccinate. Body weights of all parental males and in F_1 and F_2 females of the 0.5 and 1.0% test groups were decreased, and the body weights of pups of all three generations were decreased compared to controls. No effects on reproductive parameters, and no gross lesions or treatment-related mortalities, were observed.[1]

In developmental toxicity studies, groups of 20 gravid female mice and 20 gravid female rats were dosed by gavage with 0, 16, 80, or 400 mg/kg bw of a test substance containing 0.4% (w/v) diethylhexyl sodium sulfosuccinate. The mice were dosed on days 6-15 and killed on day 17 of gestation and the rats were dosed on days 5-19 of gestation and killed on day 20 of gestation. The NOAEL for maternal toxicity and teratogenic effects for both mice and rats was 400 mg/kg bw of the test substance containing 0.4% (w/v) diethylhexyl sodium sulfosuccinate.

Groups of 20-39 gravid female Sprague-Dawley rats were fed a diet containing 0, 1, or 2% diethylhexyl sodium sulfosuccinate (equivalent to 0, 1074, and 1983 mg/kg bw, respectively) on days 6-15 of gestation, and the dams were killed on day 21 of gestation.[9] No adverse effects on maternal or fetal parameters were observed in the 1% test group. In the 2% test group, significant incidences of resorptions and gross abnormalities, primarily exencephaly and, at times, spina bifida, anophthalmia, and associated skeletal defects, were reported. The NOAEL for maternal toxicity and teratogenic effects was 1%.

Groups of 30 female rats were dosed by gavage with 0, 16, 80, or 400 mg/kg bw of a test substance containing 0.4% (w/v) diethylhexyl sodium sulfosuccinate once daily for 14 days prior to mating with untreated males; one-half of the animals in each group were dosed until day 13 of gestation, at which time the animals were killed, and the remaining animals were dosed

until parturition and were not killed. No effects on reproductive parameters, fertility, or pup weight and condition were observed. The parental NOAEL was 400 mg/kg bw of the test substance containing 0.4% (w/v) diethylhexyl sodium sulfosuccinate.

A three-generation study was performed in which male and female CFE rats were continuously fed a diet containing 0, 0.5, and 1% of a test substance containing 50% diethylhexyl sodium sulfosuccinate in aq. beverage-grade ethanol; the number of animals per group was not stated.[9] Dosing was initiated at weaning of rats of the F_0 generation; these rats were mated twice to produce the F_{1a} and F_{1b} generation. Rats of the F_{1b} generation were mated to produce the F_2 generation, and the F_2 generation was mated twice to produce the F_{3a} and F_{3b} offspring. F_{1a} and F_{3b} offspring were the only pups weaned directly to the test diets. Because of a high incidence of pup mortality, all other dams were given a control diet on the last expected day of gestation. Necropsy and microscopic examination were performed only on pups from the first mating of the F_2 animals that died or were killed at weaning.

Up until the F_2 generation, body weights in parental males were 6-10% lower than control body weights. There were no significant treatment-related effects on mean litter size and the mean number of viable pups in each litter or on fertility or gestational indices. For all pups of the F_{1a} generation, including controls, the number of pups weaned and the average body weight of those pups at weaning was reduced; however, greater reductions were seen in the test groups than in the control group. The viability indices of the F_{3b} pups receiving the test diet were reduced. The researchers stated the most remarkable result of the study was the reduced number of offspring surviving from day 5 until weaning; it was hypothesized that pups stopped nursing because they could taste the test article. A no-observed effect level (NOEL) for parental toxicity and effects on pups was not established; the NOEL for reproduction was 1%.

GENOTOXICITY

Diethylhexyl sodium sulfosuccinate was not mutagenic in an Ames test, but with metabolic activation, it did induce chromosomal aberrations in Chinese hamster ovary cells at treatment doses close to threshold toxicity.[1]

CARCINOGENICITY

Effect on Colorectal Carcinogenesis

A group of 84 inbred male F344 rats was fed a diet containing 1% diethylhexyl sodium sulfosuccinate, and the control group was fed untreated feed.[31] As part of a rodent model for colon carcinogenesis, rats of both groups were given a subcutaneous injection of 20 mg/kg bw of 1,2-dimethylhydrazine, once weekly for 20 wks. Twenty rats per group were killed after 3, 4, 5, and 6 mos. The test group tolerated the diethylhexyl sodium sulfosuccinate feed well. There was no statistically significant difference between the test and control group in the percentage of rats bearing tumors, and the number of tumors per rat increased progressively throughout the study. However, at 5 and 6 mos, each rat in the test group had fewer tumors of all histologic types (combined), at all organ sites, compared to controls; this difference was statistically significant for the duodenum, colon, rectum, and total number of gastrointestinal tumors at 5 mos.

IRRITATION AND SENSITIZATION

Dermal Irritation and Sensitization

Non-Human

In rabbits, a 24-h patch of 2% diethylhexyl sodium sulfosuccinate resulted in an irritation score of 3.7/8 for intact skin and 1.7/8 for abraded skin. In a single-insult occlusive patch test, a 10% solution of a product containing 84% diethylhexyl sodium sulfosuccinate in propylene glycol was minimally irritating to rabbit skin. In a 2-wk study, 10 applications of 1% diethylhexyl sodium sulfosuccinate to intact abdominal skin in rabbits resulted in moderate hyperemia; a test concentration of 5% produced a burn from two to four 24-h applications and of 25% produced a burn with one 24-h application. Application of 1, 5, and 25% diethylhexyl sodium sulfosuccinate to abraded rabbit abdominal skin for 3 days was moderately to severely irritating. In a study examining acanthosis following repeated (number not stated) dermal applications of 2, 10, and 20% diethylhexyl sodium sulfosuccinate, an acanthosis factor (AF) was calculated from the difference in epidermal thickness, with 1 unit being equivalent to 2.7 μm. The AFs were 1.8, 2.5, and 3.3, respectively.[1]

Occlusive patches containing 0.5 ml diethylhexyl sodium sulfosuccinate were applied to intact and abraded skin of six rabbits; the duration of exposure was not stated.[9] For intact skin, the mean Draize scores for erythema and edema were 2.33 and 2.50, respectively, after 24 h and 1.66 and 1.0, respectively, after 72 h. For abraded skin the mean scores for erythema and edema were 2.50 and 2.50, respectively, after 24 h and 1.66 and 1.60, respectively, after 72 h.

Human

In a 50-subject study, a single 24-h occlusive patch of a formulation containing 2.5% diethylhexyl sodium sulfosuccinate was not an irritant. In mini-cumulative irritancy tests, the primary irritation index (PII) of four products containing a 3.5% solution of 84% diethylhexyl sodium sulfosuccinate ranges from 0.25 – 0.80; the PIIs of two products containing a 0.25% solution of 84% diethylhexyl sodium sulfosuccinate were 1.78 and 1.85; and the PII of a product containing a 0.1% solution of 84% diethylhexyl sodium sulfosuccinate was 0.04. In a 21-day cumulative irritancy test of a product containing 1.13% solu-

tion of diethylhexyl sodium sulfosuccinate performed in 7 volunteers, the total irritation score was 324/578 for all seven subjects over the 21-day period; the average score per panelist was 46.3/84.[1]

In a 110-subject human repeated insult patch test (HRIPT) of 1, 3, and 5% diethylhexyl sodium sulfosuccinate and a 107-subject HRIPT of a 50/50 dilution in distilled water of an eyebrow pencil containing 2.5% diethylhexyl sodium sulfosuccinate, reactions were observed during induction, but not at challenge. In a number of additional HRIPTs with 0.21 or 0.42% diethylhexyl sodium sulfosuccinate or with a product containing 0.1% diethylhexyl sodium sulfosuccinate (84% pure), the test articles were not sensitizers, although some mild reactions were observed during induction.[1]

Diethylhexyl sodium sulfosuccinate produced irritation, but it was not a sensitizer.[9] For induction, a 15 mm occlusive patch containing 0.30 g of 2.5% ethylhexyl sodium sulfosuccinate in petrolatum was applied to the backs or forearms of 100 subjects; the patches were applied for 10 alternate 24-h periods. Challenge patches containing 0.30 g diethylhexyl sodium sulfosuccinate were applied to a previously untreated site on the back or forearm following a 7-day non-treatment period. The challenge sites were scored upon patch removal and 24 h later. During induction, the following observations were made: mild erythema in 11 subjects on days 3-10 and in 1 subject on days 3-7; mild erythema on all days except day 7 and intense erythema on day 7 in one subject; mild erythema on days 3-6/7 followed by intense erythema on days 6/7-10 in 6 subjects. No reactions were observed at challenge.

In a case report, a female subject had allergic contact dermatitis from diethylhexyl sodium sulfosuccinate that was an ingredient in a topical corticosteroid.[32] In patch testing, the patient had a +++ reaction to 1% aq. diethylhexyl sodium sulfosuccinate on day 2 and day 4. The researchers noted that this was a rare reaction.

Phototoxicity/Photoallergenicity

Human

In a study investigating the photocontact allergenic potential of a product containing 0.25% diethylhexyl sodium sulfosuccinate in 25 subjects, there were no reactions during the induction or the challenge phase that were attributable to ethylhexyl sodium sulfosuccinate.[1]

Ocular Irritation

In the eyes of rabbits, concentrations of ≥25% diethylhexyl sodium sulfosuccinate were severely irritating, and concentrations of ≤10% produced little or no irritation.[1]

Diethylhexyl sodium sulfosuccinate, 0.1 g, was instilled into the conjunctival sac of the eyes of six rabbits.[9] The eyes were scored for irritation after 24, 48, and 72 h, and the following scores were reported: 11.66, 12.50, and 4.16, respectively, (cornea); 1.66 at all three times (iris); and 5.33, 4.33, and 1.66, respectively (conjunctivae). No destruction or irreversible changes of the tissue in 24 h were reported.

Diethylhexyl sodium sulfosuccinate, 10%, was used as a positive control in a Draize eye irritancy test.[33] One-tenth ml of the test substance was instilled into the conjunctival sac of one eye of each of three rabbits for 2 sec; the eyes were rinsed. Diethylhexyl sodium sulfosuccinate, 10%, was severely irritating to rabbit eyes, inducing perforated damages.

Diisobutyl sodium sulfosuccinate is irritating to eyes and mucous membranes.[12] (Details were not provided.)

SUMMARY

(New Data Only)

Diethylhexyl sodium sulfosuccinate (previously named dioctyl sodium sulfosuccinate), an anionic surfactant, was reviewed by the CIR Expert Panel in 1994, and the report was amended in 1998. In 1998, the Panel concluded that diethylhexyl sodium sulfosuccinate is safe as used in cosmetic formulations. Since the 1998 report was issued, the number of reported uses in cosmetic formulations has increased from 35 to 62 uses. However, the concentration of use has not changed. The data that were available for the 1998 report indicated that diethylhexyl sodium sulfosuccinate was used in a variety of product-types at concentrations of ≤5%; current information report that the maximum use concentration is 4.4% in eyebrow pencil formulations.

[If the Panel agrees to the add-on ingredients: The Panel has determined that the data included in the original safety assessment, as well as in this re-review document, support the safety of an additional 19 alkyl sulfosuccinate salts. These salts are diesters and monoesters of 2-sulfosuccinic acid, and also are anionic surfactants. All share a sulfo-substituted, succinic acid, core. All contain an ester linkage, and are theoretically sensitive to hydrolysis, especially under acidic conditions. Two of these salts are reported to be in use; ammonium lauryl sulfosuccinate is used in two shampoos at 1.6%, and disodium lauryl sulfosuccinate is used in 44 cosmetic formulations at up to 3% in leave-on and at up to 7% in rinse-offs.]

Metabolism and excretion studies have given mixed results on the primary route of excretion of diethylhexyl sodium sulfosuccinate; it does appear that diethylhexyl sodium sulfosuccinate is metabolized prior to excretion, and most of the dose is excreted within 24 h of dosing. In one oral study in rats, 66% of the radioactivity was excreted in the feces and only 25-35% in urine, within 24-48 h after dosing. In other rat studies, with oral and i.v. administration, the majority of the radioactivity

was excreted in the urine, rather than in the feces. Studies were also performed in rabbits and dogs, and again conflicting results were obtained. In rabbits, 87% and 69.7% of the radioactivity was excreted in the urine following oral and i.v. dosing, respectively; in dogs, approximately 70% of the radioactivity was excreted in the feces at 24-48 h after oral and i.v. dosing.

Diethylhexyl sodium sulfosuccinate increased the penetration of curcumin and resveratrol, *in vitro*, through excised guinea pig and Yucatan micro-pig skin.

The dermal LD_{50} of undiluted diethylhexyl sodium sulfosuccinate in rabbits was >10 g/kg; skin irritation was observed following the single dermal dose of 10 g/kg test material. The oral LD_{50} was 2.64 g/kg bw in male albino ARS/ICR mice and approximately 0.65 g/kg bw in guinea pigs.

In repeated-dose oral studies in which rats were given feed containing 1% diethylhexyl sodium sulfosuccinate for 90 days or up to 1.5% for 26 wks, and in studies in which Beagle dogs were given tablets containing 30 mg/kg bw/day diethylhexyl sodium sulfosuccinate for 1 yr, no remarkable toxic effects were reported.

In an inhalation study in rabbits, a 5-min exposure to 0.2% DSS, followed 30 min later by a 5 min exposure to 2% diethylhexyl sodium sulfosuccinate, greatly enhanced the alveolar absorption of ^{99m}Tc-DTPA.

Numerous studies examining the effect of the oral administration of diethylhexyl sodium sulfosuccinate, both dietary and by gavage, on the reproductive and developmental toxicity in rats were performed. One study was performed in mice. In a developmental study in mice and rats of a test substance containing 0.4% (w/v) diethylhexyl sodium sulfosuccinate, the NOAEL for maternal toxicity and teratogenic effects for both mice and rats was 400 mg/kg bw. In another developmental toxicity study in rats, the parental NOAEL was 400 mg/kg bw for a test substance containing 0.4% (w/v) diethylhexyl sodium sulfosuccinate. In a study in which gravid female Sprague-Dawley rats were fed a diet containing up to 2% diethylhexyl sodium sulfosuccinate, no adverse effects on maternal or fetal parameters were observed in the 1% test group, but in the 2% test group, significant incidences of resorptions and gross abnormalities, primarily exencephaly and, at times, spina bifida, anophthalmia, and associated skeletal defects, were reported. The NOAEL for maternal toxicity and teratogenic effects was 1%. In a three-generation study in which rats were fed a diet containing up to 1% of a test substance containing 50% diethylhexyl sodium sulfosuccinate in aq. beverage-grade ethanol, a NOEL for parental toxicity and effects on pups was not established because of reduced body weight gains in the parents and reduced viability indices in the pups, but the NOEL for reproduction was 1%; the reduced viability index most likely was attributed to the pups discontinuing nursing because they could taste the test article.

In rats, a diet containing 1% diethylhexyl sodium sulfosuccinate did not have an effect on 1,2-dimethylhydrazine-induced colorectal carcinogenesis.

In clinical studies, 2.5% diethylhexyl sodium sulfosuccinate was an irritant, but not a sensitizer.

Diethylhexyl sodium sulfosuccinate was used as a positive control in a Draize ocular irritation study; 10% diethylhexyl sodium sulfosuccinate was severely irritating to rabbit eyes, inducing perforated damages.

DISCUSSION

From the 1998 Report

The CIR Expert Panel previously determined that a conclusion for Dioctyl Sodium Sulfosuccinate (now, diethylhexyl sodium sulfosuccinate) could be based on the available experimental data. A concentration of 0.42% was the highest level for which there was sufficient data to substantiate safety. This level was found not to induce sensitization in a human RIPT. While no effect was found in a clinical 21-day cumulative assay testing at a higher concentration (approximately 1%), the assay used seven panelists whereas the RIPT had 100 participants. In the absence of current data on concentration of use for this ingredient, the Expert Panel was unable to suggest how these experimental concentrations relate to actual use. This ingredient may be safe as currently used, but in the absence of use data, the Expert Panel concluded that a concentration limit is necessary.

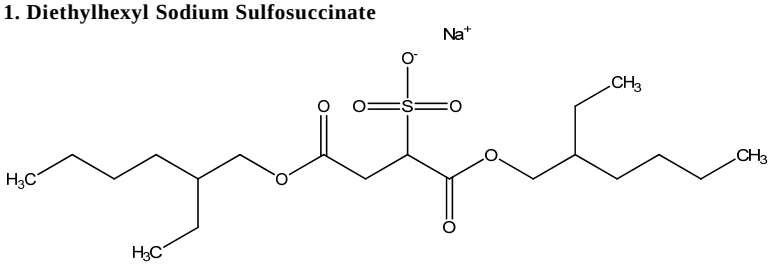
In addition, the Panel recognized that positive results in the CHO mutagenicity assay were only found with toxicity. Thus, the findings are of questionable significance.

After reviewing additional data, the CIR Expert Panel decided that there was sufficient evidence to eliminate the need for a limit on concentration. The Panel considered Dioctyl Sodium Sulfosuccinate to be safe used in cosmetic formulations. It was acknowledged that under the exaggerated exposure conditions of the two RIPTs (continuous occlusive patch testing), the ingredient is a cumulative irritant, though not a sensitizer. The Panel recognized that a surfactant would most likely produce irritation under such conditions. The Panel stressed that care should be taken to avoid irritancy, especially in those products intended for prolonged contact with the skin.

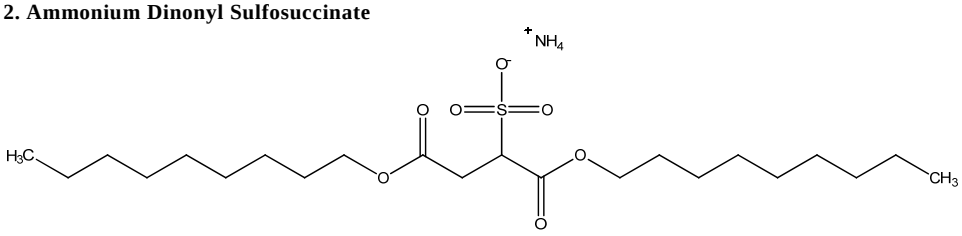
FIGURES

Structures – Diesters

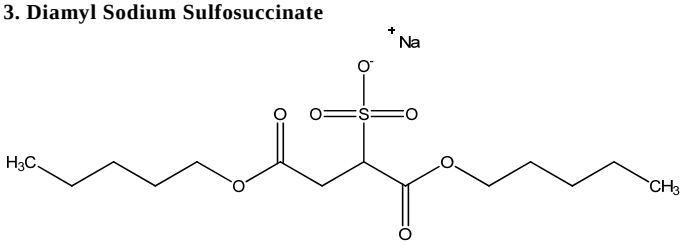
1. Diethylhexyl Sodium Sulfosuccinate



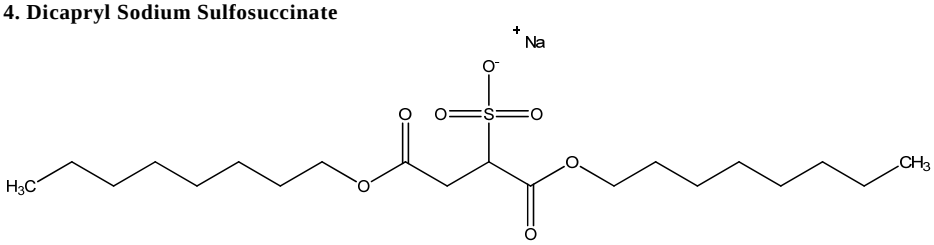
2. Ammonium Dinonyl Sulfosuccinate



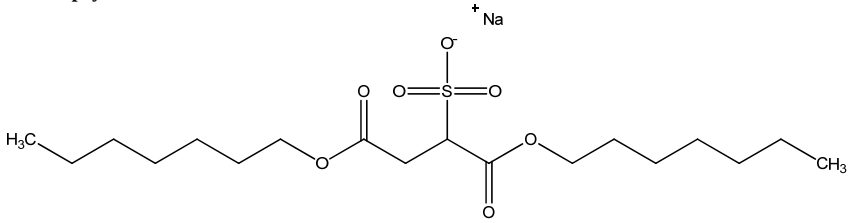
3. Diamyl Sodium Sulfosuccinate



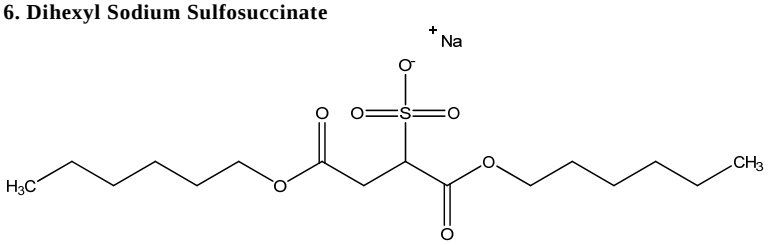
4. Dicapryl Sodium Sulfosuccinate



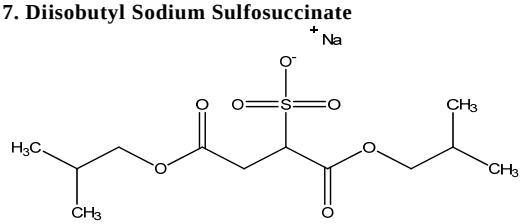
5. Diheptyl Sodium Sulfosuccinate



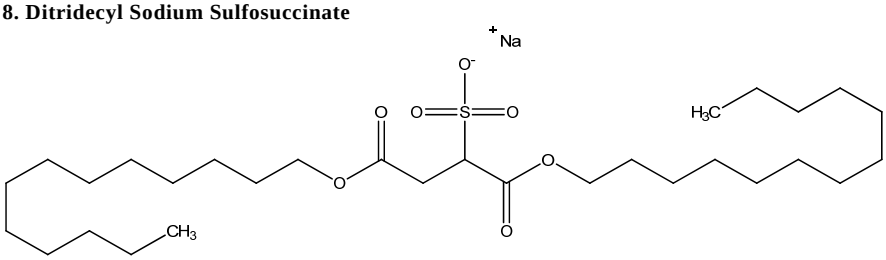
6. Dihexyl Sodium Sulfosuccinate



7. Diisobutyl Sodium Sulfosuccinate

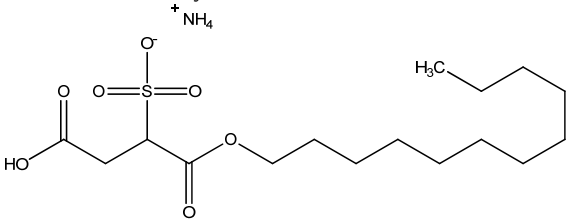


8. Ditridecyl Sodium Sulfosuccinate

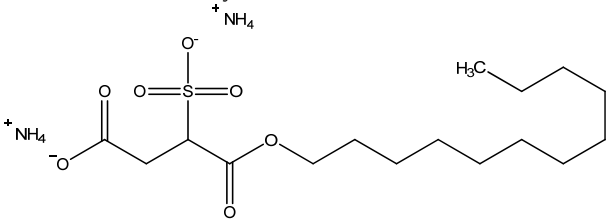


Structures – Monoesters

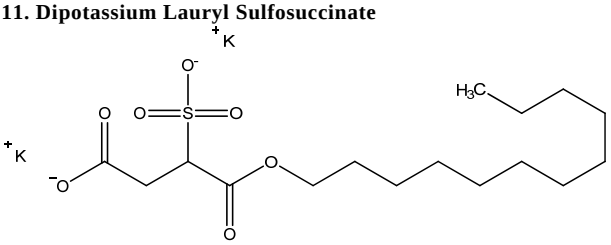
9. Ammonium Lauryl Sulfosuccinate



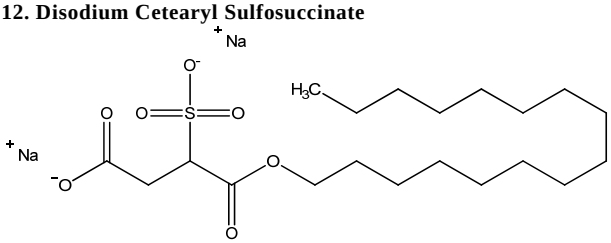
10. Diammonium Lauryl Sulfosuccinate

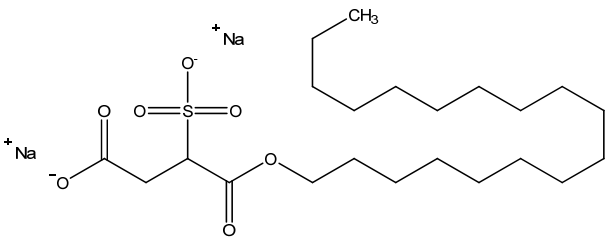


11. Dipotassium Lauryl Sulfosuccinate

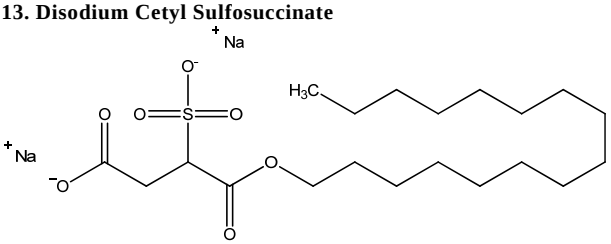


12. Disodium Cetearyl Sulfosuccinate

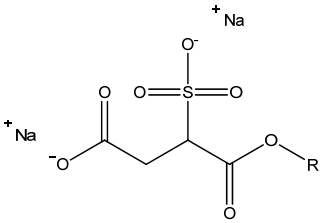




13. Disodium Cetyl Sulfosuccinate

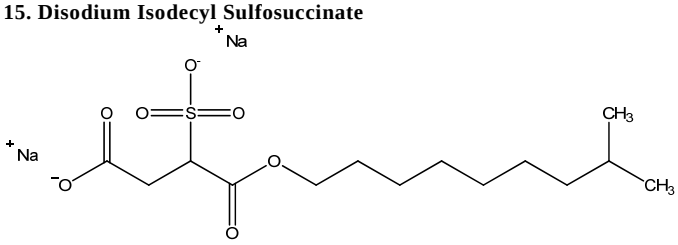


14. Disodium Coco-Sulfosuccinate



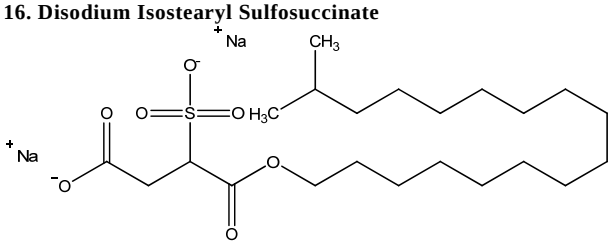
Wherein R represents the residue of the fatty alcohols derived from coconut acid

15. Disodium Isodecyl Sulfosuccinate



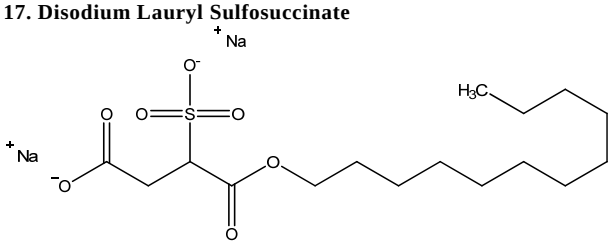
An example of an “iso**”**

16. Disodium Isostearyl Sulfosuccinate

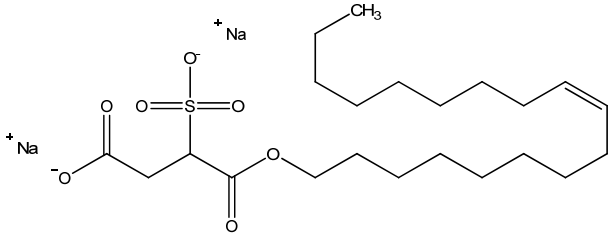


An example of an “iso”

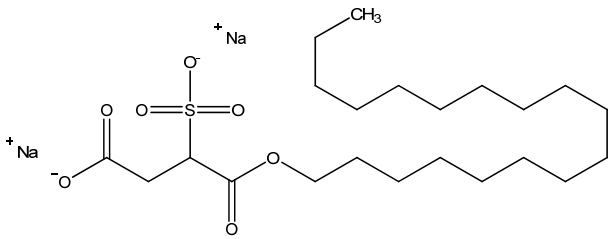
17. Disodium Lauryl Sulfosuccinate



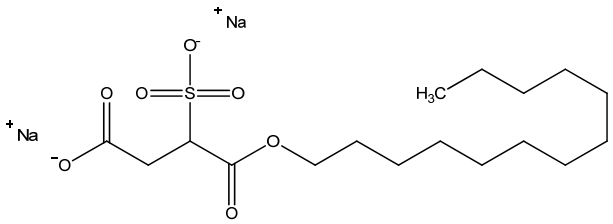
18. Disodium Oleyl Sulfosuccinate



19. Disodium Stearyl Sulfosuccinate



20. Disodium Tridecylsulfosuccinate



TABLES

Table 1. Definitions and Functions

Ingredient/CAS No.	Definition[2]	Function[2]
	DIESTERS	
Diethylhexyl Sodium Sulfosuccinate 577-11-7	the sodium salt of the diester of an 2-ethylhexyl alcohol and sulfosuccinic acid	surfactant – cleansing agent; hydrotrope
Ammonium Dinonyl Sulfosuccinate 27501-55-9	the ammonium salt of a nonyl alcohol diester of sulfosuccinic acid	surfactant – cleansing agent
Diamyl Sodium Sulfosuccinate 922-80-5	the sodium salt of the diester of an amyl alcohol and sulfosuccinic acid;[2] the amyl or 1-methylbutyl diester of the monosodium salt of sulfosuccinic acid or a mixture of both[10]	surfactant - hydrotrope
Dicapryl Sodium Sulfosuccinate 1639-66-3	the sodium salt of the diester of an capryl alcohol and sulfosuccinic acid	surfactant - hydrotrope
Diheptyl Sodium Sulfosuccinate 4680-44-8	the sodium salt of the diester of an heptyl alcohol and sulfosuccinic acid	surfactant - hydrotrope
Dihexyl Sodium Sulfosuccinate 6001-97-4	the sodium salt of the diester of 1-methylamyl alcohol and sulfosuccinic acid;[2] the bis(1-methylamyl) ester of sulfosuccinic acid monosodium salt, perhaps in an admixture with the dihexyl ester[11]	surfactant - hydrotrope
Diisobutyl Sodium Sulfosuccinate 127-39-9	the sodium salt of the diester of an isobutyl alcohol and sulfosuccinic acid;[2] the isobutyl or butyl or 1-methylpropyl diester of the monosodium salt of sulfosuccinic acid, or a mixture of all three[12]	surfactant - hydrotrope
Ditridecyl Sodium Sulfosuccinate 2673-22-5	the sodium salt of the diester of an tridecyl alcohol and sulfosuccinic acid	surfactant – cleansing agent; foam booster; hydrotrope
	MONOESTERS	
Ammonium Lauryl Sulfosuccinate 140852-23-9	the ammonium salt of a lauryl alcohol half ester of sulfosuccinic acid	surfactant – cleansing agent
Diammonium Lauryl Sulfosuccinate 123776-54-5	the ammonium salt of a lauryl alcohol half ester of sulfosuccinic acid	surfactant – cleansing agent; hydrotrope
Dipotassium Lauryl Sulfosuccinate	the dipotassium salt of a lauryl alcohol half ester of sulfosuccinic acid	surfactant – cleansing agent
Disodium Cetearyl Sulfosuccinate	the disodium salt of a cetearyl alcohol half ester of sulfosuccinic acid	surfactant – cleansing agent; emulsifying agent; foam booster; hydrotrope
Disodium Cetyl Sulfosuccinate 26838-10-8	the disodium salt of a cetyl alcohol half ester of sulfosuccinic acid	surfactant – hydrotrope; cleansing agent; foam booster
Disodium Coco-Sulfosuccinate 90268-37-4	the disodium salt of a half ester of coconut alcohol and sulfosuccinic acid	surfactant –cleansing agent; hydrotrope; skin conditioning agent - emollient
Disodium Isodecyl Sulfosuccinate 37294-49-8; 55184-70-8	the disodium salt of a half ester of a branched decyl alcohol and sulfosuccinic acid	surfactant – hydrotrope; cleansing agent; foam booster
Disodium Isostearyl Sulfosuccinate	the disodium salt of a half ester of isostearyl alcohol and sulfosuccinic acid	surfactant – hydrotrope; cleansing agent; foam booster
Disodium Lauryl Sulfosuccinate 13192-12-6; 19040-44-9; 26838-05-1	the disodium salt of a lauryl alcohol half ester of sulfosuccinic acid	surfactant – hydrotrope; cleansing agent; foam booster
Disodium Oleyl Sulfosuccinate 131456-48-9; 94021-02-0	the disodium salt of an oleyl alcohol half ester of sulfosuccinic acid	surfactant – hydrotrope; cleansing agent; foam booster
Disodium Stearyl Sulfosuccinate	the disodium salt of a stearyl alcohol half ester of sulfosuccinic acid	surfactant – hydrotrope; cleansing agent; foam booster
Disodium Tridecylsulfosuccinate 68133-71-1; 83147-64-2	the disodium salt of a tridecyl alcohol half ester of sulfosuccinic acid	surfactant – hydrotrope; cleansing agent; foam booster

Table 2. Physical and chemical properties

Property	Description	Reference
	Diethylhexyl Sodium Sulfosuccinate	
physical appearance	*waxy solid*; usually in rolls of tissue-thin material	1,34
molecular wt	444.56	34
melting point	153-157°C	9
partition coefficient	approx.. 3.95 (25° C; estimated)	28
density	1.1 g/m^3	9
solubility	*soluble in water and in organic solvents, especially in water and water-miscible solvent combinations*	1
	dissolves slowly in water; freely soluble in alcohol and in glycerin; very soluble in solvent hexane	13
stability	*acid and neutral solutions are stable; alkaline solutions hydrolyze*	1
	Ammonium Dinonyl Sulfosuccinate	
molecular wt	467.66	35
	Diamyl Sodium Sulfosuccinate	
physical appearance	mixture of white, hard pellets and powder	10
molecular wt	360.40	10
solubility	soluble in water, organic solvents, pine oil, oleic acid, acetone, hot kerosene, carbon tetrachloride, hot olive oil, glycerol; insoluble in liquid petrolatum	10
stability	stable in acid and neutral solutions; hydrolyzes in alkaline solutions	10
	Dicapryl Sodium Sulfosuccinate	
molecular wt	445.57	36
	Diheptyl Sodium Sulfosuccinate	
molecular wt	416.51	35
	Dihexyl Sodium Sulfosuccinate	
physical appearance	white, slightly hygroscopic, wax-like pellets	11
molecular wt	388.45	11
solubility	must be soaked to dissolve in cold water; dissolves rapidly in hot water	11
	also soluble in pine oil, oleic acid, acetone, kerosene, carbon tetrachloride, 2B ethanol, benzene, hot olive oil, glycerol; insoluble in liquid petrolatum	
stability	stable in acid and neutral solutions; hydrolyzes in alkaline solutions	11
	Diisobutyl Sodium Sulfosuccinate	
physical appearance	white, powder-like, easily grindable material	12
molecular wt	332.35	12
solubility	soluble in water, organic solvents, glycerol, pine oil, and oleic acid; insoluble in acetone, kerosene, carbon tetrachloride, 2B ethanol, benzene, olive oil, and liquid petrolatum	12
stability	stable in acid and neutral solutions; hydrolyzes in alkaline solutions	12
	Disodium Isodecyl Sulfosuccinate	
molecular wt	384.4	36
	Disodium Lauryl Sulfosuccinate	
molecular wt	410.43	35
	Disodium Oleyl Sulfosuccinate	
molecular wt	492.21	35
	Disodium Tridecylsulfosuccinate	
molecular wt	424.46	35
	Ditridecyl Sodium Sulfosuccinate	
molecular wt	585.84	36

Table 3. Current and historical frequency and concentration of use of diethylhexyl sodium sulfosuccinate according to duration and exposure

	# of Uses		*Max Conc of Use (%)*	
	2013[15]	**1995[1]**	**2012[16]**	**1984[1]**
Totals*	**62**	**38**	**0.0002-4.4**	**5****
Duration of Use				
Leave-On	*34*	*21*	*0.0002-4.4*	**
Rinse-Off	*25*	*12*	*0.1-1.2*	**
Diluted for (Bath) Use	*3*	*5*	*NR*	**
Exposure Type				
Eye Area	14	5	0.06-4.4	**
Incidental Ingestion	NR	NR	NR	**
Incidental Inhalation-Spray	NR	NR	0.15 (aerosol) 0.25 (pump spray)	**
Incidental Inhalation-Powder	NR	NR	NR	**
Dermal Contact	28	30	0.0002-4.4	**
Deodorant (underarm)	2[a]	NR	0.0002	**
Hair - Non-Coloring	12	1	0.15-0.75	**
Hair-Coloring	10	5	NR	**
Nail	2	2	1	**
Mucous Membrane	3	5	NR	**
Baby Products	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.
**Only the maximum reported concentration of use was reported in the 1998 safety assessment.
[a] It is not know whether or not these products are sprays.
NR – no reported use

Table 4. Frequency and concentration of use according to duration and type of exposure

	# of Uses[15]	*Max Conc of Use (%)[16]*	*# of Uses[15]*	*Max Conc of Use (%)[16]*
	Ammonium Lauryl Sulfosuccinate		**Disodium Lauryl Sulfosuccinate**	
Totals*	**2**	**1.6**	**44**	**0.00004-7**
Duration of Use				
Leave-On	*NR*	*NR*	*2*	*2-3*
Rinse-Off	*2*	*1.6*	*41*	*0.00004-7*
Diluted for (Bath) Use	*NR*	*NR*	*1*	*NR*
Exposure Type				
Eye Area	NR	NR	1	NR
Incidental Ingestion	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	NR	NR
Incidental Inhalation-Powder	NR	NR	NR	NR
Dermal Contact	NR	NR	38	0.00004-7
Deodorant (underarm)	NR	NR	NR	NR
Hair - Non-Coloring	2	1.6	6	0.4-3.5
Hair-Coloring	NR	NR	NR	0.04-1.1
Nail	NR	NR	NR	NR
Mucous Membrane	NR	NR	20	1.9-3
Baby Products	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.
NR – no reported use

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DIETHYLHEXYL SODIUM SULFOSUCCINATE	02A - Bath Oils, Tablets, and Salts	3
DIETHYLHEXYL SODIUM SULFOSUCCINATE	03A - Eyebrow Pencil	11
DIETHYLHEXYL SODIUM SULFOSUCCINATE	03B - Eyeliner	3
DIETHYLHEXYL SODIUM SULFOSUCCINATE	05G - Tonics, Dressings, and Other Hair Grooming Aids	6
DIETHYLHEXYL SODIUM SULFOSUCCINATE	05H - Wave Sets	5
DIETHYLHEXYL SODIUM SULFOSUCCINATE	05I - Other Hair Preparations	1
DIETHYLHEXYL SODIUM SULFOSUCCINATE	06G - Hair Bleaches	9
DIETHYLHEXYL SODIUM SULFOSUCCINATE	06H - Other Hair Coloring Preparation	1
DIETHYLHEXYL SODIUM SULFOSUCCINATE	07C - Foundations	1
DIETHYLHEXYL SODIUM SULFOSUCCINATE	08E - Nail Polish and Enamel	2
DIETHYLHEXYL SODIUM SULFOSUCCINATE	10A - Bath Soaps and Detergents	5
DIETHYLHEXYL SODIUM SULFOSUCCINATE	10B - Deodorants (underarm)	2
DIETHYLHEXYL SODIUM SULFOSUCCINATE	10E - Other Personal Cleanliness Products	1
DIETHYLHEXYL SODIUM SULFOSUCCINATE	11E - Shaving Cream	2
DIETHYLHEXYL SODIUM SULFOSUCCINATE	12A - Cleansing	1
DIETHYLHEXYL SODIUM SULFOSUCCINATE	12D - Body and Hand (exc shave)	6
DIETHYLHEXYL SODIUM SULFOSUCCINATE	12F - Moisturizing	1
DIETHYLHEXYL SODIUM SULFOSUCCINATE	12H - Paste Masks (mud packs)	1
DIETHYLHEXYL SODIUM SULFOSUCCINATE	12J - Other Skin Care Preps	1
		62
AMMONIUM LAURYL SULFOSUCCINATE	05F - Shampoos (non-coloring)	2
DISODIUM LAURYL SULFOSUCCINATE	02A - Bath Oils, Tablets, and Salts	1
DISODIUM LAURYL SULFOSUCCINATE	03E - Eye Makeup Remover	1
DISODIUM LAURYL SULFOSUCCINATE	05F - Shampoos (non-coloring)	6
DISODIUM LAURYL SULFOSUCCINATE	10A - Bath Soaps and Detergents	4
DISODIUM LAURYL SULFOSUCCINATE	10E - Other Personal Cleanliness Products	15
DISODIUM LAURYL SULFOSUCCINATE	12A - Cleansing	14
DISODIUM LAURYL SULFOSUCCINATE	12C - Face and Neck (exc shave)	1
DISODIUM LAURYL SULFOSUCCINATE	12D - Body and Hand (exc shave)	1
DISODIUM LAURYL SULFOSUCCINATE	12H - Paste Masks (mud packs)	1

AMENDED FINAL REPORT ON THE SAFETY ASSESSMENT OF DIOCTYL SODIUM SULFOSUCCINATE[1]

Dioctyl Sodium Sulfosuccinate is an anionic surfactant used in a wide variety of cosmetic formulations. In September 1994, the Cosmetic Ingredient Review (CIR) Expert Panel evaluated the ingredient to be safe up to 0.42% in cosmetic formulations. Since that time, CIR received a petition to re-open the safety assessment based on new clinical data. This amendment is a compilation of data contained in the original plus the data received in the petition; the latter appear at the end of this document. Studies conducted in the 1940's indicate that the oral LD_{50} in rats can be as low as 1.9 g/kg. Short-term subchronic and chronic animal studies of the same vintage found little toxicity at levels around 1% of the LD_{50} level. Inhalation studies likewise had few findings. Dioctyl Sodium Sulfosuccinate was minimally irritating to intact animal skin, but moderate to severely irritating to abraded skin. A concentration of 25% was a severe ocular irritant, but 10% produced little or no irritation. Mutagenesis tests were negative. A repeated insult patch test (RIPT) in 110 individuals produced no sensitization at a concentration of 5%. Erythema was noted during induction in a number of subjects at concentrations ≤5%. The CIR Expert Panel recognized that surfactants such as Dioctyl Sodium Sulfosuccinate would likely produce irritation under the conditions of a RIPT. The Panel cautioned that as the ingredient is a cumulative irritant, care should be taken to avoid irritancy in formulations intended for prolonged contact with the skin. The Panel concluded that Dioctyl Sodium Sulfosuccinate is safe for use in cosmetics.

Dioctyl Sodium Sulfosuccinate is an anionic surfactant used in cosmetics, in over-the-counter (OTC) and prescription drugs, as a food additive, and in a wide variety of other applications. The following report reviews the data available on Dioctyl Sodium Sulfosuccinate applicable to its cosmetic use.

In September 1994, the CIR Expert Panel evaluated the surfactant Dioctyl Sodium Sulfosuccinate (CAS No. 577-11-7) to be safe up to 0.42% in cosmetic formulations. Since that time CIR received a petition to re-open the safety assessment based on new clinical data. The following

Received 20 January 1998; accepted 30 April 1998.

[1]Reviewed by the Cosmetic Ingredient Review Expert Panel. The original scientific literature review was prepared by Lynn Willis, former Scientific Analyst and Writer. Additional information contained in this amendment was prepared by Bindu Nair, Scientific Analyst and Writer.

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is the original report plus the new clinical data received. The discussion section from the original report has been retained and expanded to include consideration of the new data.

CHEMICAL AND PHYSICAL PROPERTIES

Definition and Structure

Dioctyl Sodium Sulfosuccinate, CAS No. 577-11-7, is the sodium salt of the diester of a 2-ethylhexyl alcohol and sulfosuccinic acid that conforms to the formula (Wenninger and McEwen 1997) shown in Figure 1.

Other names for this compound include: 1,4-Bis(2-Ethylhexyl)Sulfobutanedioate, Sodium Salt; Butanedioic Acid, Sulfo-1,4-Bis(2-Ethylhexyl) Ester, Sodium Salt; Di-(2-Ethylhexyl)Sodium Sulfosuccinate; Docusate Sodium; Sodium Di-(2-Ethylhexyl)Sulfosuccinate; Sulfosuccinic Acid, Di-(2-Ethylhexyl) Ester, Sodium Salt; and Sodium Dioctyl Sulfosuccinate (Wenninger and McEwen 1997). In Japan it is referred to as Di(2-Ethylhexyl)Sodium Sulfosuccinate (Rempe and Santucci 1997).

Physical Properties

Dioctyl Sodium Sulfosuccinate has a molecular weight of 444.56 and appears as a waxy solid. It is soluble in both water and organic solvents, especially in water and water-miscible solvent combinations. Its water solubilities as a function of temperature are: 15 g/l at 25°C, 23 g/l at 40°C, 30 g/l at 50°C, and 55 g/l at 70°C. Acid and neutral solutions of Dioctyl Sodium Sulfosuccinate are stable; alkaline solutions hydrolyze (Budavari 1989). Results from mass, ^{1}H-NMR, and ^{13}C-NMR spectroscopy are available (Ahuja and Cohen 1983).

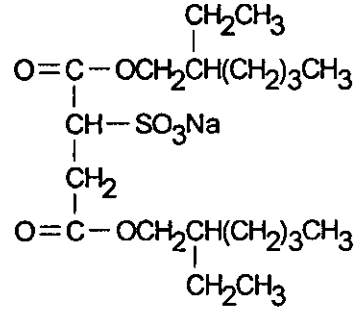

Figure 1. Chemical formula for dioctyl sodium sulfosuccinate.

Method of Manufacture

Maleic anhydride is reacted with 2-ethylhexanol to produce bis(2-ethylhexyl)maleate. This, in turn, is combined with sodium bisulfite under conditions conducive to the formation of the sulfonate structure through rearrangement with an accompanying saturation of the olefinic bond, producing Dioctyl Sodium Sulfosuccinate (Gennaro 1990).

Analytic Methods

Ahuja and Cohen (1983) described a number of methods available for the assay of Dioctyl Sodium Sulfosuccinate. Titration assays for anionic surfactants can be used to determine Dioctyl Sodium Sulfosuccinate: a two-phase mixed indicator titration using 2:3 (v:v) chloroform:1-nitropropane solvent system and an extractive titration technique using carbethopendecinium bromide. Colorimetric analysis methods involving extraction with ethyl violet, bis[2-(2-pyridylazo)-5-diethylaminophenolato] cobalt (III) ion, 1-(4-nitrobenzyl)-4-(4-diethylaminophenylazo)pyridinium bromide, and bis[2-(5-chloro-2-pyridylazo)-5-diethylaminophenolato] cobalt (III) chloride are also described. Turbidimetric, polarographic, and nitrogen blowing techniques are also available.

Impurities

According to the National Formulary (1980), calculated on an anhydrous basis, Dioctyl Sodium Sulfosuccinate should contain between 99 and 100.5% (inclusively) $C_{20}H_{37}NaO_7S$; water should be no more than 2.0%; arsenic, 3 ppm; heavy metals, 0.001%; bis(2-ethylhexyl)maleate, 0.4%.

USE

Cosmetic

Dioctyl Sodium Sulfosuccinate is a surfactant used as an emulsifier and a hydrotrope in cosmetic products (Wenninger and McEwen 1997). As of 1995, Dioctyl Sodium Sulfosuccinate is reported to be used in 38 cosmetic formulations (FDA 1995) (Table 1).

Concentrations of use are no longer reported to the FDA (FDA 1992). However, FDA data from 1984 reported that Dioctyl Sodium Sulfosuccinate was used in a variety of products at concentrations $\leq$5% (FDA 1984).

Table 1. Product formulation data for dioctyl sodium sulfosuccinate

Product category	No. formulations in category	Formulations containing dioctyl sodium sulfosuccinate
Bath oils, tablets, and salts	146	5
Eyeliner	588	5
Hair straighteners	59	1
Hair bleaches	112	5
Blushers (all types)	283	1
Foundations	333	3
Other Makeup preparations	155	1
Nail polish and enamel	108	2
Shaving cream	152	3
Cleansing	771	2
Body and hand (excluding shaving)	987	7
Moisturizing	873	1
Night	220	1
Paste masks (mud packs)	276	1
1995 totals		**38**

Source. FDA, 1995.

International

Dioctyl Sodium Sulfosuccinate is approved by Japan for use in cosmetics (Rempe and Santucci 1997).

OTC

The OTC Drug Review Ingredient Status Report (FDA 1989) reported on the use of Dioctyl Sodium Sulfosuccinate, listed as Docusate Sodium, in three different pharmaceutic or therapeutic use categories. It was generally recognized as safe and effective when used as a stool softener and when used to lower surface tension and produce a mucolytic effect. Dioctyl Sodium Sulfosuccinate, however, was not recognized as an effective pediculicide.

Prescription Drug

Dioctyl Sodium Sulfosuccinate is used in both generic and trade name prescriptions as a mild contact laxative. Usual dosage is 50 to 250 mg daily for adults and children over 12 and 50 to 150 mg for children ages 2 to 12 (AMA 1983).

Veterinary Drug

Dioctyl Sodium Sulfosuccinate is used as a stool softener and a surfactant in veterinary medicine. In addition, it is used to clean ear canals and to treat cattle bloat (Rossoff 1974).

Food

Dioctyl Sodium Sulfosuccinate has a number of applications as a food additive, which are regulated by the FDA. Used as a wetting agent in fumaric acid–acidulated foods, Dioctyl Sodium Sulfosuccinate is limited to a maximum of 15 ppm in finished gelatin desserts or 10 ppm in finished beverages or fruit-juice drinks. It is used in the production of unrefined cane sugar and can be detected in the final juice, syrup, or massecuite product at concentrations of 0.5 ppm per 1% sucrose. It may be used at a concentration of 25 ppm in molasses. Noncarbonated beverages containing cocoa fat may use Dioctyl Sodium Sulfosuccinate as an emulsifying agent, not to exceed 25 ppm in the finished beverage. Gums and hydrophilic colloids may be thickened with Dioctyl Sodium Sulfosuccinate, with a maximum concentration of 0.5% of gums or colloids by weight. As a diluent in color additive mixtures for food, Dioctyl Sodium Sulfosuccinate is limited to a concentration of 9 ppm in the finished product. Other regulated uses for Dioctyl Sodium Sulfosuccinate include: dispersing agent, diluent in color additive mixtures for egg shells, hair remover for hog carcasses, and a cooling and water retort treatment for the exterior of canned goods (Furia 1980).

Other Uses

Dioctyl Sodium Sulfosuccinate has a broad range of uses as a detergent and an emulsifier. Applications include: wetting agents, antifog preparations, emulsion and suspension polymerizations, industrial cleaning solutions, battery separators, and film coating products (McCutcheon's Division 1973).

GENERAL BIOLOGY

Cytotoxicity

Gaginella et al. (1977) studied the cytotoxic effects of intestinal secretagogues on epithelial cells. Cells were isolated from male Syrian hamsters using the methods of Harrison and Webster (1969). The viability of cells was established by the exclusion of trypan blue, and cells were counted and divided into 200- to 500-μl aliquots. For ^{51}Cr studies, cells were incubated with $Na_2{}^{51}Cr$ for 30 minutes at 37°C; a portion of these cells was

set aside for use as the control. The remaining cells were incubated with sample buffer alone or sample buffer and the test material for 15 minutes at 37°C. ^{51}Cr release was expressed as a percentage of dpm before and after test incubation. There was a dose-dependent release of ^{51}Cr with Dioctyl Sodium Sulfosuccinate: a 0.1% concentration effected an 18% release; 0.5% concentration, a 25% release; 1.0% concentration, a 30% release; 2.0% concentration, a 33% release; and 5.0%, a 42% release.

ANIMAL TOXICOLOGY

Oral and Intravenous

Acute

The oral LD_{50} in rats of a product containing 84% Dioctyl Sodium Sulfosuccinate was 3.69 g/kg (CTFA 1991).

Harlan albino mice were matched for sex, divided into groups of 10 and given varying doses of test compounds. For ingestion studies, doses were delivered by means of a stomach tube at different concentrations such that mice received 0.5 ml of solution per 20 g animal weight. Mice were observed for 72 hours after dosing. Using this method, the LD_{50} for a commercial product containing an unspecified amount of Dioctyl Sodium Sulfosuccinate as the active material was 4.8 g/kg. For intravenous studies, the same methods were used with the exception of a 24-hour observation period after intravenous injection. The LD_{50} for a commercial ingredient containing an unspecified amount of Dioctyl Sodium Sulfosuccinate as the active agent was 60 mg/kg (Hopper, Hulpieu, and Cole 1949).

Female albino rats weighing 135 to 180 g were used in an acute feeding study of a number of commercially available surfactants including Dioctyl Sodium Sulfosuccinate. Doses ranged from 0.25 to 7.95 g/kg, administered either by intubation as a 10% aqueous solution or as an emulsion. A 2-week period followed to determine mortality. The LD_{50} for Dioctyl Sodium Sulfosuccinate was 1.9 g/kg (Olson et al. 1962).

Short-Term

Hopper, Hulpieu, and Cole (1949) studied the subacute toxicity of surface-active ingredients in a commercial product containing an unspecified amount of Dioctyl Sodium Sulfosuccinate as the active ingredient. Harlan albino mice were intubated and received 0.1% of the LD_{50} concentration (previously determined) of test product daily, 6 days a week. There were 10 mice per group, and each group received a different number of doses per day such that the sum of the total exposure was equal to 0.1% of the LD_{50}. The group which received 5 doses of the commercial product had five deaths; 10 doses, seven deaths; 15 doses,

eight deaths; and 20 doses, eight deaths. The mortality for the group receiving 25 doses was not reported.

Subchronic

Bengalia et al. (1943) studied the subchronic toxicity of Dioctyl Sodium Sulfosuccinate in a commercial product in four animal species. Wistar rats were divided into six groups of five males and five females each. One group served as a control; the other groups received feed containing calculated doses of 0.25, 0.50, 0.75, 1.00, and 1.25 g of Dioctyl Sodium Sulfosuccinate/kg body weight. Actual doses, due to reduced consumption of feed, were 0.19, 0.37, 0.55, 0.75, and 0.87 g/kg, respectively. Animals were weighed and feed consumption was monitored twice a week. Blood samples were taken irregularly. All of the animals survived to the end of the 24-week experimental period. Mean weight gain for the test groups was about the same as controls. Erythrocyte and leukocyte counts were unaffected by the test material, although there was a small shift in differential counts: Neutrophils increased and lymphocytes decreased. During this period, the only clinical effect noted was the occasional occurrence of diarrhea. No lesions were found at necropsy.

Subchronic toxicity was studied in dogs: three dogs received a dietary dose of 0.10 g/kg of a commercial surfactant containing Dioctyl Sodium Sulfosuccinate as the active ingredient; three dogs received 0.25 g/kg. All dogs lived to the end of the 24-week period in good health. A decrease in animal weight was not considered to be due to any toxic effect of the test material. No lesions were found at necropsy (Bengalia et al. 1943).

In an experiment similar to that done with dogs, three monkeys received a 0.125 g/kg dose of the commercial preparation containing Dioctyl Sodium Sulfosuccinate. All three survived 24 weeks and had no lesions at necropsy (Bengalia et al. 1943).

Groups of five male Osborne-Mendel rats were fed 2, 4, and 8% Dioctyl Sodium Sulfosuccinate over a period of 4 months. These doses were considered by the investigators to be very toxic. Only rats in the 2% feeding group lived to the end of the experiment; their mean weight gain was 220 g as compared to 393 g in control animals (Fitzhugh and Nelson 1948).

Chronic

Groups of 12 male Osborne-Mendel rats were fed diets containing 0.25, 0.5, and 1% Dioctyl Sodium Sulfosuccinate. Controls received diets with no surfactant. Animals were studied for 2 years, with weekly body-weight and feed-consumption determinations. All groups receiving Dioctyl Sodium Sulfosuccinate had 10 animals surviving after 1 year. The 0.25% dose animals had a 436-g mean weight gain; the 0.5% group, a 441-g mean weight gain; the 1% group, a 395-g mean weight gain. The

11 surviving control rats had a mean weight gain of 472 g (Fitzhugh and Nelson 1948).

Inhalation

Sprague-Dawley rats, 12 male and 12 female, were exposed to an aerosol of a product containing an effective Dioctyl Sodium Sulfosuccinate concentration of 0.21% (CTFA 1991). The concentration of exposure was 4.2 mg/m^3, and lasted 4 hours a day, 5 days a week, for 13 weeks. An equal number of rats were kept in a control chamber during this time. During week 7, two rats from each group were killed and necropsied. At the end of the 13 weeks, the remainder of the animals were killed and necropsied. There were no statistically significant differences in dosed and control groups, attributable to Dioctyl Sodium Sulfosuccinate, for the following parameters: mean body weight gain, survival, appearance and behavior, urinalysis values, and microscopic lesions. The following significant differences were noted in hematologic parameters in treated rats as compared to control rats: elevated erythrocytic values in male rats at 7 weeks and depressed mean corpuscular hemoglobin concentration values in male rats at 13 weeks. Significant differences between dosed and treated rats in clinical chemistry parameters included: elevated serum glutamic pyruvic transaminase (SGPT) values in males at 13 weeks, depressed SGPT values in females at 7 weeks, depressed serom alkaline phosphatase (SAP) values in females at 13 weeks, and elevated glucose values in both the 7- and 13-week females. For the male rats, there was a significant difference in relative brain, liver, and testis weights. In females, there was a significant difference in the absolute, but not relative, heart weight. At 7 weeks, the lungs of animals necropsied were examined and stained with Oil Red O. One dosed male rat had some scattered foci of neutrophils along with an increase in the number of free alveolar macrophages.

Nieman and Bredenberg (1985) studied the effects of inhaled Dioctyl Sodium Sulfosuccinate on pulmonary extravascular water volume. A 1% solution of a commercial detergent containing Dioctyl Sodium Sulfosuccinate was suspended in equal volumes of 95% ethanol and isotonic saline. The final concentration of the test material was 15 mg/kg. A volume of 1.5 ml/kg was administered to mongrel dogs which had previously been anesthetized with sodium pentobarbital and attached to a piston ventilator via an endotracheal tube. The dose was administered over a period of 30–45 minutes by an ultrasonic nebulizer connected to the ventilator. Blood pressure was monitored and blood was sampled throughout the dosing. Blood gases and hemoglobin were measured. Animals were killed at 30 minutes, 2 hours, and 4 hours; photographs were taken of the lungs and the pulmonary extravascular water volume

was measured. An extract of the lungs was prepared for surface tension measurements and light microscope examination. Any airway foam present in the distal trachea or large bronchi was similarly prepared. Changes in pulmonary structure and function present in Dioctyl Sodium Sulfosuccinate–dosed dogs, but not in vehicle-alone dogs included: atelectatic areas throughout the lungs, extensive nonhemorrhagic edema fluid appearing as foam, size change and collapse of some alveoli, high surface tension and narrowed hysteresis of the lungs, and pulmonary extravascular water volume increase. Microscopic evaluation indicated a preservation of pulmonary structure and no sign of destruction of the alveolar cells. The authors suggest that the inhaled test surfactant is capable of displacing the normal alveolar surfactant into the airway and resulting in increased alveolar surface tension and instability (Nieman and Bredenberg 1985).

The effect of Dioctyl Sodium Sulfosuccinate on the clearance of radioactive diethylene triamine pentaacetate (DTPA) was studied in rabbits. Rabbits were prepared in a manner similar to the dogs in the Nieman and Bredenberg study; six received 5% Dioctyl Sodium Sulfosuccinate in vehicle and six received vehicle alone for 5 minutes. Following dosing, ^{99m}Tc-DTPA was administered to the animals through the same method as before. A small amount of ^{99m}Tc-DTPA was then given intravenously to the animals for the purpose of background calibration. Radiation was measured with a gamma camera equipped with a converging collimator. The data indicated that animals given Dioctyl Sodium Sulfosuccinate cleared ^{99m}Tc-DTPA much more rapidly than those animals given vehicle alone. This effect increased over the 15 minute post-dose observation period. There were no observable changes in arterial oxygen pressure or compliance (Evander, Wollmer, and Jonson 1988).

Dermal

Acute

Draize, Woodard, and Calvery (1944) included Dioctyl Sodium Sulfosuccinate in an early study to develop irritation and toxicity tests. Rabbits were prepared by clipping the hair from their trunks. Areas on the back were designated for patches; half of these areas were abraded. Light gauze patches were taped over the skin where 0.5 ml of 2% Dioctyl Sodium Sulfosuccinate had been introduced. The skin irritation was evaluated after the 24-hour exposure and again after 72 hours. The final irritation score is the average of these two readings, with a maximum score of 8. The average score for the intact skin was 3.7; the score of the abraded skin was 1.7 (no explanation of data given).

The primary dermal irritation of a 10% solution of a product containing 84% pure Dioctyl Sodium Sulfosuccinate in propylene glycol was minimal in rabbits using a single insult occlusive patch test (CTFA 1991).

Short-Term

Heterogeneous-stock albino rabbits were shaved and abrasions were made to two areas of the caudal region of the belly. Cotton pads containing 5 ml of 1, 5, and 25% Dioctyl Sodium Sulfosuccinate were taped to the abraded areas. Dosed pads were replaced once a day for 3 days. A similar experiment was conducted on two areas of intact rabbit skin; fresh applications of dosed pads were made 10 times in 14 days. A third experiment was conducted on the intact skin of the external ear of a rabbit using the same concentrations of Dioctyl Sodium Sulfosuccinate in a similar application procedure. For the abdominal skin, the 1% solution had an index number of 4 (moderate hyperemia on intact skin, may or may not burn abraded skin), the 5% solution had an index of 5 (burn from two to four 24-hour applications to intact skin), and the 25% solution had an index of 6 (burn from one 24-hour application to intact skin). For the external ear, the 1% solution had an index number of 1 (essentially no irritation to intact skin), the 5% solution had an index of 4, and the 25% solution had an index of 6 (Olson et al. 1962).

Sub-Chronic

Eight female Sprague-Dawley rats (weighing 125–150 g) were used in a 13-week dermal toxicity test. An effective Dioctyl Sodium Sulfosuccinate concentration of 0.00126% (in formulation) was applied to a shaved site on the back, 5 days a week for 67 days. The solution was applied at a dose of 4 ml/kg; an untreated control group was maintained. Observations were made daily for the first two experimental weeks, weekly thereafter; blood and urine samples were obtained on weeks 7 and 13. While a statistically significant increase in white blood cell count was noted in week 13 and a decrease in serum glutamic oxaloacetic transaminase activities in week 7, the values remained within the range for historical controls. One dosed animal was noted to have fluid filled kidneys at necropsy. Body weight gain, organ weight, survival, and urinalysis parameters in dosed animals were not significantly different from control animals. Treated animals did, however, have minimal to moderate skin irritation sporadically throughout the study (CTFA 1991).

A study was conducted relating dermal irritancy and acanthosis. A commercially available product containing Dioctyl Sodium Sulfosuccinate was tested on guinea pigs at concentrations of 2, 10, and 20%. After repeated skin applications, a portion of skin was removed from test

and control animals and histologic slides were prepared. The acanthosis factor (AF) was calculated from the difference in the epidermal thicknesses, where 1 unit is equal to 2.7μm (Gloxhuber 1980). The 2% concentration of the product containing Dioctyl Sodium Sulfosuccinate had an AF of 1.8; the 10% concentration had an AF of 2.5; and the AF for the 20% concentration animals was 3.3 (Schaaf 1969).

Ocular

As well as dermal irritation, Draize et al. (1944) studied the effect of Dioctyl Sodium Sulfosuccinate on the rabbit eye. Three different concentrations of Dioctyl Sodium Sulfosuccinate, in a volume of 0.1 ml, were introduced into the conjunctival sac. Irritation readings were taken at 1 and 24 hours after application. At 1 hour, the eye receiving 0.5% Dioctyl Sodium Sulfosuccinate had an irritation score of 4.0; the score for the 2.0% solution was 9.0; and the score for the 10.0% solution was 26.0. At 24 hours, animals of the 0.5% group had an irritation score of 2.0; the score for 2.0% group was 2.0; and the score for the 10.0% group was 24.0.

The ocular irritation of a 10% solution of a product containing 84% Dioctyl Sodium Sulfosuccinate in propylene glycol was minimal in rabbits using the Draize classification (CTFA 1991).

Dioctyl Sodium Sulfosuccinate was instilled in rabbit eyes at 0.1, 0.25, 0.5, 1, and 100% concentrations. Doses were delivered in either a single instillation of two drops or in repeated dosings of two drops four times a day for 6 days for all concentrations except the undiluted test group, which received one dose a day for 6 days. The single application of the 0.1% concentration produced no effects; repeated use of this concentration produced mild conjunctival injection that disappeared within 24 hours after discontinuation of the doses. The single dose at 0.5% produced conjunctival hyperemia, edema, loosening of the epithelium, and minute corneal staining; repeated use intensified these effects, along with an appearance of mucoid discharge; eyes cleared; after 48 hours. A single instillation of the 1% concentration produced conjunctival hyperemia, edematous loosening of the epithelium, blepharospasm, and corneal haziness and staining which disappeared after 24 hours; the repeated instillation had similar effects, which cleared after 72 hours. The single application of the undiluted Dioctyl Sodium Sulfosuccinate induced conjunctival injection, edema, sloughing of the epithelium, corneal haziness and staining, and superficial punctate areas which disappeared in the majority of the tested eyes within 1 week (Leopold 1945).

Hopper, Hulpieu, and Cole (1949) studied the effects produced by a number of commercially available products containing surfactants. A solution of 1% of a product containing Dioctyl Sodium Sulfosuccinate was instilled into the conjunctival sac of the eye and observations of

effects were made at 5 min, 10 min, 1 h, and 24 h. The only effect noted was the presence of inflammation in six animals.

Drops of Dioctyl Sodium Sulfosuccinate were introduced into the conjunctival sac of both eyes of groups of three rabbits. The right eye was rinsed after a 30-second exposure, the left was left unrinsed. Both eyes were evaluated at 1 hour, 24 hour, 2 days, and 1 week. The 1% concentration produced little or no effect in both the rinsed and unrinsed eyes. The 5% concentration produced similar results in the rinsed and unrinsed eye: a slight effect, disappearing within a week, with no corneal damage. In the rinsed eye, the 25% concentration was just slightly more irritating than the 5% concentration. In the unrinsed eye, however, the 25% concentration produced a severe effect, consisting of corneal injury and impairment of vision (Olson et al. 1962).

Reproductive Effects

Mackenzie et al. (1990) conducted a three-generational study to determine the effects of oral administration of Dioctyl Sodium Sulfosuccinate on reproduction. Groups of 30 rats of either sex were fed diets containing 0, 0.1, 0.5, or 1.0% Dioctyl Sodium Sulfosuccinate. The males of this F_0 generation were maintained on such a protocol for 10 weeks, the females for 2; the diets were fed beginning at 7 weeks of age and continuing through mating, gestation, and lactation. The F_0 animals were mated to produce an F_1 generation. Groups of 30 males and females from the F_1 were fed the same diets as their respective F_0 parents for 10 weeks postweaning. The breeding program was repeated to produce an F_2 generation and again to produce an F_3 generation. Test diets were fed throughout the study; F_1 and F_2 animals were exposed to the test material in utero and while nursing, before being weaned to feed dosages. The study was terminated with the F_3 weanlings; necropsy and macroscopic examinations were performed. The researchers found decreased body weight in all parental males and in F_1 and F_2 females fed diets containing 0.5 or 1.0% Dioctyl Sodium Sulfosuccinate. The body weights of pups in all three generations were lower than those of corresponding controls. However, the reduced body weight did not interfere with normal reproductive development and performance. Dioctyl Sodium Sulfosuccinate at doses up to 1.0% had no effect on reproductive function and produced no treatment-related mortality and antemortem or macroscopic abnormality.

Mutagenicity

Dioctyl Sodium Sulfosuccinate, at concentrations up to 2500 μg/plate with S-9 activation and up to 1000 μg/plate without activation, did

not induce a statistically significant increase in revertant mutants in an Ames assay conducted on *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA102 (Hazleton Microtest 1993).

A chromosomal aberration assay was conducted on Chinese hamster ovary cells (CHO). Duplicate plates of cells were incubated for 2 and 20 hours with 0.5 ml of a Dioctyl Sodium Sulfosuccinate dilution in the presence and absence of S-9 activation, respectively. Colchicine was added to the media prior to harvesting (20 hours after start of treatment) to arrest dividing cells in metaphase. Dioctyl Sodium Sulfosuccinate induced significant chromosomal aberrations in the presence of S-9 activation. Aberration values comparable to the positive control cyclophosphamide were first observed in the 120 μg/ml treatment plates where chromosomal aberrations were found in an average of 24/100 cells scored. The majority were abnormalities other than chromosomal gaps. The induction of toxicity was also demonstrated as a 62% reduction in mitotic activity at 120 μg/ml and complete toxicity at doses exceeding 140 μg/ml were observed. As a result, two subsequent attempts to repeat the above results were unsuccessful even when the dosing range was narrowed. In summary, there were no aberrations in the absence of toxicity. Cells treated for 20 hours with Dioctyl Sodium Sulfosuccinate in the absence of activation exhibited 52% mitotic inhibition at 55.29 μg/ml. In order to further test the mutagenic potential of the test agent, a delayed harvest was conducted in which cells were incubated for 44 hours with concentrations up to 130 μg/ml in the absence of S-9. The number of chromosomal aberrations in all assays treated without S-9 was within the range of the historical negative control (Hazleton Microtest 1994).

CLINICAL ASSESSMENT OF SAFETY

Sensitization and Photosensitization

Four separate 4-day mini-cumulative irritancy tests were performed testing various Dioctyl Sodium Sulfosuccinate formulations. The primary irritation index (PII) of each of four products containing an effective Dioctyl Sodium Sulfosuccinate concentration of 2.94% (3.5% solution of 84% Dioctyl Sodium Sulfosuccinate) was 0.25, 0.30, 0.80, and 0.38. The PIIs of two products containing a 0.25% solution of 84% Dioctyl Sodium Sulfosuccinate were 1.78 and 1.85 (separate studies). The PII of a product containing a 0.1% solution of 84% Dioctyl Sodium Sulfosuccinate was 0.04 (CTFA 1991).

A 21-day cumulative irritancy test was performed using seven volunteers and a product containing a 1.13% solution of Dioctyl Sodium Sulfosuccinate (84% pure). The test material was applied daily to the same

site using an occlusive patch. Areas were scored everyday on a scale of 0 (no reaction) to 4 (strong reaction). One volunteer was dropped from the study (no reason stated). The total irritation score was 324 out of a maximum score of 578 for all seven panelists over the 21-day period; the average score per panelist was 46.3 out of a maximum of 84. The lowest average reading for one panelist was 15; the highest reading was 73 (CTFA 1991).

A Repeated Insult Patch Test (RIPT) of a product containing an effective Dioctyl Sodium Sulfosuccinate concentration of 0.42% was conducted using 100 volunteers. An occlusive patch containing 0.2 ml of the product was applied to an area of the back. The patch was removed by the panelist after 24 hours. Application of induction patches was repeated for a total of nine exposures over a period of 3 weeks. After a 2-week nontreatment period, a nonspecified site was challenged with the same dose. Sites were scored before application of another patch. Four panelists had mild erythema covering most of the patch area in the last weeks of the study. None of the volunteers had a reaction to the challenge (CTFA 1991).

The above described method was used in four other RIPT studies. The challenge site was a previously untreated site. Of 119 volunteers tested with 0.21% Dioctyl Sodium Sulfosuccinate, eight had barely perceptible to mild erythema at the dose site during the induction phase; two had barely perceptible erythema during the challenge phase. Of 117 volunteers tested with a product which also had an effective Dioctyl Sodium Sulfosuccinate concentration of 0.21%, eight had barely perceptible to mild erythema at the dose site during the induction phase; three had barely perceptible erythema during the challenge phase. Of 94 volunteers tested with a product also containing 0.21% Dioctyl Sodium Sulfosuccinate, 27 had barely perceptible to mild erythema at the dose site during the induction phase; five had barely perceptible erythema during the challenge phase. Of 99 volunteers tested with a product containing 0.1% Dioctyl Sodium Sulfosuccinate (84% pure), 11 had barely perceptible to mild erythema at the dose site during the induction phase; one had mild erythema during the challenge phase. Of 94 volunteers testing a product also containing 0.1% Dioctyl Sodium Sulfosuccinate (84% pure), four had barely perceptible erythema at the dose site during the induction phase; there were no reactions during the challenge phase (CTFA 1991).

A photocontact allergenic potential study of a product containing 0.25% Dioctyl Sodium Sulfosuccinate (84% pure) was conducted using 25 volunteers. During the pretesting phase, the midback of volunteers was irradiated with a xenon arc solar simulator, 150 watt, with a UV-reflecting dichroic mirror and filtered with a 1-mm thick Schott WG-320 filter, in order to determine the minimal erythema dose (MED). During the induction phase, 10 μl/cm of the test material was applied

to a 2 × 2 cm^2 area and then covered by an occlusive patch. After 24 hours, the patch was removed, the area was wiped dry, and the site was irradiated with 3 MEDs. This was repeated twice a week for a total of six exposures. Ten to 14 days later, the same dose was applied in duplicate to nontreated sites. After 24 hours, the patches were removed and the sites wiped dry. One of the areas was then irradiated with 4 J/cm^2 ultraviolet A radiation, obtained by filtering the previous light source with a 1-mm thick UG5 filter. The duplicate site served as a control. There were no reactions in either the induction or challenge phase attributable to Dioctyl Sodium Sulfosuccinate (CTFA 1991).

Contact Dermatitis Case Study

Irritation coinciding with the application of a plaster-of-Paris cast lined with an orthopedic wool was observed in six patients. Staniforth and Lovell (1981) patch tested these patients with the four chemicals used to process the wool at 1, 10, and 100% concentrations along with gypsona (100%), benzalkonium chloride (0.1%), and cetrimide (0.1%). Only the chemical containing Dioctyl Sodium Sulfosuccinate gave a positive reaction in all patients. Gypsona, benzalkonium chloride, and cetrimide produced irritation in three patients. None of the other chemicals tested affected an irritant reaction. Following this, a product containing Dioctyl Sodium Sulfosuccinate was patch tested using eight volunteers with normal skin and ten volunteers with noninflammatory skin disease. The 1 and 10% concentrations produced neither irritation nor allergic reactions. The undiluted product caused an irritant reaction in 12 of the 18 volunteers (Staniforth and Lovell 1981).

A single 24-hour occlusive patch containing 2.5% Dioctyl Sodium Sulfosuccinate in formulation was applied to the upper back or arm of 50 panelists. No reactions were noted at the time of patch removal or after an additional 24 and 48 hours (GTLF 1994).

An RIPT was conducted on 110 panelists (demographically separated into two groups of 55) to determine the sensitization potential of 1, 3, and 5% Dioctyl Sodium Sulfosuccinate (TKL Research Inc. 1994). During the induction phase, semiocclusive patches containing 0.2 ml of the test material was applied to the back with the instruction to remove them after 24 hours. Evaluation of the treatment site and application of successive patches were done every 48 hours until a total of nine patches had been applied. A 14-day nontreatment period followed. During challenge, a 24-hour patch of the test material was applied to a previously unexposed site. The challenge site was evaluated at the time of patch removal and after additional 24- and 48-hour periods (i.e., 48 and 72 hours after application). With successive induction patch applications,

the 1% solution produced questionable reactions defined as "minimal or doubtful response, slightly different from surrounding normal skin" in an increasing number of panelists. At the ninth application, 17 panelists had such a reaction. Other reactions noted during early induction included four cases of "definite erythema, no edema" (scored +), "definite erythema, no edema with damage to epidermis; oozing, crusting, and/or superficial erosions" (scored +D), or "definite erythema, minimal or doubtful edema" (scored +*). These reactions were notably less severe by the final induction. There were no reactions during challenge. Similarly, the 3% solution produced questionable reactions in two panelists after application of the first induction patch and in 32 panelists by the ninth application. Reactions graded (+), (+D), and/or (+*) were noted in five panelists at various evaluations. There were no reactions during challenge. The 5% solution produced questionable reactions in eight panelists after application of the first induction patch and in 65 panelists by the ninth application. Reactions graded (+), (+D), and/or (+*) were noted in 16 panelists at various evaluations during induction. There were no reactions during challenge.

A second RIPT study was conducted on 107 panelists using a 50/50 dilution (with distilled water) of an eyebrow pencil containing 2.5% Dioctyl Sodium Sulfosuccinate (effective DSS concentration: 1.25%). During induction, patches containing the test material were applied to the back three times a week for 3 weeks for a total of 10 exposures. The patches remained on the skin for 48 hours; sites were evaluated at the time of patch removal, prior to application of the successive patch. A 12-day nontreatment period followed induction. During challenge, a 48-hour patch was applied to a previously untreated site on the back. Reactions were evaluated at 48 and 72 hours postapplication. During induction, 20 panelists had at least one reaction defined as "erythema throughout the entire patch area." (Ten of the twenty panelists had reactions noted at one to three evaluations, the other ten had reactions noted during at least five, and at up to eight, evaluations.) Erythema, edema, and vesicles were noted in another individual during observation 5. No reactions had been observed in this panelist during previous evaluations and further patch application was discontinued. There were no reactions during challenge (International Research Services Inc. 1995).

SUMMARY

Dioctyl Sodium Sulfosuccinate is an anionic surfactant used in a variety of leave-on and rinse-off cosmetic products. It is an approved OTC ingredient, prescription drug, and food additive. Dioctyl Sodium Sulfosuccinate had a dose-dependent cytotoxic effect on epithelial cells.

In one study using rats, the oral LD_{50} of Dioctyl Sodium Sulfosuccinate was 1.9 g/kg. Results of subchronic toxicity testing indicated little, if any, toxic effects below the LD_{50}. Mice receiving Dioctyl Sodium Sulfosuccinate orally for 2 years had reduced body weight gain as compared to controls.

Rats exposed to an aerosol containing Dioctyl Sodium Sulfosuccinate had changes in some hematology and clinical chemistry parameters. Dogs dosed similarly had significant gross, but not microscopic, changes of the lungs.

Dioctyl Sodium Sulfosuccinate was found to be minimally irritating at 10% on intact skin. Abraded skin of rabbits had moderate to severe irritation reactions to 1, 5, and 25% Dioctyl Sodium Sulfosuccinate. A 13-week dermal toxicity test using a 0.21% solution of Dioctyl Sodium Sulfosuccinate produced sporadic irritation throughout the study.

At concentrations of 25% or higher, Dioctyl Sodium Sulfosuccinate was a severe ocular irritant. Concentrations of 10% and less produced little or no irritation.

A three-generation study in rats found oral administration of up to 1.0% Dioctyl Sodium Sulfosuccinate did not affect the reproductive function nor produced treatment-related abnormalities in progeny.

Dioctyl Sodium Sulfosuccinate was nonmutagenic in an Ames assay, but with S-9 activation, it did induce chromosomal aberrations in CHO cells at treatment doses close to threshold toxicity.

The PIIs of a 2.94% solution of Dioctyl Sodium Sulfosuccinate were 0.25, 0.30, 0.80, and 0.85 in four separate studies. A 5% solution of Dioctyl Sodium Sulfosuccinate was not sensitizing in an RIPT study. However, irritation reactions were noted during induction. Irritation to Dioctyl Sodium Sulfosuccinate in orthopedic wool has been reported in six patients.

DISCUSSION

The CIR Expert Panel previously determined that a conclusion for Dioctyl Sodium Sulfosuccinate could be based on the available experimental data. A concentration of 0.42% was the highest level for which there was sufficient data to substantiate safety. This level was found not to induce sensitization in a human RIPT. While no effect was found in a clinical 21-day cumulative assay testing at a higher concentration (approximately 1%), the assay used seven panelists whereas the RIPT had 100 participants. In the absence of current data on concentration of use for this ingredient, the Expert Panel was unable to suggest how these experimental concentrations relate to actual use. This ingredient may be safe as currently used, but in the absence of use data, the Expert Panel concluded that a concentration limit is necessary.

In addition, the Panel recognized that positive results in the CHO mutagenicity assay were only found with toxicity. Thus, the findings are of questionable significance.

After reviewing additional data, the CIR Expert Panel decided that there was sufficient evidence to eliminate the need for a limit on concentration. The Panel considered Dioctyl Sodium Sulfosuccinate to be safe used in cosmetic formulations. It was acknowledged that under the exaggerated exposure conditions of the two RIPTs (continuous occlusive patch testing), the ingredient is a cumulative irritant, though not a sensitizer. The Panel recognized that a surfactant would most likely produce irritation under such conditions. The Panel stressed that care should be taken to avoid irritancy, especially in those products intended for prolonged contact with the skin.

CONCLUSION

Based on the available data, the CIR Expert Panel concluded Dioctyl Sodium Sulfosuccinate to be safe as used in cosmetic formulations.

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Final Report

On the Safety Assessment of Alkyl PEG Sulfosuccinates As Used in Cosmetics

March 6, 2012

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ABSTRACT: Alkyl PEG sulfosuccinates function mostly as surfactants/cleansing agents in cosmetic products. Dermal penetration of these ingredients would be unlikely because of their substantial polarity and molecular sizes. Negative oral carcinogenicity and reproductive and developmental toxicity data on chemically related laureths (PEG lauryl ethers) and negative repeated dose toxicity and skin sensitization data on disodium laureth sulfosuccinate supported the safety of these alkyl PEG sulfosuccinates in cosmetic products, but these ingredients do have the potential for causing ocular/skin irritation. The CIR Expert Panel concluded that the alkyl PEG sulfosuccinates are safe in the present practices of use and concentration when formulated to be non-irritating.

INTRODUCTION

The safety of the following ingredients in cosmetics is reviewed in this report:

- Disodium Laureth Sulfosuccinate
- Disodium Laureth-6 Sulfosuccinate
- Disodium Laureth-9 Sulfosuccinate
- Disodium Laureth-12 Sulfosuccinate
- Disodium Deceth-5 Sulfosuccinate
- Disodium Deceth-6 Sulfosuccinate
- Magnesium Laureth-3 Sulfosuccinate
- Disodium C12-14 Pareth-1 Sulfosuccinate
- Disodium C12-14 Pareth-2 Sulfosuccinate
- Disodium C12-15 Pareth Sulfosuccinate
- Disodium Coceth-3 Sulfosuccinate
- Disodium Laneth-5 Sulfosuccinate
- Disodium C12-14 Sec-Pareth-3 Sulfosuccinate
- Disodium C12-14 Sec-Pareth-5 Sulfosuccinate
- Disodium C12-14 Sec-Pareth-7 Sulfosuccinate
- Disodium C12-14 Sec-Pareth-9 Sulfosuccinate
- Disodium C12-14 Sec-Pareth-12 Sulfosuccinate
- Disodium Oleth-3 Sulfosuccinate

These ingredients function mostly as surfactants-cleansing agents in cosmetic products.

An amended CIR final safety assessment on alkyl PEG ethers, with a conclusion that these ingredients were safe in the present practices of use and concentration, was completed in 2011,[1] and data on laureths (PEG lauryl ethers) from that review were used to fill pertinent data gaps (i.e., carcinogenicity and reproductive and developmental toxicity) in the current safety assessment. These data have relevance because the first level metabolites of alkyl PEG sulfosuccinates would likely include the corresponding alkyl PEG ethers; e.g., magnesium laureth-3 sulfosuccinate may be metabolized to laureth-3 (PEG-3 lauryl ether) and sulfosuccinic acid.

An amended final safety assessment on sodium laureth sulfate and related salts of sulfated ethoxylated alcohols was published in 2010, with the conclusion that these cosmetic ingredients are safe in the present practices of use and concentration when formulated to be nonirritating.[2] Furthermore, a CIR amended final safety assessment on alkyl PEG ethers with a safe as used conclusion became publicly available this year,[1] and a CIR amended final safety assessment on dioctyl sodium sulfosuccinate (diethylhexyl sodium sulfosuccinate, current INCI name) with a similar conclusion was published in 1998.[3] Based on structural similarities, the applicability of data on alkyl PEG ethers (other than laureths), sodium laureth sulfate, and diethylhexyl sodium sulfosuccinate from the respective safety assessments has been considered in this safety assessment of alkyl PEG sulfosuccinates in cosmetic products.

CHEMISTRY

Definition and Structure

The definitions, structures, and functions of the anionic surfactants reviewed in this safety assessment are included in Table 1.[4] The ingredients in this review share a sulfo-substituted, succinic acid core. Accordingly, the salts of these materials are sulfosuccinates. The ingredients in this review are the salts of alkyl polyethylene glycol (PEG), mono-esters of

sulfosuccinic acid (even though none of the INCI names includes PEG, these ingredients are collectively referred to as alkyl PEG sulfosuccinates).[5] For example, disodium laureth sulfosuccinate consists of a twelve-carbon alkyl chain (lauryl), connected to the sulfosuccinate core via a PEG chain, wherein the average number of ethoxy repeat units (n) is between 1 and 4 (i.e., laureth-1 through laureth-4) (Figure 1).

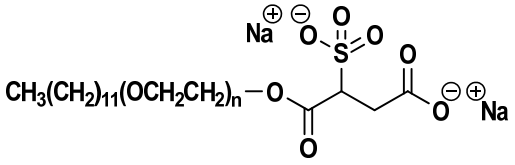


Figure 1. Disodium Laureth Sulfosuccinate

Chemical and Physical Properties

Sulfosuccinate monoesters contain a hydrophobic end that consists of a fatty alcohol chain.[5] The chain length and degree of saturation of the fatty acid may vary this hydrophobicity. The level of hydrophobicity imparted by the fatty alcohol is also affected by the different degrees of ethoxylation of the PEG chain. For instance, monoesters based on linear fatty alcohols are only partially soluble in water. Those based on fatty alcohol ethoxylates have greater water solubility. Water solubility is also increased when the structure contains branched chains. Solubility in less-polar solvents, such as isopropanol and 1,2-propylene glycol, is considered more difficult to achieve. Due to the ester linkage, these sulfosuccinate ingredients are sensitive to hydrolysis, especially under acidic conditions. Properties of sulfosuccinate ingredients (trade name materials included) are found in Table 2. Tables 3 and 4 contain specifications/actual composition data for disodium laureth sulfosuccinate trade name mixtures tested at various concentrations of disodium laureth sulfosuccinate in studies summarized later in the Toxicology section of this report.

Methods of Production

The synthesis of these ingredients occurs according to a 2-step procedure.[5] In the first step, maleic anhydride is reacted with an ethoxylated fatty alcohol. The second step involves sulfonation of the resulting maleic ester. In the production of disodium laureth sulfosuccinate, for example, a monoester is formed by reacting the ethoxylated alcohol (e.g., Laureth-2) with maleic anhydride.[6] The monoester is then reacted with sodium bisulfite to form the sulfosuccinate.[7,8]

Impurities

According to one report, disodium laureth sulfosuccinate contained the following impurities/by-products: residual sodium sulfite (< 0.1%), residual sodium sulfate (1 to 3%), residual laureth-2 (1 to 5%), and 1,4-dioxane by-product (< 10 ppm).[6] Another source indicates that a disodium laureth sulfosuccinate trade name material (active ingredient [40%]; anionic active matter [33%]) contains: < 1 ppm 1,4-dioxane and < 1 ppm ethylene oxide (if presence of either is technically unavoidable in good manufacturing practice); < 1 ppm residual monomers; and heavy metals, Pb (< 10 ppm), Ni (< 10 ppm), Cd (< 1 ppm), As (< 1 ppm), Sb (< 1 ppm), and Hg (< 0.2 ppm).[8] A third source indicates that disodium laureth sulfosuccinate contains formaldehyde at a maximum level of 0.056% and 1,4-dioxane at a maximum level of 0.001%.[9]

USE

Cosmetic

The ingredients reviewed in this safety assessment function mostly as surfactants-cleansing agents in cosmetic products. These and additional functions are included in Table 1.

According to information supplied to the Food and Drug Administration (FDA) by industry as part of the Voluntary Cosmetic Registration Program (VCRP), the following ingredients were being used in personal care products (mostly rinse-off products): disodium laureth sulfosuccinate, disodium laureth-6 sulfosuccinate, disodium deceth-6 sulfosuccinate, and disodium C12-14 pareth-2 sulfosuccinate.[10] These data are summarized in Table 5. Independent of these data, the results of a survey of ingredient use concentrations that was conducted by the Personal Care Products Council (Council) in 2011, also in Table 5, provided use concentrations for disodium laureth sulfosuccinate (0.06 to 10%).[11] The highest use concentration of this ingredient was in shampoos (noncoloring). Subsequent inclusion of magnesium laureth-3 sulfosuccinate in another Council survey yielded no use concentration data on this ingredient.[12] No uses of the remaining ingredients reviewed in this safety assessment were reported in the VCRP database or in the Council survey.

Cosmetic products containing the ingredients reported as being used may be applied to the skin and hair, or, incidentally, may come in contact with the eyes and mucous membranes. Products containing these ingredients may be applied as frequently as several times per day and may come in contact with the skin or hair for variable periods following application. Daily or occasional use may extend over many years.

Disodium laureth sulfosuccinate is used in hair color sprays at a maximum reported concentration of 2%, and could be inhaled. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 μm.[13,14] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and thoracic regions of the respiratory tract and would not be respirable (i.e., able to enter the lungs) to any appreciable amount.[15,16] [**Consult Ivan's revision of this paragraph after March 2012 Panel meeting!!!!!**]

Noncosmetic

Reportedly, sulfosuccinates are used to improve the wetting and spreading characteristics of water-soluble pesticide sprays and are found in liquid fertilizer, insecticides, fungicides, and herbicides.[5]

TOXICOKINETICS

Studies on the toxicokinetics of sulfosuccinate ingredients in this safety assessment, following oral, dermal, or inhalation exposure, were not found in the published literature.

TOXICOLOGICAL STUDIES

Acute Oral Toxicity

Disodium Laureth Sulfosuccinate

According to a material safety data sheet (MSDS) on disodium laureth sulfosuccinate (30 to 39.9% % by weight), the acute oral LD50 for this chemical is > 10,000 mg/kg (rats), based on data on components or similar materials. Additional details were not provided.[9]

In an acute oral toxicity test involving rats, the LD50 for a disodium laureth sulfosuccinate trade name material (active ingredient [40%]; anionic active matter [33%]) was > 3,000 mg/kg.[8] Additional study details were not provided.

Groups of 5 male and 5 female NMRI mice (~ 6 to 8 weeks old) were used to evaluate the genotoxicity of disodium laureth sulfosuccinate in a micronucleus test.[17] Test animals received a single oral dose of the test substance (dose = 2,000 mg/kg body weight) in distilled water and were monitored for signs of acute toxicity, up to 48 h post-dosing. None of the animals died and there was no evidence of clinical signs. Genotoxicty test results are summarized later in the report text.

The acute oral toxicity of disodium laureth sulfosuccinate (trade name material, 40% active matter) was evaluated using fasted, young adult male albino rats (number not stated).[18] After a single dose of the test substance (dose volume = 10 ml/kg) was administered by gavage, no adverse effects were observed. An LD50 of > 2,000 mg/kg was reported.

The acute oral toxicity of a trade name mixture containing 24% active material was evaluated using 10 Sprague-Dawley rats (5 males, 5 females; ages not stated).[19] Data on the composition of this material are included in Table 4. The total active material (disodium laureth sulfosuccinate plus sodium lauryl sulfoacetate) in this mixture was 24%. Of this 24%, 70% (16.8% of the total mixture) was disodium laureth sulfosuccinate and 30% (7.2% of the total mixture) was sodium lauryl sulfoacetate. Each rat received a 5,000 mg/kg oral dose (gavage) of the test substance, and the animals were observed for 15 days. Because the concentration of active material in the test material was 16.8%, each rat received an 840 mg/kg dose of disodium laureth sulfosuccinate (0.168 x 5,000 = 840 mg/kg). All of the female rats died within 24 h of dose administration, but all male rats survived to the end of the study. The following signs were observed in the male rats and in female rats: decreased activity, diarrhea, labored breathing, and an unsteady gait. Gross necropsy findings in the female rats included: distended/gas-filled stomach, red stomach mucosa and mucosal erosion of the stomach (with rugae absent), red intestinal mucosa, and red substance in the intestines. The trade name material containing 16.8% disodium laureth sulfosuccinate was classified as a toxic substance.

Disodium C12-14 Pareth-2 Sulfosuccinate

Similarly, information in an MSDS on Disodium C12-14 Pareth-2 Sulfosuccinate (~ 40% disodium mono-[polyoxyethylene alkyl) sulfosuccinate in trade name material) indicates that the acute oral LD50 of this chemical is 3,490 mg/kg (rats).[20] Additional details were not provided.

Acute Dermal Toxicity

Disodium Laureth Sulfosuccinate

According to an MSDS on disodium laureth sulfosuccinate (30 to 39.9% by weight), the acute dermal LD50 for this chemical is > 2,000 mg/kg (rabbits), based on data on components or similar materials. Additional details were not provided.[9]

Repeated Dose Oral Toxicity

Disodium Laureth Sulfosuccinate

The repeated dose oral toxicity of a disodium laureth sulfosuccinate trade name material (active ingredient [40%]; anionic active matter [33%]) was evaluated using groups of Sprague-Dawley Crl:CD (SD) BR rats.[21] The control (deionized water) and 1,000 mg/kg/day dose groups each contained 10 males and 10 females, and the 62.5 and 250 mg/kg dose groups each contained 5 males and 5 females. The test material was administered (dose volume = 10 ml/kg) 7 days per week for 4 consecutive weeks. At the end of the dosing period, some of the animals were observed during a 4-week recovery period and the remaining animals were killed for pathological investigations.

There were no treatment-related deaths or changes, based on ophthalmological examinations and evaluations for clinical signs, body weight changes, or food consumption. In the highest dose group (1,000 mg/kg/day), treatment-related increases in alkaline phosphatase (moderate) and in SGPT (slight) were observed in both sexes, and there was a trend toward increased protein in the urine in males of this group. These changes were not observed at the end of the recovery period. Mild reversible changes in the liver (increased weight and hypertrophy) were also observed in the highest dose group. The NOEL was considered to be 250 mg/kg/day.[21]

In another study, groups of Sprague-Dawley CD, SPF-quality rats (10 males, 10 females/group) received oral doses of disodium laureth sulfosuccinate (trade name material, composition not stated) daily for 28 days.[18] Three groups received doses of 100, 300, and 1,000 mg/kg body weight per day, and the fourth group served as the untreated control group. Additionally, a recovery group consisting of 5 males and 5 females was used to determine the reversibility of possible test substance-related findings. None of the animals died and, compared to the control group, there was no deviation in body weight development in any of the 3 dose groups.

The following test substance-related findings, all in the highest dose group, were reported: stimulation of propulsion (swallowing and peristalsis) and salivation, alterations in hematological parameters and in clinical chemistry (i.e., alterations in alanine aminotransferase [ALT] values), significantly increased liver weight, and ulceration and edema of the forestomach mucosa (local irritation effects) at macroscopic examination. Effects on the forestomach mucosa were not observed after a 34-day recovery period. Other findings included small cellular infiltrations (no further details) in 100 and 300 mg/kg dose groups. The systemic NOAEL was 300 mg/kg body weight in this study. Additionally, a no observed adverse effect concentration (NOAEC) of < 1% for local compatibility was deduced. It was stated that the labeling of this disodium laureth sulfosuccinate trade name material for possible toxic effects after chronic exposure is not necessary.[18]

Ocular Irritation

Disodium Laureth Sulfosuccinate

The ocular irritation potential of diluted disodium laureth sulfosuccinate (25% active matter in a trade name material) was evaluated according to OECD Guideline No. 405 using 4 rabbits of the Kleinrusse Chbb:HM strain.[18] The test substance (0.1 ml) was instilled once into the eye of each animal, and untreated eyes served as controls. Mean ocular irritation scores (24 h, 48 h, and 72 h) were as follows: 0.9 (cornea), 2.5 (conjunctival erythema), 1.1 (conjunctival edema), and 0 (iris). At the end of the observation period, slight conjunctival erythema (sore = 1) and slight corneal opacity (score = 1) persisted in one rabbit. It was concluded that the test material has to be classified and labeled to pose a risk of serious damage to the eyes.

According to an MSDS on disodium laureth sulfosuccinate (30 to 39.9% by weight), this chemical substance is considered a moderate to strong eye irritant, based on data on components or similar materials.[9] Additional details were not provided.

The ocular irritation potential of a trade name mixture containing 10% active material was evaluated using 6 New Zealand white, young adult rabbits (ages not stated).[22] Data on the composition of this material are included in Table 4. The total active material (disodium laureth sulfosuccinate plus sodium lauryl sulfoacetate) in this mixture is 24%. Of this 24%, 70% (16.8% of the total mixture) is disodium laureth sulfosuccinate and 30% (7.2% of the total mixture) is sodium lauryl sulfoacetate. Because the trade mixture evaluated contained 10% active material, the concentration of disodium laureth sulfosuccinate tested was 1.68% (0.10 x 0.168 = 1.68%). The undiluted test substance (0.1 ml) was instilled into the right eye of each rabbit. Contralateral eyes served as controls. Ocular irritation reactions were scored according to the method of Draize at 24 h, 48 h, and 72 h post-instillation. A positive ocular response was observed in all rabbits tested, and the trade name mixture was classified as a primary ocular irritant.

Disodium C12-14 Pareth-1 Sulfosuccinate

According to an MSDS on disodium C12-14 pareth-1 sulfosuccinate (~ 30% disodium mono-[polyoxyethylene alkyl) sulfosuccinate in trade name material), a 3% solution in physiological saline of a similar chemical is a minimal ocular irritant (unrinsed eyes) and a non-irritant (rinsed eyes) in guinea pigs.[23] Additional details were not provided.

Disodium C12-14 Pareth-2 Sulfosuccinate

Similarly, information in an MSDS on disodium C12-14 pareth-2 sulfosuccinate (~ 40% disodium mono-[polyoxyethylene alkyl) sulfosuccinate in trade name material) indicates that a 3% solution of this material in physiological saline is a minimal ocular irritant (unrinsed eyes) and that a 3% solution in physiological saline of a similar chemical is a non-irritant (rinsed eyes) in guinea pigs.[20] Additional details were not provided.

Irritation and Sensitization

Disodium Laureth Sulfosuccinate

Non-Human Studies

A disodium laureth sulfosuccinate trade name material (active ingredient [40%]; anionic active matter [33%]) was evaluated in skin irritation tests involving rabbits.[8] At a concentration of 3% active matter (effective concentration = 1.2% active ingredient; procedure not stated), the test substance was non-irritating. In the Duhring chamber test, the test substance was non-irritating at a concentration of 2% active matter (effective concentration = 0.40 x 0.02 = 0.8% active ingredient). Details relating to either test procedure were not provided. [18] The same test material did not induce mucous membrane irritation in rabbits when tested at a concentration of 3% active matter (effective concentration = 0.40 x 0.03 = 1.2% active ingredient).[8] Details relating to the test procedure were not provided.

The skin sensitization potential of the same disodium laureth sulfosuccinate trade name material (active ingredient [40%]; anionic active matter [33%]) was evaluated in the maximization test using 2 groups of 20 guinea pigs of the Pirbright White strain.[8] One of the groups served as the control group. Test concentrations administered during induction included 10% disodium laureth sulfosuccinate (4% active matter; effective concentration = 1.6% active ingredient) in physiological saline (intradermal induction) and 5% (2% active matter; effective concentration = 0.8% active ingredient) in physiological saline (dermal induction). The challenge concentration was 2% active matter (effective concentration = 0.8% active ingredient), and reactions were scored at 24 h and 48 h post-exposure. None of the animals had signs of primary skin irritation or sensitization, and the test substance was considered non-sensitizing.

The skin irritation potential of a disodium laureth sulfosuccinate trade name material (25% active matter) was evaluated using 5 albino rabbits according to OECD guideline No. 404.[18] The test substance was applied to one flank (shave dorsal skin) of each animal. An untreated area served as the control. The contact time under occlusive conditions was 4 h. Skin reactions were described as weak, with scores of 0.2 for erythema and 0 for edema at 24 h, 48 h, and 72 h.

A skin sensitization study on the same disodium laureth sulfosuccinate trade name material (25% active matter), performed according to the Magnusson-Kligman method, involved guinea pigs of the Pirbright Hoe: DHPK strain.[18] The number of animals tested was not stated. Based on the results of a preliminary study on a 10% dilution of the test substance in deionized water, a 5% dilution of the test substance (effective concentration = 1.6% active matter) was applied during induction (intracutaneous and epicutaneous; 48 h occlusive conditions) and during the challenge (epicutaneous) phase. Following both induction procedures, the animals were challenged with the test substance under occlusive conditions for 24 h. Challenge application did not result in any signs of adverse dermal reactions.

Ten guinea pigs per sex were initially injected with 10% disodium laureth sulfosuccinate in water (0.05 ml), followed by injection with 10% disodium laureth sulfosuccinate in Freund's Complete Adjuvant (FCA, 0.05 ml), and, then, FCA (0.05 ml).[24] After a 7-day non-treatment period, the animals were challenged dermally with 5% disodium laureth sulfosuccinate in water and then re-challenged with 5% disodium laureth sulfosuccinate in water. Control animals were treated with water only. Skin sensitization was not observed in any of the animals tested with disodium laureth sulfosuccinate or water.

According to an MSDS on disodium laureth sulfosuccinate (30 to 39.9% by weight), this chemical substance is considered a severe skin irritant, based on data on components or similar materials. Additional details were not provided.[9]

Disodium C12-14 Pareth-1 Sulfosuccinate

According to an MSDS on a disodium C12-14 pareth-1 sulfosuccinate trade name material (~ 30% disodium mono-[polyoxyethylene alkyl] sulfosuccinate), a 10% aqueous solution of a similar chemical is neither a primary nor cumulative skin irritant in guinea pigs.[23] Additional details were not provided.

Disodium C12-14 Pareth-2 Sulfosuccinate

Information in an MSDS on a disodium C12-14 pareth-2 sulfosuccinate trade name material (~ 40% disodium mono-[polyoxyethylene alkyl] sulfosuccinate) indicates that a 10% aqueous solution of this chemical is neither a primary nor cumulative skin irritant in guinea pigs.[20] Additional details were not provided.

Human Studies

The skin irritation potential of disodium laureth sulfosuccinate was evaluated using 12 healthy subjects (between ages of 22 and 64 years).[25] The test substance was diluted in a citrate buffer (final pH = 6 ± 0.5). Finn chambers (12 mm) containing 10% disodium laureth sulfosuccinate (50 µl) were applied to the left volar forearm and removed after 48 h. Citrate buffer (10 mM) served as the control. Sites were examined 1 h after patch removal on day 1 and after 24 h on day 2. Transepidermal water loss, cutaneous blood flow, and skin capacitance were also measured. Erythema (mild irritation) was observed on day 1. Application of the citrate buffer control also resulted in erythema. Compared to the control, transepidermal water loss was significantly elevated on day 2 after test substance application. The test substance did not induce a significant increase in cutaneous blood flow, but caused a decrease in skin capacitance.

Patch tests were performed to evaluate the role of pre-existing dermatitis in the response to irritants.[26] The study involved 40 healthy subjects and 480 patients with the following types of skin disease: active atopic dermatitis (n =40), psoriasis (n = 57), eczema (n = 124), urticaria (n = 79), and pruritus (n = 40). The 6 groups (males and females; mean age range: 18 to 55) were patch tested with 5% and 10% aqueous solutions of disodium laureth sulfosuccinate (volume = 17 µl). Patch tests were applied on both sides of the upper back for 48 h using Al-test on Fixomul. Reactions were scored 1 h after removal of the strips. For urticaria patients, 2 additional strips were applied to both sides of the back and then removed 30 minutes later. There were no positive reactions to either test concentration of disodium laureth sulfosuccinate in healthy subjects or patients with pre-existing dermatitis.

The skin irritation potential of a trade name mixture containing 24% active material was evaluated in a 14-day cumulative irritation test using 28 subjects (ages not stated).[27] Disodium laureth sulfosuccinate comprised 70% of the active material; thus, the effective concentration of disodium laureth sulfosuccinate in the trade name mixture was 16.8%. Sodium lauryl sulfoacetate was also included in the mixture. The effective concentration was diluted (1% dilution) to a test concentration of 0.168% disodium laureth sulfosuccinate in the trade mixture. The test concentration (100 µl) was applied repeatedly to estimate the mean number of days of continuous exposure that would produce a clinical irritation grade of 2. The positive control (1% SLS) was similarly applied. The mean number of days of continuous exposure to the 0.168% disodium laureth sulfosuccinate trade mixture that produced a clinical irritation grade of 2 was 9.86 days (3.93 days for positive control). A cumulative irritation score of 163 (based on N = 10) was reported for this trade mixture (score of 346 for positive control), classifying it as possibly a mild irritant during normal use. The positive control was classified as an experimental irritant.

The skin irritation and sensitization potential of a trade name mixture containing 10% active material was evaluated in a repeated insult patch test using 51 subjects (males and females; 19 to 65 years old).[28] Data on the composition of this material are included in Table 3. The total active material (disodium laureth sulfosuccinate plus sodium lauryl sulfoacetate) in this mixture) is 24%. Of this 24%, 70% (16.8% of the total mixture) is disodium laureth sulfosuccinate and 30% (7.2% of the total mixture) is sodium lauryl sulfoacetate. Because the trade mixture evaluated contained 10% active material, the concentration of disodium laureth sulfosuccinate tested was 1.68% (0.1 x 16.8% = 1.68%). During induction, an occlusive patch containing the test material (0.2 ml) was applied (24 h) repeatedly to the back of each subject for a total of 9 applications. After a 10- to 21-day non-treatment period, a challenge patch was applied to a new test site and reactions were scored at 24 h and 48 h post-application. Barely perceptible erythema (1 subject) and barely perceptible to moderate cumulative irritant reactions (3 subjects) were observed during induction. Reactions were not observed during the challenge phase. It was concluded that the trade name mixture containing 1.68% disodium laureth sulfosuccinate did not induce clinically significant irritation or any evidence of allergic contact dermatitis.

Disodium Pareths Sulfosuccinates

The following skin irritation study is included because the CAS Number 68115-56-5 for the chemical tested [poly(oxy-1,2-ethanediyl), alpha-(3-carboxy-1-oxosulfopropyl)-omega- hydroxy-, C10-C16 alkyl ethers, disodium salts] is generic for any disodium C10-16 alkyl laureth sulfosuccinate. It contains disodium sulfosuccinate and other components (e.g., sodium lauryl sulfoacetate) that differ from disodium laureth sulfosuccinate only by modest variations in chain length. The test article is also identified as 15% Alconate L-3. In this study, 6 New Zealand white rabbits each received a single dermal application of 15% Alconate-L3 (0.5 ml) at two 2 cm^2 sites, abraded and intact, on opposite sides. Each site was covered with an occlusive patch (2 cm^2) for 24 h, and reactions were scored at 24 and 72 h. The test substance was not classified as a dermal irritant under the conditions of this test (primary irritation index = 3.15).[29]

Comedogenicity

The comedogenicity of a trade name mixture containing 24% active material was evaluated using 3 young adult New Zealand white rabbits (1 male, 2 females; ages not stated).[30] Data on the composition of this material are included in Table 3. The total active material (disodium laureth sulfosuccinate plus sodium lauryl sulfoacetate) in this mixture) is 24%. Of this 24%, 70% (16.8% of the total mixture) is disodium laureth sulfosuccinate and 30% (7.2% of the total mixture) is sodium lauryl sulfoacetate. The test substance (undiluted; volume not stated) was applied to the left ear of each rabbit for 3 consecutive weeks (5 consecutive days/week). Untreated right ears served as controls. At the end of the dosing period, control and treated ears were excised and subjected to microscopic examination for comedone formation. Neither follicular hyperkeratosis nor comedone formation was observed during week 1. However, hyperkeratosis and dry, flaky skin were observed on all treated ears from week 2 to the end of the study. Reactions were not observed on untreated ears throughout the study. Acanthotic thickening (hyperplasia) of the epithelium, mild hyperkeratosis, and mild acute inflammatory infiltrates in the dermal layers were observed at microscopic examination of treated ears. However, there was no evidence of comedone formation. Based on microscopic findings, the trade name mixture containing 16.8% disodium laureth sulfosuccinate received a comedogenic score of 1, defined as an increase in visible hyperkeratosis without comedone formation.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

The following reproductive toxicity study summaries are included in the amended CIR final safety assessment on alkyl PEG ethers.[1]

Laureths

The reproductive and teratogenic toxicity of compounds analogous to laureth-9 was evaluated.[31] Groups of 25 gravid female rabbits were dosed orally with 0, 50, 100, or 200 mg/kg bw $C_{12}AE_6$ (alcohol ethoxylate[AE] with 12 carbon atoms in alkyl chain; average number of ethylene oxide units = 6) on days 2-16 of gestation, and the animals were killed and necropsied on day 28 of gestation. In the 100 and 200 mg/kg groups, ataxia and a slight decrease in body weights was evidence of maternal toxicity. No effects on reproductive parameters were noted. Nine control animals and 1 test animal died during the study. Based on maternal toxicity, the NOAEL was >50 mg/kg bw/day.

Groups of 25 male and 25 female CD rats were used to evaluate the reproductive toxicity of $C_{14-15}AE_7$ in a two-generation study. The animals were fed a diet containing 0, 0.05, 0.1, and 0.5% of the test article (equivalent to approximately 0, 25, 50, and 250 mg/kg bw/day). In three test groups, males and females were given treated feed throughout the study; in another three groups, females only were dosed, and dosing was performed on days 6-15 of gestation. Additional details regarding study and dosing regimen were not provided. No compound-related differences in fertility, gestation, or viability indices were observed, and the NOAEL for reproduction with dietary administration of $C_{14-15}AE_7$ was >0.5% (equivalent to 250 mg/kg bw/day).

In addition, effects on the F_C generation, i.e. offspring from the third mating of the F_0 and F_1 parental generation, were examined. Gravid female rats were necropsied and examined on either day 13 or day 21 of gestation. Differences in maternal and fetal indices were observed in the test groups compared to the controls, but these effects were not considered test-compound related. Parental female rats and pups of the high-dose group had reduced body weight gains. In the 0.5% continuous feeding test group, increased mean liver weights of males and females of the P_1

generation and an increase in relative liver to body weights of males of the 0.5% continuous feeding group of the P_2 generation at 60 days were considered compound-related. The NOAEL for maternal and developmental toxicity was 50 mg/kg bw/day.

The reproductive toxicity of $C_{12}AE_6$ was evaluated in a similar study, and the groups of 50 rats were fed 0, 25, 50, or 250 mg/kg bw/day of the test article in the diet. No treatment-related effects on behavior, appearance, survival, or fertility were observed in any of the test groups. Parental and offspring weight gain was reduced in the 250 m/kg group. In the 250 mg/kg group, statistically significant increases in embryo lethality and soft tissue anomalies were observed, and in the 50 mg/kg group, a statistically significant decrease in mean fetal liver weights was observed. None of these effects were considered test article-related. The NOAEL for reproduction was >250 mg/kg bw/day, and the NOAELs for maternal and developmental toxicity were 50 mg/kg bw/day $C_{12}AE_6$ in the diet.[31]

GENOTOXICITY

Disodium Laureth Sulfosuccinate

A disodium laureth sulfosuccinate trade name material (active ingredient [40%]; anionic active matter [33%]) was not mutagenic in the Ames test.[8] Details relating to the test procedure were not included. The mutagenicity of another disodium laureth sulfosuccinate trade name material (32% active matter) was evaluated using the following *Salmonella typhimurium* strains with and without metabolic activation:[18] TA 100, TA 1535, TA 1537, TA 1538, and TA 98. The test substance was evaluated at concentrations ranging from 0.32 µl to 200 µl/plate. A bacteriotoxic effect was observed at a dose of 200 µl/plate. The test material was not mutagenic, with or without metabolic activation, over the range of concentrations tested.

The genotoxicity of a trade name material identified as disodium laureth sulfosuccinate was evaluated in the micronucleus test using groups of 5 male and 5 female NMRI mice (~ 6 to 8 weeks old).[17] Test animals received a single oral dose of the test substance (dose = 2,000 mg/kg body weight) in distilled water. Results relating to acute oral toxicity are included in that section of the safety assessment. Cyclophosphamide (CPA) and distilled water served as positive and negative controls, respectively. Two thousand polychromatic erythrocytes (PCE's) per mouse were analyzed for the presence of micronuclei in bone marrow smears. For an investigation of bone marrow toxicity, the proportion of PCE's among total erythrocytes was evaluated on the basis of ~ 200 erythrocytes. The frequency of micronucleated PCE's in the vehicle control group was within the physiological range, whereas, the positive control was genotoxic. Disodium laureth sulfosuccinate did not induce an increase in the number of micronucleated PCE's in any of the test groups. There was also no statistically significant difference in the proportion of PCE's among total erythrocytes when compared to the vehicle control. Disodium laureth sulfosuccinate was not genotoxic.

CARCINOGENICITY

The following carcinogenicity study summaries are included in the amended CIR final safety assessment on alkyl PEG ethers.[1]

Laureths

The carcinogenic potential of compounds analogous to laureth-9 was evaluated.[31] *Groups of 65 rats/gender were fed a diet containing 0, 0.1, 0.5, and 1% $C_{14-15}AE_7$ for 2 yrs. At 1 yr, 14-15 animals per gender were killed and necropsied. No compound-related changes were seen in behavior or appearance at any time. Survival rate was comparable between test and control animals. Body weight gains were significantly decreased in females of the 0.5 and 1.0% groups and males of the 1% group. At necropsy, no differences in relative or absolute organ weights were observed between test and control animals. There was no evidence of a carcinogenic effect.*

$C_{12-13}AE_{6.5}$ was fed to 100 Sprague-Dawley rats at concentrations up to 1% in feed for 2 yrs. Feed consumption, and correspondingly, body weight gain, was decreased for females fed 0.5 or 1% and for males fed diets containing 1% of the test compound. No microscopic effects were seen, and $C_{12-13}AE_{6.5}$ was not carcinogenic.[31]

SUMMARY

The safety of the following ingredients in cosmetics is reviewed in this safety assessment: disodium laureth sulfosuccinate, disodium laureth-6 sulfosuccinate, disodium laureth-9 sulfosuccinate, disodium laureth-12 sulfosuccinate, disodium deceth-5 sulfosuccinate, disodium deceth-6 sulfosuccinate, magnesium laureth-3 sulfosuccinate, disodium C12-14 pareth-1 sulfosuccinate, disodium C12-14 pareth-2 sulfosuccinate, disodium C12-15 pareth sulfosuccinate, disodium coceth-3 sulfosuccinate, disodium laneth-5 sulfosuccinate, disodium C12-14 sec-pareth-3 sulfosuccinate, disodium C12-14 sec-pareth-5 sulfosuccinate, disodium C12-14 sec-pareth-7 sulfosuccinate, disodium C12-14 sec-pareth-9 sulfosuccinate, disodium C12-14 sec-pareth-12 sulfosuccinate, and disodium oleth-3 sulfosuccinate.

Together, data reported to the Food and Drug Administration's Voluntary Cosmetic Registration Program in 2011 and the results of a 2011 Personal Care Products Council (Council) survey indicated use of the following ingredients in cosmetics, mostly in rinse-off products: disodium laureth sulfosuccinate (0.06% [eyeliner] to 10% [noncoloring shampoos]), disodium laureth-6 sulfosuccinate, disodium deceth-6 sulfosuccinate, and disodium C12-14 pareth-2 sulfosuccinate. Subsequent inclusion of magnesium laureth-3 sufosuccinate in a 2011 Council Survey yielded no use concentration data on this ingredient. Therefore, of the 18 ingredients included in the survey, only use concentration data on disodium laureth sulfosuccinate were reported.

A method for the production of disodium laureth sulfosuccinate involves ethoxylation of a fatty alcohol, esterification with maleic acid anhydride, addition of sodium sulfite, and neutralization with sodium hydroxide. Impurities present in disodium laureth sulfosuccinate include 1,4-dioxane, ethylene oxide, and formaldehyde. According to an MSDS on disodium laureth sulfosuccinate, this chemical contains formaldehyde at a maximum level of 0.056% and 1,4-dioxane at a maximum level of 0.001%.

Studies on the toxicokinetics of sulfosuccinates, following oral, dermal, or inhalation exposure, reviewed in this safety assessment were not found in the published literature. However, certain predictions may be made based on their chemical and physical properties. Due to the ester linkage, these sulfosuccinate ingredients are sensitive to hydrolysis, especially under acidic conditions. Accordingly, if these ingredients have the ability to penetrate the skin, then first level metabolites would likely include the corresponding alkyl PEG ethers (e.g., magnesium laureth-3 sulfosuccinate may be metabolized to Laureth-3 and sulfosuccinic acid).

In 2 acute oral toxicity studies on disodium laureth sulfosuccinate trade name materials involving rats, LD50's of >10,000 mg/kg and > 2,000 mg/kg were reported. However, all of the female rats that received a single 840 mg/kg oral dose of a trade name material containing 16.8% disodium laureth sulfosuccinate died within 24 h of dosing, whereas, all male rats survived to the end of the study. An acute oral LD50 of 3,490 mg/kg (rats) was reported for disodium C12-14 pareth-2 sulfosuccinate. Reportedly, the acute dermal LD50 for one disodium laureth sulfosuccinate trade name material is > 2,000 mg/kg (rabbits), based on data on components or similar materials. In two 28-day oral toxicity studies (rats) on disodium laureth sulfosuccinate trade name materials, an NOEL of 250 mg/kg/day and a systemic NOAEL of 300 mg/kg/day were reported. Increased liver weight was observed in both studies.

A disodium laureth sulfosuccinate trade name material (25% active matter) was classified as posing a risk of serious ocular damage in rabbits. Furthermore, a trade name mixture containing 1.68% active disodium laureth sulfosuccinate was classified as a primary ocular irritant in rabbits. Disodium C12-14 pareth-2 sulfosuccinate (~ 40% disodium mono-[polyoxyethylene alkyl) sulfosuccinate in trade name material) was minimally irritating to the eyes of guinea pigs when tested as a 3% solution in physiological saline.

Disodium laureth sulfosuccinate (10% in citrate buffer) was classified as a mild skin irritant in healthy subjects. In dermatitis patients and healthy subjects in another study, disodium laureth sulfosuccinate (5% and 10% aqueous solutions) did not induce skin irritation. The results of a human cumulative skin irritation study on a trade name mixture containing 0.168% disodium laureth sulfosuccinate predicted that this material would be a mild skin irritant during normal use. A trade name mixture containing 1.68% disodium laureth sulfosuccinate did not induce clinically significant irritation or any evidence of allergic contact dermatitis in normal human subjects. A disodium C10-16 alkyl laureth sulfosuccinate, similar to

disodium laureth sulfosuccinate, and a disodium laureth sulfosuccinate trade name material (effective test concentrations = 0.8% and 1.2% active ingredient) did not induce skin irritation in rabbits. Skin sensitization was not observed at an effective challenge concentration of 0.8% active ingredient in a separate study (guinea pigs) involving the same tradename material. At a higher concentration (25% active matter), a different disodium laureth sulfosuccinate tradename material also did not induce skin irritation, and sensitization was not observed in guinea pigs when the material was diluted to an effective concentration of 1.6% active matter. A 10% aqueous solution of a disodium C12-14 pareth-2 sulfosuccinate tradename material (~ 40% disodium mono-[polyoxyethylene alkyl] sulfosuccinate) induced neither primary nor cumulative irritation in guinea pigs.

A trade name mixture containing 16.8% disodium laureth sulfosuccinate induced an increase in visible hyperkeratosis, without comedone formation, in rabbits.

In two-generation oral reproductive studies with dietary administration of compounds analogous to laureth-9, the NOAEL for reproductive toxicity was >250 mg/kg bw/day, and the NOAELs for maternal and developmental toxicity was 50 mg/kg bw/day.

Ames test and micronucleus test results for disodium laureth sulfosuccinate trade name materials were negative. Compounds that are analogous to laureth-9 were not carcinogenic in feeding studies in which rats were given up to 1% in the diet for 2 years.

DISCUSSION

The CIR Expert Panel noted that negative mammalian genotoxicity data on disodium laureth sulfosuccinate were received in response to a previous request for data, but dermal absorption and inhalation toxicity data were not received. In the absence of inhalation and dermal absorption data, the Panel reasoned that skin penetration of these alkyl PEG sulfosuccinates would be unlikely because of their substantial polarity and molecular sizes. In addition, the high acute LD50s reported in oral animal studies suggested that the absorption of these substances through the skin at relevant doses has little potential to cause systemic effects.

The Panel did acknowledge that statistically significant increases in liver weights in animals that received repeated oral doses of disodium laureth sulfosuccinate were reported, but given the absence of any other findings indicative of liver toxicity, such findings were not considered to be relevant. The Panel noted that sulfosuccinates have the potential for causing ocular/skin irritation, but not sensitization. Therefore, products containing these ingredients should be formulated to be non-irritating.

Because disodium laureth sulfosuccinate can be used at maximum reported concentration of 2% in cosmetics that may be sprayed (hair color sprays), the Panel discussed the issue of incidental inhalation exposure. In the absence of sufficient inhalation data, the Panel considered data characterizing the potential for alkyl PEG sulfosuccinates to cause systemic toxicity, genotoxicity, ocular or dermal irritation, or sensitization, and the potential for laureths to cause reproductive and developmental toxicity or carcinogenicity. The Panel noted that 95 – 99% of the droplets/particles produced in cosmetic aerosols would be deposited in the nasopharyngeal and thoracic regions of the respiratory tract and would not be respirable to any appreciable amount. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, this information suggested that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic toxic effects.

The Panel also addressed the potential for ethylene oxide and 1,4-dioxane impurities in alkyl PEG sulfosuccinates. Due to the volatility of ethylene oxide, it would be unexpected to find any appreciable quantity of the chemical residing as an impurity in these ingredients. The available data bear out that current methods of manufacture do not result in significant levels of ethylene oxide. The available data have demonstrated contaminant levels of 1,4-dioxane to be less than 10 ppm in these ingredients, again supporting that current methods of manufacture do not result in significant levels of 1,4-dioxane. Because of the toxicity of ethylene oxide and 1,4-dioxane, the Panel stressed that the cosmetics industry should continue to

use the necessary procedures to remove these impurities from the alkyl PEG sulfosuccinates before blending them into cosmetic formulations.

According to an MSDS on disodium laureth sulfosuccinate, this chemical may contain formaldehyde at a maximum level of 0.056%. The Panel noted that this level is less than the 0.076% formaldehyde limit established by the Panel in its final safety assessment on this ingredient, and is well below the threshold for any toxicological concerns relating to this chemical. Furthermore, the effective formaldehyde concentration yielded by disodium laureth sulfosuccinate in formulation would be even lower, considering that this ingredient is being used at concentrations up to 10% in rinse-off products and at concentrations up to 2% in leave-on products. At the maximum use concentration of 10%, the formaldehyde concentration would be no more than 0.006%.

CONCLUSION

The CIR Expert Panel concluded that the following cosmetic ingredients are safe in the present practices of use and concentration described in this safety assessment when formulated to be non-irritating:

- Disodium Laureth Sulfosuccinate
- Disodium Laureth-6 Sulfosuccinate
- Disodium Laureth-9 Sulfosuccinate*
- Disodium Laureth-12 Sulfosuccinate*
- Disodium Deceth-5 Sulfosuccinate*
- Disodium Deceth-6 Sulfosuccinate
- Magnesium Laureth-3 Sulfosuccinate*
- Disodium C12-14 Pareth-1 Sulfosuccinate*
- Disodium C12-14 Pareth-2 Sulfosuccinate
- Disodium C12-15 Pareth Sulfosuccinate*
- Disodium Coceth-3 Sulfosuccinate*
- Disodium Laneth-5 Sulfosuccinate*
- Disodium C12-14 Sec-Pareth-3 Sulfosuccinate*
- Disodium C12-14 Sec-Pareth-5 Sulfosuccinate*
- Disodium C12-14 Sec-Pareth-7 Sulfosuccinate*
- Disodium C12-14 Sec-Pareth-9 Sulfosuccinate*
- Disodium C12-14 Sec-Pareth-12 Sulfosuccinate*
- Disodium Oleth-3 Sulfosuccinate*

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

Table 1. Definitions, Functions, and Structures of the Sulfosuccinate Ingredients[4]

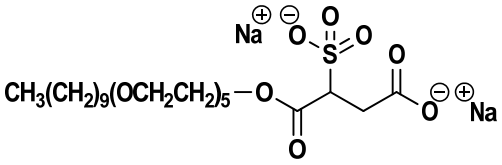
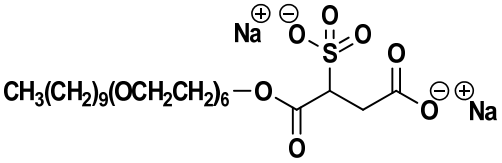
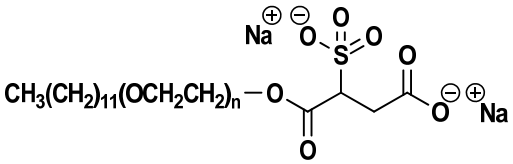
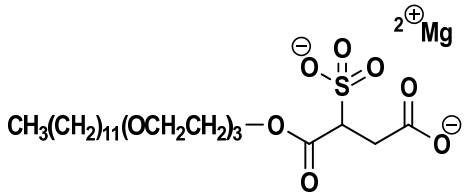
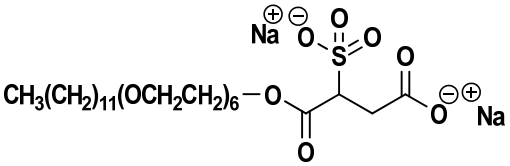
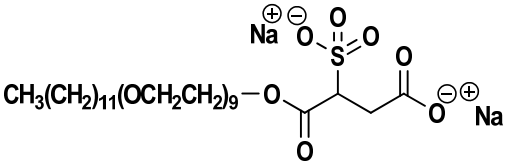
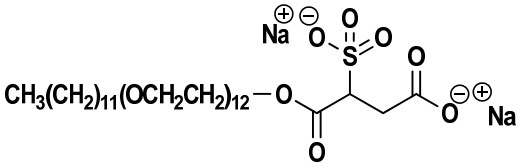
Ingredient CAS No.	Definition	Function(s)	Formula/structure
Disodium Deceth-5 Sulfosuccinate 68311-03-5 (CAS No. is generic for any disodium deceth sulfosuccinate)	Disodium Deceth-5 Sulfosuccinate is a disodium salt of the half ester of an ethoxylated decyl alcohol and sulfosuccinic acid.	Surfactant - Cleansing Agent; Surfactant - Foam Booster; Surfactant – Hydrotrope	
Disodium Deceth-6 Sulfosuccinate 68311-03-5 (CAS No. is generic for any disodium deceth sulfosuccinate)	Disodium Deceth-6 Sulfosuccinate is a disodium salt of the half ester of an ethoxylated decyl alcohol and sulfosuccinic acid.	Surfactant - Cleansing Agent; Surfactant - Foam Booster; Surfactant - Hydrotrope	
Disodium Laureth Sulfosuccinate 39354-45-5 58450-52-5 (CAS Nos. are generic for any disodium laureth sulfosuccinate)	Disodium Laureth Sulfosuccinate is the disodium salt of an ethoxylated lauryl alcohol half ester of sulfosuccinic acid. 40754-59-4 42015-08-0 (CAS Nos. are specific to triethoxylated (i.e. laureth-3))	Surfactant - Cleansing Agent; Surfactant - Foam Booster; Surfactant – Hydrotrope 68815-56-5 (CAS No. is generic for any disodium C10-16 alkyl laureth sulfosuccinate)	 wherein n averages between 1 and 4 (i.e. Laureth-1 through Laureth-4)
Magnesium Laureth-3 Sulfosuccinate	Magnesium Laureth-3 Sulfosuccinate is the magnesium salt of the half ester of an ethoxylated lauryl alcohol and sulfosuccinic acid.	Surfactant - Cleansing Agent	
Disodium Laureth-6 Sulfosuccinate 39354-45-5 (CAS No. is generic for any disodium laureth sulfosuccinate)	Disodium Laureth-6 Sulfosuccinate is the disodium salt of an ethoxylated lauryl alcohol half ester of sulfosuccinic acid. 40754-59-4[sic; specific to disodium laureth-3 sulfosuccinate]	Surfactant - Cleansing Agent; Surfactant - Foam Booster; Surfactant - Hydrotrope	
Disodium Laureth-9 Sulfosuccinate 39354-45-5 (CAS No. is generic for any disodium laureth sulfosuccinate)	Disodium Laureth-9 Sulfosuccinate is the disodium salt of an ethoxylated lauryl alcohol half ester of sulfosuccinic acid.	Surfactant - Cleansing Agent; Surfactant - Foam Booster; Surfactant - Hydrotrope	
Disodium Laureth-12 Sulfosuccinate 39354-45-5 (CAS No. is generic for any disodium laureth sulfosuccinate)	Disodium Laureth-12 Sulfosuccinate is the disodium salt of an ethoxylated lauryl alcohol half ester of sulfosuccinic acid.	Surfactant - Cleansing Agent; Surfactant - Foam Booster; Surfactant - Hydrotrope	

Table 1. Definitions, Functions, and Structures of the Sulfosuccinate Ingredients[4]

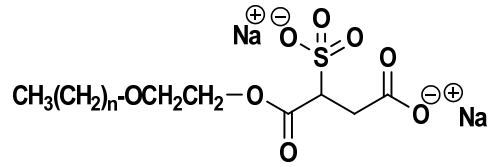
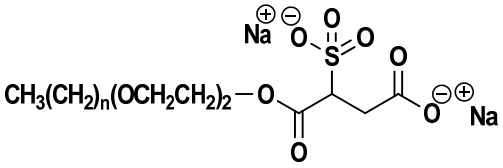
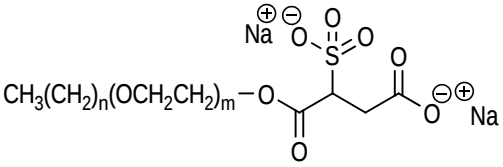
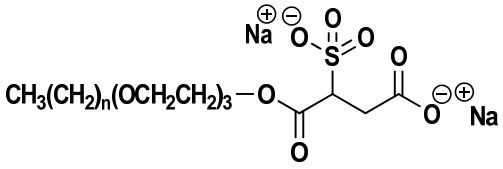
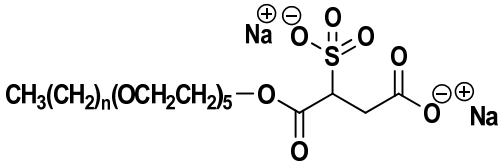
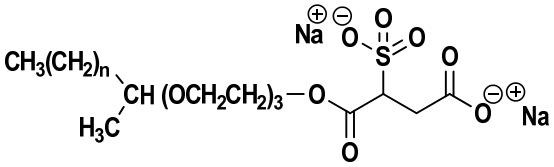
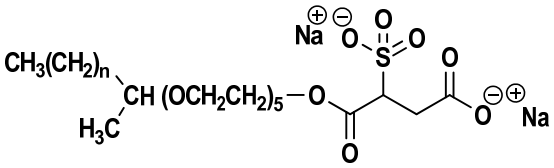
Ingredient CAS No.	Definition	Function(s)	Formula/structure
Disodium C12-14 Pareth-1 Sulfosuccinate	Disodium C12-14 Pareth-1 Sulfosuccinate is the disodium salt of an ethoxylated, partially esterified sulfosuccinic acid.	Surfactant - Cleansing Agent	 wherein n averages between 11 and 13 (i.e. Laureth-1 through Myreth-1)
Disodium C12-14 Pareth-2 Sulfosuccinate	Disodium C12-14 Pareth-2 Sulfosuccinate is the disodium salt of an ethoxylated, partially esterified sulfosuccinic acid.	Surfactant - Cleansing Agent; Surfactant - Foam Booster; Surfactant - Hydrotrope	 wherein n averages between 11 and 13 (i.e. Laureth-2 through Myreth-2)
Disodium C12-15 Pareth Sulfosuccinate	Disodium C12-15 Pareth Sulfosuccinate is the disodium salt of an ethoxylated, partially esterified sulfosuccinic acid.	Surfactant - Cleansing Agent; Surfactant - Foam Booster; Surfactant - Hydrotrope	 wherein n averages between 11 and 14, and m averages between 1 and 4 (i.e. Laureth-2 through Pentadeceth-4)
Disodium Coceth-3 Sulfosuccinate	Disodium Coceth-3 Sulfosuccinate is the disodium salt of the half ester of Coceth-3 and sulfosuccinic acid.	Surfactant - Cleansing Agent; Surfactant - Emulsifying Agent	 wherein n represents the alkyl groups derived from coconut alcohol
Disodium Laneth-5 Sulfosuccinate 68890-92-6 (CAS No. is generic for any disodium laneth sulfosuccinate)	Disodium Laneth-5 Sulfosuccinate is a disodium salt of the half ester of Laneth-5 and sulfosuccinic acid.	Surfactant - Cleansing Agent; Surfactant - Foam Booster; Surfactant - Hydrotrope	 wherein n represents the alkyl groups derived from lanolin alcohol.
Branched			
Disodium C12-14 Sec-Pareth-3 Sulfosuccinate	Disodium C12-14 Sec-Pareth-3 Sulfosuccinate is a disodium salt of the half ester of a mixture of ethoxylated, secondary C12-14 alcohols and sulfosuccinic acid.	Surfactant - Cleansing Agent; Surfactant - Foam Booster; Surfactant - Hydrotrope	 wherein n averages between 9 and 11 (i.e. *sec*-Laureth-3 through *sec*-Myreth-3)
Disodium C12-14 Sec-Pareth-5 Sulfosuccinate	Disodium C12-14 Sec-Pareth-5 Sulfosuccinate is a disodium salt of the half ester of a mixture of ethoxylated, secondary C12-14 alcohols and sulfosuccinic acid.	Surfactant - Cleansing Agent; Surfactant - Foam Booster; Surfactant - Hydrotrope	 wherein n averages between 9 and 11 (i.e. *sec*-Laureth-5 through *sec*-Myreth-5)

Table 1. Definitions, Functions, and Structures of the Sulfosuccinate Ingredients[4]

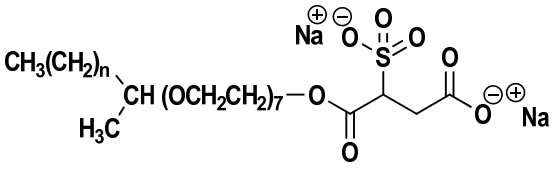
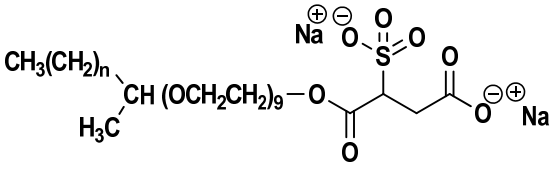
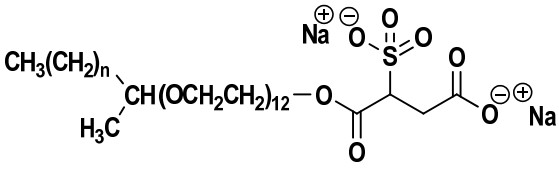
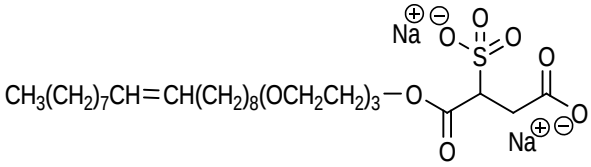
Ingredient CAS No.	Definition	Function(s)	Formula/structure
Disodium C12-14 Sec-Pareth-7 Sulfosuccinate	Disodium C12-14 Sec-Pareth-7 Sulfosuccinate is a disodium salt of the half ester of a mixture of ethoxylated, secondary C12-14 alcohols and sulfosuccinic acid.	Surfactant - Cleansing Agent; Surfactant - Foam Booster; Surfactant - Hydrotrope	 wherein n averages between 9 and 11 (i.e. *sec*-Laureth-7 through *sec*-Myreth-7)
Disodium C12-14 Sec-Pareth-9 Sulfosuccinate	Disodium C12-14 Sec-Pareth-9 Sulfosuccinate is a disodium salt of the half ester of a mixture of ethoxylated, secondary C12-14 alcohols and sulfosuccinic acid.	Surfactant - Cleansing Agent; Surfactant - Foam Booster; Surfactant - Hydrotrope	 wherein n averages between 9 and 11 (i.e. *sec*-Laureth-9 through *sec*-Myreth-9)
Disodium C12-14 Sec-Pareth-12 Sulfosuccinate	Disodium C12-14 Sec-Pareth-12 Sulfosuccinate is a disodium salt of the half ester of a mixture of ethoxylated, secondary C12-14 alcohols and sulfosuccinic acid.	Surfactant - Cleansing Agent; Surfactant - Foam Booster; Surfactant - Hydrotrope	 wherein n averages between 9 and 11 (i.e. *sec*-Laureth-12 through *sec*-Myreth-12)
Unsaturated			
Disodium Oleth-3 Sulfosuccinate	Disodium Oleth-3 Sulfosuccinate is the disodium salt of an Oleth-3 (Ω-9 unsaturated) half ester of sulfosuccinic acid.	Surfactant - Cleansing Agent; Surfactant - Foam Booster; Surfactant - Hydrotrope	

Table 2. Properties of Sulfosuccinate Ingredients

Properties	Disodium Laureth Sulfosuccinate (and as trade name materials)	Disodium C12-14 Pareth-1 Sulfosuccinate (Beaulight ESS-10P)	Disodium C12-14 Pareth-2 Sulfosuccinate (Beaulight ESS)
Form	~32% active solution in water (clear liquid).[6] water white liquid, as CHEMCCINATE™ DSLS SURFACTANT [CAS No. 68815-56-5]).[9] Clear, colorless to slightly yellowish liquid surfactant raw material (as TEXAPON® SB 3 KC [CAS No. 68815-56-5], average of 3 moles of ethylene oxide).[7] Colorless liquid (as SETACIN 103 SPEZIAL [CAS No. 39354-45-5]).[32]	Cololorless or pale yellow liquid at 20^0C.[23]	Colorless or pale yellow liquid at 20^0C.[20]
% Composition	CHEMCCINATE™ DSLS SURFACTANT: 30 to 39.9% by weight disodium laureth sulfosuccinate.[9] TEXAPON® SB 3 KC: dry residue (38 to 42%); anionic surfactant, m.w. 550 (31.5 to 34.5%); sulfate content (max. 1%); 0.5% citric acid and 0.4% potassium sorbate as preservatives.[7] SETACIN 103 SPEZIAL: active ingredient (40%), anionic active matter (33%), and water content (60%).[32]	~ 30% disodium mono-(polyoxyethylene alkyl) sulfosuccinate (CAS No. 68911-93-3); ~ 70% water.[23]	~ 40% disodium mono-(polyoxyethylene alkyl) sulfosuccinate (CAS No. 68911-93-3); ~ 60% water.[20]
Odor	Alcohol (as CHEMCCINATE™ DSLS SURFACTANT).[9]	Slightly specific.[23]	Slightly specific.[20]
Molecular weight	~ 548;[6] 550 (as SETACIN 103 SPEZIAL).[32]		
Specific Gravity	1.11;[6] also 1.11 (at 20^0C) as CHEMCCINATE™ DSLS SURFACTANT and as SETACIN 103 SPEZIAL.[9,32,33]	1.10 (at 25^0C).[23]	1.15 (at 30^0C).[20]
pH	6.6 to 7 (at 10% in water) as CHEMCCINATE™ DSLS SURFACTANT;[9] 4.5 to 5.5 (TEXAPON® SB 3 KC 10% solution);[7] 6.3 (SETACIN 103 SPEZIAL 10% solution).[32]	~ 6.8 (10% aqueous solution).[23]	~ 7 (2% aqueous solution).[20]
Solubility	Water soluble, as CHEMCCINATE™ DSLS SURFACTANT and as SETACIN 103 SPEZIAL.[9,32]	Water soluble.[23]	Water soluble.[20]
Freezing point	Not determined (as CHEMCCINATE™ DSLS SURFACTANT).[9]	~ 0^0C.[23]	below 0^0C.[20]
Boiling point	100^0C (as CHEMCCINATE™ DSLS SURFACTANT).[9]	~ 100^0C.[23]	~ 100^0C.[20]

Table 3. Specifications for a Disodium Laureth Sulfosuccinate (16.8% active)/Sodium Lauryl Sulfoacetate (7.2% active) Trade Name Mixture[34]

Composition	Limits
% Active (molecular weight 491)	23-27
% Solids	30-35
pH (10% aqueous)	5.5-6.5
% Sodium Sulfate	3% max
% Sodium Chloride	2% max
Residual peroxide	Nil
Viscosity (CPS) @ 25°C	10,000 max
Formaldehyde	Positive

Table 4. Composition Data on a Disodium Laureth Sulfosuccinate (16.8% active)/Sodium Lauryl Sulfoacetate (7.2% active) Trade Name Mixture[35]

Composition	Value
% Active (molecular weight 491)	24
% Solids	32
pH (10% aqueous)	6.3
% Sulfate	2.2
% Sulfite	Nil
% Chloride	1.4
Bleach (% H_2O_2)	Nil
Viscosity (CPS) @ 25°C	236
Sodium Citrate	0.14
Formalin	Positive

Table 5. Current Frequency and Concentration of Use According to Duration and Type of Exposure[10,11,12]

	Disodium Laureth Sulfosuccinate		Disodium Laureth-6 Sulfosuccinate		Disodium Deceth-6 Sulfosuccinate	
	# of Uses	Conc. (%)	# of Uses		# of Uses	
Exposure Type						
Eye Area	2	0.06	NR		6	
Incidental Ingestion	NR	NR	NR		NR	
Incidental Inhalation-sprays	2	2	NR		NR	
Incidental Inhalation-powders	NR	NR	NR		NR	
Dermal Contact	480	0.06 to 9	NR		NR	
Deodorant (underarm)	NR	NR	NR		NR	
Hair - Non-Coloring	125	2 to 10	3		NR	
Hair-Coloring	1	2	NR		NR	
Nail	NR	NR	NR		NR	
Mucous Membrane	417	0.8 to 8	NR		NR	
Baby Products	5	NR	3		NR	
Duration of Use						
Leave-On	15	0.06 to 2	NR	NR	6	NR
Rinse-Off	592	0.4 to 10	3	NR	NR	NR
Diluted for (bath) use	59	1 to 4	NR	NR	NR	NR
Totals/Conc. Range	607	0.06 to 10	3	NR	6	NR
	Disodium C12-14 Pareth-2 Sulfosuccinate					
	# of Uses					
Exposure Type						
Eye Area	NR					
Incidental Ingestion	NR					
Incidental Inhalation-sprays	NR					
Incidental Inhalation-powders	NR					
Inhalation	NR					
Dermal Contact	NR					
Deodorant (underarm)	NR					
Hair - Non-Coloring	4					
Hair-Coloring	NR					
Nail	NR					
Mucous Membrane	NR					
Baby Products	NR					
Duration of Use						
Leave-On	NR					
Rinse-Off	4					
Diluted for (bath) use	NR					
Totals/Conc. Range	4					

NR = Not Reported; Totals = Rinse-off + Leave-on Product Uses.
Notes: Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure type uses may not equal the sum total uses. Omission of Conc.(%) column indicates the absence of ingredient use concentration data;

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Ethylhexyl Alcohol	- Absorption, Distribution, Metabolism, and Excretion: in vitro dermal absorption rates were determined for ethylhexyl alcohol in rats and humans; in rats, the rate was 0.22 mg/cm^2/h and in the human it was 0.038 mg/cm^2/h; accordingly, the human rate of ethylhexyl alcohol absorption was 5.78 times slower than the rate in the rat - Dermal Toxicity: in three different acute dermal toxicity studies on rabbits with ethylhexyl alcohol, the LD_{50} values reported were 2380, >2600 and > 5000 mg/kg bw; 10 rats were dosed with 2 ml/kg bw/day (1600mg/kg/day) via single application on shaved backs; absolute and relative thymus wts, liver granulomas, brochiectasis in the lung, renal tubular epithelial necroses, edematous heart and testes, and spermatogenesis, all decreased; 10 rats/sex were dosed with 0, 500, or 1000 mg/kg bw/day (5 days occlusive, 2 days untreated, 4 days treated); 500 and 1000 mg treated rats exhibited minimal exfoliation, decreased spleen wt and increased serum triglycerides in females - Ocular Irritation: instillation of 20 µg of ethylhexyl alcohol into the conjunctival sac of rabbits caused moderately severe irritation of the cornea - Dermal Irritation – Non-Human: ethylhexyl alcohol was applied under occlusion to the skin of 3 male rabbits for 4 hours and found to be irritating; in another study with rabbits, 0.5 ml of ethylhexyl alcohol was applied under occlusion on intact skin for 1, 2, 4, and 24 hours; irritation was considered high, and effects seen after 7 days were not reversible - Dermal Irritation and Sensitization Human: tested at a concentration of 4% in petrolatum, ethylhexyl alcohol produced no irritation in a 48 h occlusive-patch test in 29 male volunteers; in a maximization study, ethylhexyl alcohol did not induce any sensitization reactions - Reproductive and Developmental Toxicity: a group of female rats was exposed for 7 h/day to 850 mg/m^3 of ethylhexyl alcohol on gestation days 1-19; dams were sacrificed at day 20; ethylhexyl alcohol reduced maternal feed intake, but did not produce any malformations; the estrogenic activity of 2-ethylhexanoic acid was examined using an E-SCREEN assay using T47D human breast cancer cells; weak estrogenic activity was observed; additional details were not provided. - Genotoxicity: in vitro, ethylhexyl alcohol was negative in a number of Ames assays, a liquid suspension assay, mouse lymphoma assay, and unscheduled DNA synthesis assay; in a ^{3}H-thymidine assay, there was a dose-dependent inhibition of 3H-thymi¬dine into replicating DNA, with a dose-dependent increase in the ratio of acid-soluble DNA incorporated into the thymidine; the urine of rats dosed orally with 1000 mg/kg bw ethylhexyl alcohol was not mutagenic; in vivo, ethylhexyl alcohol was not genotoxic in a mouse micronucleus test or a transformation assay Carcinogenicity: B6C3F$_1$ mice (50/sex/group) were administered 0, 50, 200, or 750 mg/kg bw/day via gavage, 5 days/wk for 18 mos; at the 750 mg/kg dose, weak hepatocellular carcinoma increased in females, bw gain decreased and mortality increased; F344 rats (50/sex/group) were administered 0, 50, 150, or 500 mg/kg bw/day via gavage, 5 days/wk for 24 mos; rats dosed ≥150 mg/kg were characterized with bw gain decrease, lethargy and unkemptness; at 500 mg/kg, mortality in females was at 52%

From: Fiume MM, Heldreth BA, Bergfeld WF, Belsito DV, Hill RA, Klaassen CD, Liebler DC, Marks JG, Shank RC, Slaga TJ, Snyder PW, and Andersen FA. (2013) Amended safety assessment of alkyl ethylhexanoates as used in cosmetics. http://www.cir-safety.org/sites/default/files/ethylh032013rep.pdf

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5

Final Report on the Safety Assessment of Cetearyl Alcohol, Cetyl Alcohol, Isostearyl Alcohol, Myristyl Alcohol, and Behenyl Alcohol

Cetearyl, Cetyl, Isostearyl, Myristyl, and Behenyl Alcohols are long-chain aliphatic alcohols that are, at most, only slightly toxic when administered orally at doses of 5 g/kg and greater. In acute dermal toxicity studies (rabbits), doses of up to 2.6 g/kg of Cetyl Alcohol and 2.0 g/kg of a product containing 0.8% Myristyl Alcohol were both practically nontoxic. Mild irritation was observed when a cream containing 3.0% Cetearyl Alcohol was applied to the skin of New Zealand albino rabbits. Cetyl Alcohol (50.0% in petrolatum) applied to abraded and intact skin of albino rabbits produced minimal to slight skin irritation. Cetyl Alcohol was considered to be practically nonirritating when instilled into the eyes of albino rabbits. An aerosol antiperspirant containing 3.0% Myristyl Alcohol induced mild to moderate irritation; a moisturizing lotion containing 0.8% Myristyl Alcohol was nonirritating to rabbit eyes. Corneal irritation was reported following an ocular test using a 5.0% Isostearyl Alcohol antiperspirant. Conjunctival irritation was observed 2 and 6 h after instillation of 1.0% Behenyl Alcohol. Isostearyl Alcohol (5.0% in propylene glycol) and an antiperspirant containing 5.0% Isostearyl Alcohol were not sensitizers in guinea pigs. Cetyl Alcohol was not mutagenic in *Salmonella typhimurium* LT2 mutant strains in the spot test. Clinical skin irritation and sensitization studies of product formulations containing up to 8.4% Cetyl Alcohol produced no evidence of irritation or sensitization. Moisturizing lotions containing 0.8% Myristyl Alcohol were nonirritating to human skin, and moisturizers containing 0.25% Myristyl Alcohol were neither irritants nor sensitizers. No signs of skin irritation or sensitization were observed in humans following the dermal application of 25% Isostearyl Alcohol. In a human skin sensitization study of a cream containing 3.0% Cetearyl Alcohol, none of the subjects had positive reactions. An analysis of the data and comparison with

data from other toxicity studies on long-chain aliphatic alcohols is presented. Based on the available data included in this report, it is concluded that Cetearyl Alcohol, Cetyl Alcohol, Isostearyl Alcohol, Myristyl Alcohol, and Behenyl Alcohol are safe as cosmetic ingredients in the present practices of use.

INTRODUCTION

The toxicity of long-chain aliphatic alcohols is reviewed in this report. In other toxicological reviews, the Cosmetic Ingredient Review Expert Panel has assessed the safety of related compounds: Stearyl Alcohol, Oleyl Alcohol, Octyl Dodecanol, Isopropyl Stearate, Isobutyl Stearate, Butyl Stearate, Octyl Stearate, Myristyl Stearate, Isocetyl Stearate, Cetyl Stearate, Isopropyl Palmitate, Octyl Palmitate, Cetyl Palmitate, Myristyl Lactate, Cetyl Lactate, Isopropyl Myristate, Myristyl Myristate, Cetearyl Octanoate, Isostearyl Neopentanoate, and Isostearic Acid.[1-5]

CHEMISTRY

Chemical and Physical Properties

Cetearyl, Cetyl, Myristyl, and Behenyl alcohols are straight-chain aliphatic alcohols. Isostearyl Alcohol is a branched-chain aliphatic alcohol. These long-chain aliphatic alcohols conform to the empirical formula, $C_nH_{2n+1}OH$, and have been produced via high-temperature, high-pressure, catalytic hydrogenation of fatty acids[6]:

$$RCOOH + 4\,[H] \xrightarrow[\text{catalyst, pressure}]{\Delta} RCH_2OH + H_2O$$

A significant development since 1955 has been the manufacture of straight-chain primary alcohols by the Ziegler process[7]:

$$Al + 3/2\ H_2 + 2\ Et_3Al \longrightarrow 3\ Et_2AlH$$

$$3\ Et_2AlH + CH_2 = CH_2 \longrightarrow 3\ Et_3Al$$

$$Et_3Al + n\ CH_2 = CH_2 \longrightarrow R \cdot Al \begin{matrix} R' \\ R'' \end{matrix}$$

$$R \cdot Al \begin{matrix} R' \\ R'' \end{matrix} + O_2 \xrightarrow{H_2O} (C_nH_{2n+1})\ OH + Al(OH)_3$$

Branched-chain fatty alcohols may be produced by the Oxo process.[7] This process involves the passage of olefin hydrocarbon vapors over cobalt catalysts

in the presence of carbon monoxide and hydrogen.[8] Regardless of the method of production of the saturated fatty alcohols, they are sold either as high purity fractions or mixtures.[6] Some of the physical and chemical properties of Cetearyl, Cetyl, Isostearyl, Myristyl, and Behenyl Alcohols are listed in Table 1.

Cetearyl Alcohol

Cetearyl Alcohol (CAS No. 8005-44-5) is a white, waxy solid, usually in flake form.[9] It is a mixture of mostly cetyl (hexadecanol) and stearyl (octodecanol) alcohols.[10] Cetearyl Alcohol is also known as cetostearyl alcohol and cetyl/stearyl alcohol.[10] It is insoluble in water and soluble in alcohol and oils.[9]

Cetyl Alcohol

Cetyl Alcohol (CAS No. 36653-82-4) is a white, waxy solid in flake or powder form.[9] It is a 16-carbon alcohol, known also as 1-hexadecanol and n-hexadecyl alcohol.[10] Cetyl Alcohol is the oldest known of the long-chain alcohols, having been discovered by Chevrenl in 1913. It is insoluble in water and soluble in alcohol and oils.[9]

Isostearyl Alcohol

Isostearyl Alcohol (CAS No. 27458-93-1 and 41744-75-6) is a clear water-white liquid, consisting essentially of a mixture of branched-chain, aliphatic 18-carbon alcohols.[13] It is a primary alcohol having monomethyl branching randomly distributed along its C_{17} straight chain.[6] Isostearyl Alcohol is insoluble in water and miscible in most oils and waxes.[13]

Myristyl Alcohol

Myristyl Alcohol (CAS No. 112-72-1) or 1-tetradecanol is a white unctuous mixture of solid alcohols consisting chiefly of 14-carbon alcohols (n-tetradecanol); it is soluble in ether, slightly soluble in ethanol, and insoluble in water.[12]

Behenyl Alcohol

Behenyl Alcohol or n-docosanol (CAS No. 661-19-8) is a 22-carbon aliphatic alcohol. It is a colorless, waxy solid that is soluble in ethanol and chloroform and insoluble in water.[8]

Reactivity

No specific information concerning the chemical reactivity of long-chain aliphatic alcohols has been identified. However, it is believed that they are oxidized to their respective fatty acids.

Analytical Methods

Analytical methods that are used to detect and identify fatty alcohols include gas–liquid chromatography, liquid chromatography, thin-layer chromatography, gas chromatography, and mass spectrometry.[14–17]

TABLE 1. Properties of Long-Chain Aliphatic Alcohols

	Cetearyl Alcohol	*Cetyl Alcohol*	*Isostearyl Alcohol*	*Myristyl Alcohol*	*Behenyl Alcohol*
Formula	$CH_3(CH_2)_{15-17}OH$[a]	$CH_3(CH_2)_{14}CH_2OH$[b]	$C_{18}H_{38}O$[b]	$CH_3(CH_2)_{12}CH_2OH$[b]	$CH_3(CH_2)_{20}CH_2OH$[b]
Molecular weight		242.45[c]	280[d]	214.40[c]	326.61[c]
Form	White, waxy solid[a]	White, waxy solid[a]	Water-white liquid[e]	White solid[e]	Colorless, waxy solid[f]
Boiling point		344°C, bp_{15} 190°C[c]	$bp_{0.7}$ 136–160°C[d]	263.2°C, bp_{15} 167°C[c]	$bp_{0.22}$ 180°C[c]
Melting point	50–55°C[a]	50°C[c]	5°C[d]	39–40°C[c]	71°C[c]
Density		0.8176[c]		0.8236[c]	
Refractive index		1.4283[c]	1.4615 at 20°C[d]		
Solubility	Alcohol, oils[a]	Alcohol, ether,[c] acetone, benzene	Oils, waxes[e]	Alcohol, ether,[c] acetone, benzene, chloroform	Alcohol, chloroform[c]
Acid value		0[g]	1.0 maximum[e]		
Iodine value		3.0 maximum[g]	12.0 maximum[e]	1.0 maximum[g]	
Saponification value		1.0 maximum[g]	2.0 maximum[e]	1.0 maximum[g]	
Hydroxyl value		218–232[g]	180–200[e]	250–260[g]	

[a]Ref. 9.
[b]Ref. 10.
[c]Ref. 11.
[d]Ref. 6.
[e]Ref. 13.
[f]Ref. 8.
[g]Ref. 12.

Impurities

Cetearyl Alcohol

Technical grade Cetearyl Alcohol contains approximately 65% to 80% stearyl and 20% to 35% cetyl alcohols.[18] Though Cetearyl Alcohol consists mostly of cetyl and stearyl alcohols, small quantities of alcohols with longer and shorter chain lengths are usually present in this mixture.[9] Additionally, the following impurities have been reported for Cetearyl Alcohol mixtures.[16]

Hydrocarbons (consisting principally of n-hexadecane and n-octadecane)	0.1–1.4%
Odd-numbered straight-chain alcohols	1–3.5%
Branched-chain primary alcohols	0.2–2%

Even-numbered straight-chain alcohols (C_8–C_{22}) comprise 90% to 95% of this mixture.[16]

Cetyl Alcohol

Cetyl Alcohol (National Formulary) contains a minimum of 90% Cetyl Alcohol.[9] Cetyl Alcohol is generally believed to be 1-hexadecanol, but commercial grades often contain measurable amounts of stearyl alcohol and other long-chain aliphatic alcohols.[19] The Cosmetic, Toiletry and Fragrance Association (CTFA) Specification for Cetyl Alcohol includes the following impurities[12]:

Hydrocarbons	1.5% maximum
Ash	0.05% maximum
Lead (as elemental lead)	20 ppm maximum
Arsenic (as elemental arsenic)	3 ppm maximum

Isostearyl Alcohol

Published data concerning impurities within Isostearyl Alcohol mixtures have not been identified.

Myristyl Alcohol

The CTFA Specification for Myristyl Alcohol includes the following impurities[12]:

Hydrocarbons	1.5% maximum
Ash	0.05% maximum
Lead (as elemental lead)	20 ppm maximum
Arsenic (as elemental arsenic)	3 ppm maximum

Behenyl Alcohol

Technical grade Behenyl Alcohol contains 99% Behenyl Alcohol.[8] Published data concerning impurities within Behenyl Alcohol mixtures have not been identified.

USE

Purpose in Cosmetics

Long-chain aliphatic alcohols are widely used in skin lotions and creams; those most commonly used range from 12 to 18 carbons in length.[6] In lotions, long-chain aliphatic alcohols serve as emollients, emulsion stabilizers, viscosity control agents, coupling agents, and foam stabilizers.[6] Particularly, Cetyl Alcohol is used as an emollient to prevent drying and chapping of the skin because of its water-binding property.[20]

The cosmetic product formulation listing that is made available by the Food and Drug Administration (FDA) is compiled through voluntary filing of such data in accordance with Title 21 Part 720.4 of the Code of Federal Regulations.[21] Ingredients are listed in prescribed concentration ranges under specific product type categories. Since certain cosmetic ingredients are supplied by the manufacturer at less than 100% concentration, the value reported by the cosmetic formulator may not necessarily reflect the actual concentration found in the finished product; the actual concentration in such a case would be a fraction of that reported to the FDA. The fact that data are only submitted within the framework of preset concentration ranges also provides the opportunity for overestimation of the actual concentration of an ingredient in a particular product. An entry at the lowest end of a concentration range is considered the same as one entered at the highest end of that range, thus introducing the possibility of a 2- to 10-fold error in the assumed ingredient concentration. See Table 2 for this list of cosmetic products containing long-chain aliphatic alcohols.

Surfaces to Which Applied

Cosmetic products containing long-chain aliphatic alcohols are applied to the skin, hair, nails, and vaginal mucosa and may come in contact with the eyes and nasal mucosa; small amounts of the ingredients may be ingested because of their presence in lipstick (Table 2).

Frequency and Duration of Application

Product formulations containing long-chain aliphatic alcohols may be applied once per week or as often as several times per day. Many of the products may be expected to remain in contact with the skin for as briefly as a few hours or as long as a few days. Each cosmetic product formulated with long-chain aliphatic alcohols may be used repeatedly over a period of many years (Table 2).

Noncosmetic Use

Long-chain aliphatic alcohols are used in pharmaceuticals as emulsifying and stiffening agents.[22] They occur in textile soaps as emulsifying agents and are components of synthetic fibers and lubricants.[23,24] According to Section 172.864 of the Title 21 Code of Federal Regulations,[25] synthetic long-chain aliphatic alcohols may be used safely in food and in the synthesis of food compo-

nents. In keeping with this Section, Cetyl Alcohol must contain not less than 98% of total alcohols and not less than 94% of straight-chain alcohols; Myristyl Alcohol must contain not less than 99% of total alcohols and not less than 96% of straight chain alcohols.[25] Also, technical grade Cetearyl Alcohol, approximately 65% to 80% stearyl alcohol and 20% to 35% Cetyl Alcohol, is required for some indirect food additives.[18]

Of the ingredients reviewed in this report, Cetyl Alcohol is the only one listed in the 1984 FDA Over-The-Counter (OTC) Drug Review. The Miscellaneous External Drug Products Advisory Review Panel to the FDA lists Cetyl Alcohol as an ingredient of both external analgesics and skin protectants.[26] That panel has not issued a proposed or final ruling concerning the safety of Cetyl Alcohol in such compositions. However, before 1984, various advisory review panels to the FDA issued recommendations regarding the safety of Cetyl Alcohol; these recommendations appear in Table 3.[27]

The uses of Cetearyl, Cetyl, and Myristyl Alcohols as direct and indirect food additives and any limitations existing for these ingredients are listed in Table 4.

BIOLOGICAL PROPERTIES

Antimicrobial Activity

The effect of Myristyl Alcohol on bacterial growth was assessed in *Streptococcus mutans* BHT.[31] After a 4-h culture interval, the mean growth response in the presence of 12.4 m*M* Myristyl Alcohol was 45% of that in the untreated cultures. At the end of 6 h and throughout the remainder of the 24-h culture interval, the growth response to Myristyl Alcohol remained at 82–89% of that in untreated controls.

The inhibitory activity of Myristyl, Cetyl, and Behenyl Alcohols on the growth of *Mycoplasma gallisepticum* and *Mycoplasma pneumoniae* has been reported.[32] The proposed mechanism of action of these long-chain aliphatic alcohols is a change in cell membrane permeability that either blocks absorption of essential nutrients or causes the outward diffusion of vital cellular components. Growth was indicated by a decrease in pH and was monitored by the change in percent transmittance at 560 nm, using a spectrophotometer. The effect of treatment with long-chain aliphatic alcohols (64 μM) on *Mycoplasma* growth for 6 days is as follows:

	% Inhibition	
Alcohol	*M. gallisepticum*	*M. pneumoniae*
Myristyl	0	20.7
Cetyl	97.9	90.8
Behenyl	0	44.9

Inhibition of Lipolysis

The inhibition of methyl oleate hydrolysis by pancreatic lipase has been demonstrated in a solution of rat pancreatic juice.[33] Approximately 15.8 μmoles of Cetyl Alcohol added to the reaction mixture (225 μmoles of methyl oleate/55 ml of pancreatic juice) caused 50% inhibition of hydrolysis.

TABLE 2. Product Formulation Data[170]

Product category	*Total no. of formulations in category*	*Total no. containing ingredient*	*No. of product formulations within each concentration range (%)*			
			>10–25	*>5–10*	*>1–5*	*>0.1–1*
Cetearyl Alcohol						
Eye makeup remover	81	1	–	–	1	–
Mascara	397	1	–	–	1	–
Hair conditioners	478	6	–	1	4	1
Hair straighteners	64	3	–	3	–	–
Hair rinses (noncoloring)	158	1	–	–	–	1
Hair shampoos (noncoloring)	909	1	–	–	1	–
Makeup foundations	740	2	–	–	–	2
Rouges	211	1	–	–	–	1
Other makeup preparations (not eye)	530	1	–	–	1	–
Bath soaps and detergents	148	1	1	–	–	–
Other personal cleanliness products	227	1	–	1	–	–
Aftershave lotions	282	2	–	–	–	2
Shaving cream (aerosol, brushless, and lather)	114	4	–	–	1	3
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	680	4	–	–	2	2
Face, body, and hand skin care preparations (excluding shaving preparations)	832	11	–	1	9	1
Moisturizing skin care preparations	747	7	1	1	3	2
Night skin care preparations	219	2	–	–	2	–
Paste masks (mud packs)	171	4	–	1	3	–
Other skin care preparations	349	3	1	–	2	–
1982 TOTALS		56	3	8	30	15

Product category	Total no. of formulations in category	Total no. containing ingredient	No. of product formulations within each concentration range (%)					
			>25–50	>10–25	>5–10	>1–5	>0.1–1	≤0.1
Cetyl Alcohol								
Baby lotions, oils, powders, and creams	56	12	–	–	–	8	4	–
Bath oils, tablets, and salts	237	8	–	–	–	4	2	2
Other bath preparations	132	4	–	–	–	2	2	–
Eyebrow pencil	145	6	–	–	–	6	–	–
Eyeliner	396	30	–	–	–	16	11	3
Eye shadow	2582	169	–	–	7	94	67	1
Eye lotion	13	1	–	–	–	–	1	–
Eye makeup remover	81	4	–	–	–	3	1	–
Mascara	397	8	–	–	–	5	3	–
Other eye makeup preparations	230	26	–	–	–	13	13	–
Colognes and toilet waters	1120	12		2	–	6	4	–
Perfumes	657	7	1	–	–	6	–	–
Fragrance powders (dusting and talcum, excluding aftershave talc)	483	4	–	–	–	1	3	–
Sachets	119	59	4	–	9	20	26	–
Other fragrance preparations	191	26	–	–	1	10	14	1
Hair conditioners	478	163	–	3	10	104	37	9
Hair sprays (aerosol fixatives)	265	2	–	–	–	1	–	1
Hair straighteners	64	32	–	6	8	1	17	–
Permanent waves	474	3	–	–	–	–	2	1
Hair rinses (noncoloring)	158	52	–	–	–	20	29	3
Hair shampoos (noncoloring)	909	9	–	–	–	3	4	2
Tonics, dressings, and other hair grooming aids	290	17	–	–	2	5	8	2
Other hair preparations (noncoloring)	177	9	–	–	–	2	3	4
Hair dyes and colors (all types requiring caution statement and patch test)	811	1	–	–	–	–	1	–
Hair shampoos (coloring)	16	2	–	–	–	–	2	–
Hair bleaches	111	12	–	–	4	3	5	–
Other hair coloring preparations	49	5	–	2	–	2	1	–
Blushers (all types)	819	40	–	1	–	14	24	1
Face powders	555	24	–	–	–	10	14	–
Makeup foundations	740	68	–	–	1	12	53	2

TABLE 2. (Continued)

Product category	Total no. of formulations in category	Total no. containing ingredient	No. of product formulations within each concentration range (%)					
			>25–50	>10–25	>5–10	>1–5	>0.1–1	≤0.1
Leg and body paints	4	3	–	–	–	–	3	–
Lipstick	3319	573	–	2	11	538	20	2
Makeup bases	831	134	–	–	1	23	108	2
Rouges	211	13	–	–	–	8	4	1
Makeup fixatives	22	2	–	–	–	–	1	1
Other makeup preparations (not eye)	530	11	–	–	–	5	6	–
Cuticle softeners	32	6	–	–	–	3	3	–
Nail creams and lotions	25	8	–	–	1	4	3	–
Other manicuring preparations	50	2	–	–	–	1	1	–
Bath soaps and detergents	148	1	–	–	1	–	–	–
Deodorants (underarm)	239	20	–	–	–	16	4	–
Feminine hygiene deodorants	21	1	–	–	–	–	1	–
Other personal cleanliness products	227	29	–	–	2	19	8	–
Aftershave lotions	282	11	–	–	–	3	6	2
Preshave lotions (all types)	29	1	–	–	–	–	1	–
Shaving cream (aerosol, brushless, and lather)	114	25	–	–	–	1	22	2
Other shaving preparation products	29	10	–	–	–	5	5	–
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	680	169	–	1	3	79	81	5
Depilatories	32	9	–	–	4	5	–	–
Face, body, and hand skin care preparations (excluding shaving preparations)	832	322	–	1	3	153	160	5
Foot powders and sprays	17	2	–	–	–	1	1	–
Hormone skin care preparations	10	3	–	–	1	1	1	–

Moisturizing skin care preparations	747	287	–	–	4	143	133	7
Night skin care preparations	219	95	–	–	1	63	29	2
Paste masks (mud packs)	171	13	–	–	–	5	8	–
Skin lighteners	44	13	–	–	–	11	2	–
Skin fresheners	260	2	–	–	–	1	1	–
Wrinkle smoothers (removers)	38	6	–	–	–	5	1	–
Other skin care preparations	349	47	–	2	1	23	21	–
Suntan gels, creams, and liquids	164	42	–	–	–	14	27	1
Indoor tanning preparations	15	7	–	–	–	3	4	–
Other suntan preparations	28	12	–	–	–	5	6	1
1982 TOTALS		2694	5	20	75	1509	1022	63

Product category	*Total no. of formulations in category*	*Total no. containing ingredient*	*No. of product formulations within each concentration range (%)*				
			>25–50	*>10–25*	*>5–10*	*>1–5*	*>0.1–1*
Isostearyl Alcohol							
Bath oils, tablets, and salts	237	2	–	–	–	2	–
Colognes and toilet waters	1120	3	2	–	–	1	–
Other fragrance preparations	191	2	–	–	1	1	–
Hair conditioners	478	1	–	–	–	–	1
Hair rinses (noncoloring)	158	2	–	–	–	1	1
Blushers (all types)	819	21	–	–	–	21	–
Lipstick	3319	5	–	1	2	1	1
Other makeup preparations (not eye)	530	1	1	–	–	–	–
Face, body, and hand skin care preparations (excluding shaving preparations)	832	1	–	–	–	–	1
Moisturizing skin care preparations	747	2	–	–	–	1	1
Night skin care preparations	219	1	–	–	–	1	–
1982 TOTALS		41	3	1	3	29	5

TABLE 2. (Continued)

Product category	Total no. of formulations in category	Total no. containing ingredient	No. of product formulations within each concentration range (%)		
			>1–5	>0.1–1	≤0.1
Myristyl Alcohol					
Hair conditioners	478	1	1	–	–
Hair shampoos (noncoloring)	909	1	–	1	–
Makeup foundations	740	1	1	–	–
Makeup bases	831	4	4	–	–
Cuticle softeners	32	1	1	–	–
Aftershave lotions	282	1	–	1	–
Beard softeners	4	2	2	–	–
Shaving cream (aerosol, brushless, and lather)	114	1	1	–	–
Other shaving preparation products	29	2	1	1	–
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	680	1	–	–	1
Face, body, and hand skin care preparations (excluding shaving preparations)	832	5	2	3	–
Moisturizing skin care preparations	747	8	3	5	–
Night skin care preparations	219	1	–	1	–
Paste masks (mud packs)	171	1	–	1	–
Other skin care preparations	349	1	1	–	–
1982 TOTALS		31	17	13	1

Product category	Total no. of formulations in category	Total no. containing ingredient	No. of product formulations within each concentration range (%)		
			>25–50	>10–25	>5–10
Behenyl Alcohol					
Eyebrow pencil	145	4	–	4	–
Eyeliner	396	18	3	14	1
Eye shadow	2582	9	2	7	–
Lipstick	3319	11	1	10	–
Other makeup preparations (not eye)	530	1	–	1	–
1982 TOTALS		43	6	36	1

Absorption, Metabolism, and Excretion

Summaries of various studies indicate that long-chain aliphatic alcohols are oxidized to their corresponding fatty acids in mammalian tissues.[4,5] Much of the data concerning the absorption, metabolism, and excretion of long-chain aliphatic alcohols has been accumulated for Cetyl (C_{16}) and Stearyl (C_{18}) Alcohols. The Federation of American Societies for Experimental Biology (FASEB) has

TABLE 3. OTC Panel Recommendations for Cetyl Alcohol[27]

Advisory review panel	*Date of action*	*Reference document*	*Recommended category*[a]	*Final conditions*
Hemorrhoidal Drug Panel	3/9-10/74	OTC Panel (6th meeting)	I	Pharmaceutical necessity (stabilizant and emulsification aid) for use as an emulsifying aid based on hydrating properties; dispersant abilities and stabilizing properties for washable ointment base
Hemorrhoidal Drug Panel	5/12-14/74	OTC Panel (7th meeting)	III	Tentatively
Miscellaneous External Drug Products	8/3-4/79	OTC Panel (32nd meeting)	I	For safety as an active ingredient in concentrations of 8% or less
Miscellaneous External Drug Products	8/3-4/79	OTC Panel (32nd meeting)	I	For effectiveness for antimicrobial action
Miscellaneous External Drug Products	4/20-21/80	OTC Panel (38th meeting)	I	For safety in any concentration for topical application and for effectiveness in low concentration as a pharmaceutic aid; has no function as a "skin antiseptic"

[a]Category I: Conditions under which OTC drug products are generally recognized as safe and effective and are not misbranded. Category II: Conditions under which OTC drug products are not generally recognized as safe and effective or are misbranded. Category III: Conditions for which the available data are insufficient to permit final classification at this time as category I or II.

published an evaluation of stearyl alcohol.[34] That document contains a review of the literature, dating from 1933 to 1978, concerning the absorption, metabolism, and excretion of Stearyl Alcohol. Because Cetyl and Stearyl Alcohols have structural similarities, the FASEB literature review may be applicable to Cetyl Alcohol. The absorption, metabolism, and excretion of Cetyl Alcohol are discussed below.

In one study, tracer doses (0.2 mg of Cetyl Alcohol-1-^{14}C) were dissolved in 0.5 ml of corn oil and administered by stomach tube to male Sprague-Dawley rats in which the thoracic duct had been cannulated; the rats were killed after 24 h.[35] Results from this study indicate that 75% of the absorbed radioactivity appeared in the thoracic duct lymph. Furthermore, 85% of the Cetyl Alcohol was converted during lymphatic absorption to saponifiable material, presumed to be palmitic acid. Similar findings were reported in an earlier study by Bloomstrand and Rumpf.[36] In that study, radioactively labeled Cetyl Alcohol was fed to rats (strain not identified) with thoracic duct fistulas. Most of the radioactivity

TABLE 4. Direct and Indirect Food Additives

Ingredient	*Noncosmetic use*	*Limitations*	*Reference*
Cetearyl Alcohol	Indirect food additives: Adhesives and components of coatings	–	18
Cetyl Alcohol	Direct food additives: Synthetic flavoring substances and adjuvants	–	28
	Indirect food additives: Adhesives and components of coatings	–	18
	Indirect food additives: Surface lubricants used in the manufacture of metallic articles	–	29
Myristyl Alcohol	Indirect food additives: Adhesives and components of coatings	–	18
	Indirect food additives: defoaming agents used in the manufacture of paper and paperboard	–	30
Myristyl Alcohol (in primary alcohol mixtures containing not more than 5% C_{11}–C_{15} alcohols)	Indirect food additives: Surface lubricants used in the manufacture of metallic articles	For use at a level not to exceed 8% by weight of the finished lubricant formulation	29

(63–96%) appeared in the lymph, indicating good absorption. Approximately 15% of the alcohol was unchanged during its passage through the mucosal cells of the small intestine; most of the Cetyl Alcohol was oxidized to palmitic acid and incorporated into triglycerides and phospholipids. Consequently, the extent of fatty acid absorption may depend on the animal species. For example, Yoshida et al.[37] reported that alcohols containing more than 14 carbon atoms were poorly used in poultry because of their low absorbability. The value reported for the absorption of Cetyl Alcohol was 26%.

Cetyl Alcohol has been isolated from sterile feces of infants and in sterile experimental intestinal loops of dogs.[38] The presence of Cetyl Alcohol in the feces may result from the conversion of fatty acids to corresponding long-chain aliphatic alcohols, which enter the intestinal lumen. Bandi and Mangold[39] demonstrated the interconvertibility of fatty acids and alcohols by the rat. Cetyl Alcohol was detected in the feces of rats whose dietary lipids contained palmitic

acid (C_{16}). It has been concluded that the conversion of fatty acids to long-chain aliphatic alcohols occurs during their passage through the intestinal mucosal cells.[36] Cetyl Alcohol was also excreted in the urine as conjugated glucuronic acid and as expired carbon dioxide.[40]

ANIMAL TOXICOLOGY

Inhalation Toxicity

Cetyl Alcohol

A study involving a single 6-h exposure of groups of 10 mice, rats, and guinea pigs to Cetyl Alcohol vapors (26 ppm) under dynamic conditions, followed by a 24-h holding period, was reported[41] (Table 5). Necropsies were performed on the animals at the end of the holding period. Local irritation due to the alcohol vapor was slight and involved the mucous membranes of the eyes, nose, throat, and respiratory passages. There were no signs of systemic toxicity, and no deaths were reported. In a second inhalation study,[41] a group of 10 rats and 10 guinea pigs was exposed to Cetyl Alcohol vapor (10-min exposures of 9.6 mg/L) every 30 min for a period of 4 h (Table 5). A comparable control group was exposed to room air for the same period. Half of the animals were killed immediately after the exposures, and the rest were killed after a 14-day holding period. The lungs of some of the exposed animals had lesions indicative of chronic respiratory disease (rats) and interstitial or bronchial pneumonia (guinea pigs). The incidence and severity of these changes were comparable to such observations in the control group. No effects related to Cetyl Alcohol exposure were noted. Alternatively, the inhalation of 2220 mg/m^3 of synthetic Cetyl Alcohol for 6 h has resulted in the death of all exposed rats[40] (Table 5).

Myristyl Alcohol

Ten young adult Albino rats of the Sprague-Dawley Strain (average weight, 250 g) were exposed to an aerosol containing 3.0% Myristyl Alcohol. Exposures were conducted in a 0.038 m^3 glass chamber and comprised 20 10-sec aerosol bursts (one burst every 3 min) during a 1-h period. Approximately 7.4 g of the test substance were delivered with each burst, and the average test substance concentration was approximately 192 mg/L of air. Following 10 min of exposure, ataxia and moderate nasal irritation were noted in all animals and persisted throughout the remainder of the exposure period. These reactions were also noted in all animals up to 4 h after their removal from the chamber. No deaths were reported[42] (Table 5).

Acute Oral Toxicity

According to Egan and Portwood,[6] long-chain aliphatic alcohols are nontoxic when administered orally, as defined by the Federal Hazardous Substances Labeling Act (FHSLA). The results from oral toxicological studies of long-chain aliphatic alcohols are indicated below.

Cetyl Alcohol

In a study by Scala and Burtis,[41] Cetyl Alcohol was administered via stomach tube as a corn oil suspension to groups of 5 fasted Sprague-Dawley rats (No. of groups not stated) (Table 6). Observations for signs of toxicity were made for a period of 7–14 days postadministration. The LD_{50} was not achieved at a dose of 8.2 g/kg, the highest dose administered. The principal effects noted were central nervous system depression and labored respiration.

Ten fasted rats of the Harlan Wistar strain (weight range, 110–135 g) each received an oral dose (13,000 mg/kg) of a formulation containing 4.0% Cetyl Alcohol. The animals were observed for signs of toxicity during a 7-day period. No deaths were reported, and there were no signs of toxicity during the observation period[43] (Table 6). In another study, the protocol outlined in Title 16 Part 1500.3 (6)(6)(i)(A) of the Code of Federal Regulations was used to assess the acute oral toxicity of a lipstick product containing 4.0% Cetyl Alcohol. A group of 10 or more laboratory white rats, each weighing between 200 and 300 g, were given a single dose of 50 mg/kg of the product via oral intubation. An LD_{50} of 5.0 g/kg was reported[44] (Table 6).

The acute oral toxicity of a lotion containing 3.25% Cetyl Alcohol was investigated using 10 fasted rats of the Wistar strain. The animals were approximately 6 to 9 weeks old and weighed between 200 and 300 g. Doses were administered via intragastric feeding, and observations for signs of toxicity were made at 1, 3, 6, and 24 h postadministration and at least once daily thereafter for a total of 14 days. Necropsies were performed at the end of the 14-day period. The product induced toxicity at a dose of 5 g/kg if 50% or more of the animals died. One rat died at this dose and had fibrous tissue encasing the heart and lungs at necropsy. No other gross changes were reported[45] (Table 6). No deaths were reported in a similar study (same protocol) in which 10 fasted Wistar rats received 5 g/kg of the same product. The only gross changes reported (1 animal) were a consolidated right lung and a fluid-filled fibrous tissue sac encasing the heart and lungs[46] (Table 6). In another study (same protocol), 1 of the 10 rats receiving 5 g/kg of the product died (day 13 of observation period) and had fibrous tissue encasing the heart and lungs. Identical gross changes were noted in another animal.[54] Gross changes were not observed in another study (same protocol) in which 5 g/kg of the product were administered to 10 albino rats of the Wistar strain.[55]

An oral dose (7 ml/kg) of a formulation containing 2.0% Cetyl Alcohol was administered to each of 10 fasted rats of the Harlan Wistar strain. No signs of toxicity were noted during a 7-day period postadministration[47] (Table 6). In another study, 10 rats (same strain) received a single dose of 33 ml/kg of a product containing 2.0% Cetyl Alcohol. The only effects noted during the 7-day observation period were transient appearances of poor grooming[48] (Table 6). Identical results were reported in another study in which 10 fasted rats of the Fischer 344 strain (weight range, 115–170 g) each received an oral dose (10 ml/kg) of a moisturizer containing 2.0% Cetyl Alcohol[49] (Table 6).

Myristyl Alcohol

The acute oral toxicity of Myristyl Alcohol was assessed in Holtzman albino

TABLE 5. Acute Inhalation Toxicity

Ingredient	*Alcohol concentration and vehicle*	*No. of animals*	*Procedure*	*Results*	*Reference*
Cetyl Alcohol	26 ppm vapor	10 mice, 10 rats, 10 guinea pigs	Single 6-h exposure	Local irritation of eyes, nose, throat, and respiratory passages	41
Cetyl Alcohol	9.6 mg/L of vapor	10 rats, 10 guinea pigs	8 10-min exposures over 4 h	No exposure-related effects	41
Cetyl Alcohol	2220 mg/m^3 of vapor	Rats (no. not stated	Single 6-h exposure	Death of all animals	40
Myristyl Alcohol	3.0% in aerosol (192 mg/L)	10 rats	20 10-sec bursts over 1 h	Ataxia and moderate nasal irritation (all animals)	42

TABLE 6. Acute Oral Toxicity

Ingredient	*Alcohol concentration and vehicle*	*No. of animals*	*Procedure*	*Results*	*Reference*
Cetyl Alcohol	Corn oil suspension (concentration not stated)	Groups of 5 rats (no. not stated)	Intragastic feeding	LD_{50} > 8.2 g/kg	41
Cetyl Alcohol	4.0% in formulation	10 rats	Single oral dose	LD_{50} > 13.0 g/kg	43
Cetyl Alcohol	4.0% in lipstick	10 rats	Single oral dose	LD_{50} = 5.0 g/kg	44
Cetyl Alcohol	3.25% in lotion	10 rats	Single oral dose	LD_{50} > 5.0 g/kg	45
Cetyl Alcohol	3.25% in lotion	10 rats	Intragastric feeding	LD_{50} > 5.0 g/kg	46
Cetyl Alcohol	2.0% in formulation	10 rats	Single oral dose	LD_{50} > 7.0 ml/kg	47
Cetyl Alcohol	2.0% in formulation	10 rats	Single oral dose	LD_{50} > 33.0 ml/kg	48
Cetyl Alcohol	2.0% in moisturizer	10 rats	Single oral dose	LD_{50} > 10.0 ml/kg	49
Myristyl Alcohol	100%	Rats (no. not stated)	Single oral dose	LD_{50} > 8.0 g/kg	6
Myristyl Alcohol	0.8% in moisturizing lotion	10 rats	Single oral dose	LD_{50} > 5.0 g/kg	50
Isostearyl Alcohol	100%	Rats (no. not stated)	Single oral dose	LD_{50} > 20.0 g/kg	6
Isostearyl Alcohol	27.0% in lipstick	5 rats	Single oral dose	LD_{50} > 15.0 g/kg	51
Isostearyl Alcohol	25.0% in lipstick	5 rats	Single oral dose	LD_{50} > 15.0 g/kg	52
Behenyl Alcohol	Olive oil (concentration not stated)	10 mice	Intragastric feeding	LD_{50} < 1.0 g/kg	53

rats. The number of animals involved in the study was not stated. The LD_{50} was not achieved at a dose of 8.0 g/kg[6] (Table 6).

The Protocol stated in Title 16 Part 1500.3 (b)(6)(i)(A) of the Code of Federal Regulations was used to assess the acute oral toxicity of a moisturizing lotion containing 0.8% Myristyl Alcohol. A group of 10 or more laboratory white rats, each weighing between 200 and 300 g, was used in the study. The LD_{50} was not achieved at a dose of 5.0 g/kg[50] (Table 6).

Isostearyl Alcohol

The acute oral toxicity of Isostearyl Alcohol was assessed in adult Sprague-Dawley rats. The number of animals involved in the study was not stated. The LD_{50} was not achieved at a dose of 2.0 g/kg[6] (Table 6).

The acute oral toxicity of a lipstick product containing 27.0% Isostearyl Alcohol was determined using 5 female albino rats (ages not stated). Each animal was given 15.0 g/kg of the product via stomach tube. All animals appeared normal throughout the study, and no gross lesions were found at necropsy on day 7 postadministration[51] (Table 6).

The acute oral toxicity of another lipstick product containing 25.0% Isostearyl Alcohol was evaluated in 5 female albino rats (ages not stated) according to the protocol stated immediately above. All animals appeared clinically normal throughout the study, and no gross lesions were found at necropsy[52] (Table 6). Identical results were reported in another study (same protocol) involving a different lipstick product containing 25.0% Isostearyl Alcohol.[56]

Behenyl Alcohol

The acute oral toxicity of Behenyl Alcohol was evaluated using 10 adult mice of the CF_1 strain (average weight, 25 g). The test substance was diluted with olive oil, heated, and administered (dose, 1.0 g/kg) via stomach tube. None of the animals died during the 8-day observation period. The LD_{50} was not achieved at the administered dosage[53] (Table 6).

Acute Dermal Toxicity

Cetyl Alcohol

Cetyl Alcohol was applied full-strength to the clipped intact abdominal skin of 16 albino rabbits. The animals were divided equally into four treatment groups: 0.10, 0.316, 1.00, and 3.16 ml/kg doses. Each exposed area was covered with an occlusive binding of dental damming that remained in place for 24 h. Observations for signs of toxicity were made for a total of 7 days postapplication. The LD_{50} was reported to be greater than 2.6 g/kg. One of the four animals in the 3.16 ml/kg group had decreased activity and labored respiration[41] (Table 7).

The procedures outlined in Title 16 Parts 1500.3(c)(1)(ii)(c) and 1500.40 of the Code of Federal Regulations were used to assess the acute dermal toxicity of a lipstick product containing 4.0% Cetyl Alcohol.[57] The test substance was

TABLE 7. Acute Dermal Toxicity

Ingredient	*Alcohol concentration and vehicle*	*No. of rabbits*	*Procedure*	*Results*	*Reference*
Cetyl Alcohol	100%	16	Applied to abdominal skin	LD_{50} > 2.6 g/kg	41
Cetyl Alcohol	4.0% in lipstick	5	24-h skin application	LD_{50} > 2.0 g/kg	58
Myristyl Alcohol	0.8% in moisturizing lotion	5	24-h skin application	LD_{50} > 2.0 g/kg	59

held in contact with either clipped skin (5 rabbits) or clipped abraded skin (5 rabbits) by means of an "impervious sleeve" and removed after 24 h. An LD_{50} of >2.0 g/kg was reported[58] (Table 7).

Myristyl Alcohol

The acute dermal toxicity of a moisturizing lotion containing 0.8% Myristyl Alcohol was evaluated in 5 rabbits according to the protocol stated immediately above. An LD_{50} of >2.0 g/kg was reported[59] (Table 7).

Subchronic Dermal Toxicity

Cetyl Alcohol

Five-tenths milliliter of a heated Cetyl Alcohol mixture (30% Cetyl Alcohol in methyl alcohol and propylene glycol) was massaged into a 10 × 10 cm depilated area on the right flanks of five 6-month-old female albino rabbits. The animals were treated daily for 30 days. Punch biopsies of the treated areas were taken, and tissues were examined histologically. Microscopic alterations (after 10 days) were infiltrates of lymphomononuclear cells and histiocytes in superficial portions of the dermis[60] (Table 8).

An oil-in-water cream base containing 11.5% Cetyl Alcohol was applied (concentration, 400 mg/kg) to a 5 cm diameter area of clipped skin in the lumbar region of the backs of 20 New Zealand white rabbits (2.5–3 kg). The animals were divided into groups of 4 and treated five times daily for 20 days. At necropsy, tissue specimens of skin were fixed in 10% neutral formalin and stained with hematoxylin and eosin. The following gross observations were made of the alterations in skin at treated sites:

1. By the second full day of treatment, erythema was seen in all treated groups.
2. On the third day, transverse wrinkling and an apparent thickening of the treated area were observed.
3. On the fourth day, cracking or fissuring along the wrinkle or fold lines was apparent.

The principal histological changes seen in the skin consisted of acanthosis, para-

TABLE 8. Subchronic Dermal Toxicity

Ingredient	*Alcohol concentration and vehicle*	*No. of rabbits*	*Procedure*	*Results*	*Reference*
Cetyl Alcohol	30.0% in methyl alcohol and propylene glycol	5	Applied to depilated skin during 30-day period	No substantial macroscopic changes, dermal infiltration with histiocytes	60
Cetyl Alcohol	11.5% in cream base	20	Applied to dorsal clipped skin during 20-day period	Erythema, parakeratosis, hyperkeratosis, papillary projections of epidermis	61
Cetyl Alcohol	11.5% in cream base	48	Applied to shaved and abraded dorsal skin	Exfoliative dermatitis	62
Cetyl Alcohol	2.0% in moisturizer	20	Applied to skin during 3-month period	Mild inflammation at application site	63

keratosis, hyperkeratosis, and papillary projections of the epidermis, all of which are features of exfoliative dermatitis. Intracellular and intercellular edema were prominent in the basal layer of the stratum germinativum of some of the papillary projections[61] (Table 8).

In another study, 400 mg/kg of a cream base containing 11.5% Cetyl Alcohol was applied to a 5 cm diameter area in the lumbar region of the backs of 48 New Zealand rabbits (average weight, 2.5 kg). The animals were divided into two groups of 24 each. In one group, the backs were shaved and abraded. In the other group, the backs were shaved only. Subgroups of 4 rabbits with abraded or intact skin were treated five times daily for 20 days. At the end of the study, the animals were necropsied, and tissues were examined histologically. Hemograms were also obtained. Terminal hemogram and necropsy findings were negative for systemic effects, but rabbits of both groups (abraded skin and intact skin) developed exfoliative dermatitis within 2 to 3 days of treatment[62] (Table 8).

A 3-month dermal toxicity study of a moisturizer containing 2.0% Cetyl Alcohol was conducted with two groups of New Zealand white rabbits (5 males, 5 females/group) ranging in age from 12 to 16 weeks. Doses of 5.5 and 8.8 mg/cm^2 were applied daily to the clipped dorsal skin of animals in groups 1 and 2, respectively. Applications were made to 8.4% of the body surface area. All animals survived the 3-month test period, except 1 that was killed because of a severe head tilt caused by otitis media. The treatment-related changes were mild inflammation at the application site. Hematological and clinical chemistry values were within the normal range. The authors concluded that there was no evidence of systemic toxicity that would contraindicate use of the moisturizer[63] (Table 8).

Skin Irritation

Cetearyl Alcohol

A skin irritation study of a cream containing 3.0% Cetearyl Alcohol was conducted with 6 New Zealand albino rabbits (3 males, 3 females) weighing from 3.5–4.2 kg. The product was applied to intact and abraded skin of each animal during 5 consecutive days. After each application, an occlusive dressing was placed over the test site and removed after an 8-h period. Sites were graded for signs of irritation at 8 and 24 h postapplication. Mean erythema scores for intact skin ranged from 1.0 to 3.0 at 8 h and from 1.17 to 2.67 at 24 h postapplication. For abraded skin, mean erythema scores ranged from 1.0 to 3.0 at 8 h and from 1.17 to 2.50 at 24 h. It was concluded that the cream was mildly irritating to the skin[64] (Table 9).

Cetyl Alcohol

The skin irritation potential of Cetyl Alcohol was evaluated in 9 female albino rabbits. One-tenth milliliter of the test substance was applied at a concentration of 50.0% in petrolatum to the dorsal shaved skin of each animal via an occlusive dressing. Patches remained for 24 h, and reactions were graded at 24 and 72 h postapplication. The test substance produced minimal to slight irritation[65] (Table 9). Identical results were reported in a similar study.[66]

The skin irritation potential of a cream containing 4.0% Cetyl Alcohol was evaluated in 6 New Zealand albino rabbits (male and female). The backs of 3 animals were shaved, and the backs of the remaining 3 were shaved and abraded. Five-tenths milliliter of the cream was then applied, and the sites were rinsed with water 1 h after treatment. Observations for signs of skin irritation and systemic toxicity were conducted during a 7-day period after application. Slight to well-defined erythema was observed in all animals 24–48 h after the first application, and slight edema was observed in 3 animals within 2–3 days. Irritation persisted in 5 animals for the remainder of the test period. Slight desquamation developed in all animals within 4–7 days. The irritation index was 1.4 out of a maximum possible score of 8[67] (Table 9).

In another study, the skin irritation potential of a lipstick product containing 4.0% Cetyl Alcohol was evaluated according to the methods stated in Title 16 parts 1500.3(c)(4) and 1500.41 of the Code of Federal Regulations. The product (0.5 g) was administered to both abraded and intact clipped skin of albino rabbits (a minimum of six) via a surgical gauze patch. Patches remained for 24 h, after which reactions were evaluated. Subsequent evaluations occurred 48 h later. The lipstick was nonirritating to abraded and intact skin[68] (Table 9).

Five-tenths milliliter of a conditioner containing 3.25% Cetyl Alcohol (pH 5.7) was applied to abraded and intact clipped skin (two test sites per animal) of each of 6 New Zealand white rabbits (weight, approximately 2 kg; age, 3 months). Each site was covered for 1 h with an occlusive dressing, and grading for signs of irritation occurred at 1, 24, and 72 h postapplication according to the Draize (1975) scale for skin irritation. Reactions of very slight erythema and edema (5 animals) predominated in abraded and intact skin during the observation period. The primary irritation index was 0.90. A primary irritation index of

TABLE 9. Skin Irritation

Ingredient	*Alcohol concentration and vehicle*	*No. of rabbits*	*Procedure*	*Results*	*Reference*
Cetearyl Alcohol	3.0% in cream	6	8-h occlusive dressings applied during 5-day period	Mild irritation	64
Cetyl Alcohol	100%	9	24-h occlusive dressing	Minimal to slight irritation	65
Cetyl Alcohol	4.0% in cream	6	Applied to shaved and abraded dorsal skin	Slight to well-defined erythema and slight desquamation	67
Cetyl Alcohol	4.0% in lipstick	6	24-h surgical gauze patch	No irritation	68
Cetyl Alcohol	3.25% in conditioner	6	1-h occlusive dressing	Very slight erythema and edema predominated (5 animals)	69
Cetyl Alcohol	2.0% in formulation	3	Applied to skin once daily for 4 days	Slight erythema (2 animals); well-defined erythema (1 animal)	70
Cetyl Alcohol	2.0% in cream	3	Applied to skin once daily for 4 days	Well-defined erthema and mild edema	71
Myristyl Alcohol	0.8% in moisturizing lotion	6	24-h surgical gauze patch	No irritation	72
Isostearyl Alcohol	27.0% in lipstick	9	24-h occlusive dressing	Barely perceptible erythema predominated	73
Isostearyl Alcohol	25.0% in lipstick	9	24-h occlusive dressing	Barely perceptible erythema predominated	74
Isostearyl Alcohol	5.0% in antiperspirant	6	24-h occlusive dressing	Mild irritation	75

5.0 or more would have identified the product as a primary dermal irritant[69] (Table 9). In three other studies (same protocol) of different skin conditioners containing 3.25% Cetyl Alcohol, primary irritation indexes of 0.15, 0.95, and 1.25 were reported, respectively.[76-78]

A skin irritation study of a formulation containing 2.0% Cetyl Alcohol was conducted with 3 albino rats. Five-tenths milliliter of the formulation was applied to the shaved back of each animal once daily for 4 days. Slight erythema developed within 24 h after the first application and persisted throughout the 7-day observation period. In 1 animal, erythema became well defined, and slight edema was observed. Mild desquamation was noted on day 7. The irritation index was 1.6[71] (Table 9).

In another study, the skin irritation potential of a cream containing 2.0% Cetyl Alcohol was evaluated in 3 albino rabbits during a 7-day study. The product (0.5 ml) was applied to the shaved dorsal skin of each animal for a total of four daily applications. Well-defined erythema and mild edema persisted throughout the study. The irritation index was 2.9[72] (Table 9).

Myristyl Alcohol

The protocol outlined in Title 16 Parts 1500.3(c)(4) and 1500.41 of the Code of Federal Regulations was used to assess the primary irritation potential of a moisturizing lotion containing 0.8% Myristyl Alcohol. The product (0.5 ml) was applied to abraded and intact clipped skin of albino rabbits (a minimum of 6) via a surgical gauze patch. Patches remained for 24 h, after which reactions were evaluated. Subsequent evaluations occurred 48 h later. The product did not induce irritation in either abraded or intact skin[72] (Table 9).

Isostearyl Alcohol

The skin irritation potential of a lipstick product containing 25.0% Isostearyl Alcohol was evaluated in 9 female albino rabbits. One-tenth milliliter of the product was applied to the dorsal shaved skin of each animal by means of an occlusive dressing that remained for 24 h. Reactions were evaluated 24 and 72 h after application. The following results were reported: barely perceptible erythema (7 animals), mild erythema (1 animal), and no erythema (1 animal). The primary irritation index was 0.50.[74] Results from another study (same protocol) of a lipstick product containing 25.0% Isostearyl Alcohol were as follows: barely perceptible erythema (6 animals) and mild erythema (3 animals)[79] (Table 9). In a similar study involving a lipstick product containing 27.0% Isostearyl Alcohol (same protocol), the following results were reported: barely perceptible erythema (7 animals), mild erythema (1 animal), and no erythema (1 animal)[73] (Table 9).

A skin irritation study of a pump spray antiperspirant containing 5.0% Isostearyl Alcohol was conducted with 6 New Zealand white rabbits (3 males, 3 females) according to the method of Draize.[80] Five-tenths milliliter of the product was applied to each animal by means of an occlusive dressing. Patches remained for 24 h, and reactions were scored 24 and 72 h after application. It was concluded that the product was mildly irritating to the skin[75] (Table 9).

Mucous Membrane Irritation

Cetyl Alcohol

One-tenth milliliter of a formulation containing 2.0% Cetyl Alcohol was applied topically to the genital mucosa of each of 6 albino rabbits. There were no signs of irritation during the 7-day study.[81]

Ocular Irritation

Cetearyl Alcohol

The ocular irritation potential of a cream containing 3.0% Cetearyl Alcohol was assessed in 9 albino rabbits. One-tenth milliliter of the product was instilled into one eye of each animal. The eyes of 3 animals were rinsed 30 sec after instillation. Ocular reactions were scored at 1, 2, 3, 4, and 7 days postinstillation. The product was classified as a nonirritant[82] (Table 10).

Cetyl Alcohol

The ocular irritation potential of Cetyl Alcohol (100.0%) was evaluated in 6 New Zealand albino rabbits (male and female) according to a modification of the procedure by Draize.[80] One-tenth milliliter of the test substance was instilled into one eye of each animal. Ocular irritation was scored according to the Draize scale (0–110) at 1, 2, 3, 4, and 7 days postinstillation. An average score of 1 was reported on day 1, and signs of irritation had cleared by day 2. The test material was practically nonirritating[83] (Table 10). In a similar study of Cetyl Alcohol, an average score of 1 was reported at day 1 postinstillation, and signs of ocular irritation had cleared by day 3. The test substance was either minimally irritating or nonirritating.[84] Similar results were reported in another study of 100.0% Cetyl Alcohol involving 6 rabbits.[41]

In another ocular irritation study, 0.1 ml of a moisturizing cream containing 6.36% Cetyl Alcohol was instilled into the eyes of 9 albino rabbits according to the procedure of Draize.[80] The 9 animals comprised three treatment groups: eyes rinsed 10 sec postinstillation (3 animals), eyes rinsed 20 sec postinstillation (3 animals), eyes not rinsed (3 animals). Ocular irritation was scored at 1, 2, 3, 4, and 7 days postinstillation according to the Draize[80] scale. There were no observations of ocular irritation[85] (Table 10).

The ocular irritation potential of a cream containing 5.0% Cetyl Alcohol was evaluated in 9 New Zealand white rabbits (male and female). One hundred milligrams of the product were instilled into one eye of each animal. The eyes of 3 animals were rinsed 30 sec after instillation. Ocular reactions were scored at 1, 2, 3, 4, and 7 days postinstillation on a scale of 0–110. Five of the six animals not subjected to ocular rinsing first had ocular irritation at day 1 postinstillation, and one animal had ocular irritation at day 2. Signs of irritation had cleared by day 3. The 3 animals subjected to ocular rinsing first had ocular irritation at day 1. Signs of irritation had cleared by day 2 in 2 animals and by day 4 in 1 animal. A score of 2 was the maximum reported for any animal during the study. The product was classified as a nonirritant[86] (Table 10).

TABLE 10. Ocular irritation

Ingredient	*Alcohol concentration and vehicle*	*No. of rabbits*	*Procedure*	*Results*	*Reference*
Cetearyl Alcohol	3.0% in cream	9	Instilled into one eye; eyes rinsed (3 animals)	No irritation	82
Cetyl Alcohol	100%	6	Instilled into one eye	Practically no irritation	83
Cetyl Alcohol	6.36% in moisturizing cream	9	Instilled into one eye; eyes rinsed (6 animals)	No irritation	85
Cetyl Alcohol	5.0% in cream	9	Instilled into one eye; eyes rinsed (3 animals)	No irritation	86
Cetyl Alcohol	5.0% in facial makeup product	6	Instilled into one eye; eyes rinsed (3 animals)	No irritation	87
Cetyl Alcohol	4.0% in cream	6	Instilled into one eye	Transient conjunctivitis	88
Cetyl Alcohol	4.0% in formulation	6	Instilled into one eye	No irritation	89
Cetyl Alcohol	3.25% in conditioner	9	Instilled into one eye; all eyes rinsed	No irritation	90
Cetyl Alcohol	3.25% in conditioner	9	Instilled into one eye; all eyes rinsed	No irritation	91
Cetyl Alcohol	2.85% in cleansing cream	9	Instilled into one eye; eyes rinsed (6 animals)	No irritation	92
Cetyl Alcohol	2.7% in night cream	9	Instilled into one eye; eyes rinsed (6 animals)	No irritation	93
Cetyl Alcohol	2.0% in formulation	6	Instilled into one eye	Transient conjunctival redness	94
Cetyl Alcohol	2.0% in moisturizer	6	Instilled into one eye	Transient conjunctival hyperemia	95
Cetyl Alcohol	2.0% in moisturizer	6	Instilled into one eye	Transient conjunctival hyperemia	95
Myristyl Alcohol	3.0% in antiperspirant	9	Instilled into one eye; eyes rinsed (6 animals)	Mild irritation (rinsed eyes); moderate irritation (unrinsed eyes)	96
Myristyl Alcohol	0.8% in moisturizing lotion	6	Instilled into one eye	No irritation	97
Isostearyl Alcohol	27.0% in lipstick	6	Instilled into one eye	Mild irritation	98
Isostearyl Alcohol	25.0% in lipstick	6	Instilled into one eye	Minimal irritation	99
Isostearyl Alcohol	25.0% in lipstick	6	Instilled into one eye	Minimal irritation	100
Isostearyl Alcohol	10.0% in antiperspirant	5	Sprayed into one eye	Transient corneal, conjunctival, and iridial irritation	101
Isostearyl Alcohol	5.0% in antiperspirant	6	Instilled into one eye	Transient iridial and conjunctival irritation, persistent corneal irritation	102
Behenyl Alcohol	1.0% in oil	5	Instilled into one eye	Transient conjunctival irritation	53

In another study, 0.1 g of a facial makeup product containing 5.0% Cetyl Alcohol was instilled into the eyes of 6 female rabbits of the New Zealand strain. Three animals were subjected to ocular rinsing 4 sec after instillation. Ocular reactions were scored according to the scale by Draize.[80] The product was classified as a nonirritant[87] (Table 10).

A cream containing 4.0% Cetyl Alcohol was evaluated for its ocular irritation potential in 6 New Zealand albino rabbits (3 males, 3 females). One-tenth milliliter of the product was instilled into one eye of each animal. Signs of ocular irritation were scored at 1 h and days 1, 2, 3, and 7 postinstillation. Slight conjunctivitis was observed in all animals at day 1 postinstillation and cleared within 1 to 3 days. There were no signs of corneal irritation or iritis[88] (Table 10). In another study, the ocular irritation potential of a lipstick product containing 4.0% Cetyl Alcohol was determined according to the procedures outlined in Title 16 Parts 1500.3(c)(4) and 1500.42 of the Code of Federal Regulations. One-tenth milliliter of the product was instilled into one eye of each of 6 albino rabbits. The grading of keratitis, iritis, and conjunctival redness occurred at 1, 2, and 3 days after instillation. Positive reactions were not noted, and it was concluded that the product was nonirritating under the conditions of testing[89] (Table 10).

One-tenth milliliter of a conditioner containing 3.25% Cetyl Alcohol was instilled into one eye of each of 9 New Zealand white rabbits. The eyes of 6 and 3 animals were rinsed 24 h and 15 sec after instillation, respectively. Signs of ocular irritation were scored at 1, 2, 3, 4, and 7 days postinstillation according to the scale by Draize[80] (0–110). For the 6 animals subjected to a 24-h rinsing, mean irritation scores of 5.7, 1.7, 1.7, and 0.7 were recorded on days 1, 2, 3, and 4, respectively. A mean score of 0.7 was reported on days 1, 2, and 3 postinstillation for the 3 animals subjected to a 15-sec rinsing[90](Table 10). Similar results were reported in an identical study involving another conditioner containing 3.25% Cetyl Alcohol.[103] The protocol previously mentioned was used in two other studies, each involving a different conditioner (pH 5.7) containing 3.25% Cetyl Alcohol. In one of the studies, mean irritation scores (6 animals) of 13.7, 3.7, 2.3, 2.0, and 0.7 were reported on days 1, 2, 3, 4, and 7, respectively (24-h rinse group). Mean irritation scores (3 animals) of 4.0, 1.3, 0.7, 0.7, and 0.7 were also reported on days 1, 2, 3, 4, and 7, respectively (15-sec rinse group)[91] (Table 10). Results from the second study were as follows: mean scores (6 animals) of 12.0, 4.7, 2.3, and 1.3 on days 1, 2, 3, and 4, respectively (24-h rinse group) and mean scores (3 animals) of 3.3 and 0.7 on days 1 and 2, respectively.[104]

One-tenth milliliter of a cleansing cream containing 2.85% Cetyl Alcohol was instilled into the eyes of 9 albino rabbits according to the procedure of Draize.[80] The 9 animals comprised three treatment groups: eyes rinsed 10 sec postinstillation (3 animals), eyes rinsed 20 sec postinstillation (3 animals), eyes not rinsed (3 animals). Ocular irritation was scored at 1, 2, 3, 4, and 7 days postinstillation according to the Draize[80] scale. There were no observations of ocular irritation[92] (Table 10). In another study, the ocular irritation potential of a night cream containing 2.7% Cetyl Alcohol was evaluated in 9 albino rabbits according to the protocol previously mentioned. There were no signs of ocular irritation[93] (Table 10).

The ocular irritation potential of a formulation containing 2.0% Cetyl Alco-

hol was evaluated in 6 albino rabbits. one-tenth milliliter of the product was instilled into one eye of each animal. Observations for signs of irritation occurred over a period of 7 days. Slight conjunctival redness was observed 1 h after treatment (number of animals not stated) and cleared after 24 h. Signs of irritation were not observed in the cornea and iris[94] (Table 10). Another product (cream) containing 2.0% Cetyl Alcohol was evaluated according to the protocol previously mentioned. Slight conjunctivitis was observed within 1 h postinstillation (number of animals not stated) and cleared by 24 h. Signs of irritation were not observed in the cornea and iris.[105] In two other studies, a moisturizer containing 2.0% Cetyl Alcohol was evaluated for its ocular irritation potential. One-tenth milliliter of the product was instilled into one eye of each of 6 New Zealand albino rabbits in the first study. Ocular reactions were scored at 1 h and days 1, 2, 3, and 7 postinstillation. Slight conjunctival hyperemia was observed within 1 h after instillation in 3 animals and had cleared by 3 days. In the second study, one-tenth milliliter of the product was instilled into the eyes of six New Zealand albino rabbits daily for a period of 14 days. Slight conjunctival hyperemia was observed intermittently during the first week of treatment. Signs of irritation were not observed in the cornea and iris[96] (Table 10).

Myristyl Alcohol

One-tenth milliliter of an aerosol antiperspirant containing 3.0% Myristyl Alcohol was instilled into one eye of each of 9 albino rabbits. The 9 animals comprised three treatment groups: eyes rinsed 2 sec postinstillation (3 animals), eyes rinsed 4 sec postinstillation (3 animals), eyes not rinsed (3 animals). Ocular irritation was scored according to the scale by Draize[80] (0–110) at 1 h and 1, 2, 3, 4, and 7 days after instillation. An average irritation score of 19.7 (2-sec rinse group) was reported at 1 h postinstillation, and signs of irritation had cleared by day 4. In the 4-sec rinse group, an average score of 21.3 was reported at 1 h postinstillation, and signs of irritation had also cleared by day 4. An average irritation score of 42.3 was reported at 1 h postinstillation for animals not subjected to ocular rinsing; signs of irritation had cleared by day 7. It was concluded that the product was mildly irritating to eyes that were rinsed and moderately irritating to eyes that were not rinsed[96] (Table 10).

The ocular irritation potential of a moisturizing lotion containing 0.8% Myristyl Alcohol was determined according to the procedures outlined in Title 16 Parts 1500.3(c)(4) and 1500.42 of the Code of Federal Regulations. One-tenth milliliter of the product was instilled into one eye of each of 6 albino rabbits. The scoring of ocular reactions occurred 1, 2, and 3 days after instillation. Positive reactions were not observed, and it was concluded that the product was nonirritating[97] (Table 10).

Isostearyl Alcohol

One-tenth milliliter of a lipstick product containing 27.0% Isostearyl Alcohol was instilled into the eyes of 6 New Zealand albino rabbits (male and female).

Signs of ocular irritation were scored at 1, 2, 3, 4, and 7 days postinstillation according to the scale by Draize[80] (0–110). An average irritation score of 5 was reported on day 1, and all signs of irritation had cleared by day 4. The product was considered to be a mild eye irritant[98] (Table 10). In two similar studies (same protocol), one-tenth milliliter of two different lipstick products containing 25.0% Isostearyl Alcohol was instilled into the eyes of 6 New Zealand albino rabbits. On day 1 postinstillation, average scores of 2 and 1 (Draize scale, 0–110) were reported in the two studies, respectively. Signs of irritation had cleared by day 3. The products were considered to be minimally irritating to the eye[99,100] (Table 10).

The ocular irritation potential of a pump spray antiperspirant containing 10.0% Isostearyl Alcohol was evaluated in 5 adult New Zealand albino rabbits (male and female). The aerosol was sprayed into one eye of each animal at a distance of 6 inches (1-sec exposure). Gross signs of ocular irritation were scored at 1 h and 1, 2, 3, 4, and 7 days postinstillation according to the scale by Draize[80] (0–110). The following reactions were observed at 1 h postinstillation: corneal irritation (1 animal; score, 5), conjunctival irritation (5 animals; score range 10–12), iridial irritation (4 animals; scores, 5). All reactions had cleared by day 4 postinstillation[101] (Table 10). In a similar study, 0.1 ml of a pump spray antiperspirant containing 5.0% Isostearyl Alcohol was instilled into the eyes of 6 albino rabbits (male and female). Reactions were scored at 1 h and 1, 2, 3, 7, and 14 days postinstillation according to the scale by Draize.[80] Corneal irritation was first observed at day 1 postinstillation (average score, 6.7) and persisted to day 14 (average score, 2.5). Iridial irritation was observed at 1 h postinstillation (average score, 0.8) and cleared 23 h later. Conjunctival irritation was also observed at 1 h postinstillation and cleared by day 14. It was concluded that the product induced moderate ocular irritation[102] (Table 10).

Behenyl Alcohol

The ocular irritation potential of Behenyl Alcohol was evaluated using 5 adult New Zealand rabbits. A 1% dilution of the test substance in oil was heated and instilled (50 μl) into the right eye of each animal. The left eye served as the control. Conjunctival irritation was scored at 2, 6, 24, and 48 h postinstillation according to the scale by Draize[80] (0–20). Mean conjunctival irritation scores (5 animals) at 2 and 6 h postinstillation were 18 and 10, respectively. There were no signs of conjunctival irritation at 24 and 48 h. Irritation was not observed in the cornea or iris[53] (Table 10).

Skin Sensitization

Isostearyl Alcohol

The sensitization potential of Isostearyl Alcohol was evaluated according to the Magnusson-Kligman maximization procedure[106] using albino guinea pigs

of the Hartley strain (300–350 g). The procedure was divided into four phases: (1) induction phase, (2) dose range phase, (3) booster phase, and (4) challenge phase. During induction, 0.05 ml of 5.0% Isostearyl Alcohol in propylene glycol (site 1) and 5.0% Isostearyl Alcohol in 50.0% aqueous Freund's complete adjuvant (site 2) were applied intradermally to the upper back of each of 20 animals. Occlusive patches were then placed over the shaved sites 1 week later and removed after 48 h. In the dose range phase, 5, 10, 25, and 100% concentrations of the test substances were applied to the shaved flanks of 50 extra guinea pigs to determine the subirritating concentration to be used during the challenge phase and a slightly irritating concentration for use in one booster phase. Ten percent aqueous sodium lauryl sulfate was applied to induction sites of the 20 animals (initial study group) before application of test substance boosters because significant irritation was not observed during the dose range phase. The booster phase was initiated 1 week after induction. Occlusive pads containing 100.0% Isostearyl Alcohol were placed over the induction site and removed after 48 h. The challenge phase began 2 weeks after the end of the booster phase. Five percent Isostearyl Alcohol in petrolatum (0.5 ml) was applied via an occlusive patch to a new site on the flank of each animal. Patches remained for 24 h, and sites were scored for erythema at 24 and 48 h after removal according to the scale: 1 (weak) to 5 (extreme). Isostearyl Alcohol did not have any discernible potential for allergic skin sensitization[107] (Table 11). The same conclusion was stated in a similar study (same protocol).[108]

A pump spray antiperspirant containing 5.0% Isostearyl Alcohol was tested at a concentration of 4.0% in ethanol (effective Isostearyl Alcohol concentration, 0.2%) in a sensitization study involving 10 adult albino guinea pigs (weight, approximately 300 g). A semiocclusive coverlet containing 0.1 ml of the test substance was applied to two sites, one shaved and the other shaved and abraded, on the back of each animal. Patches were removed after 5 h. Each animal was given a total of nine doses (one dose/day). The challenge phase was initiated 2 weeks after the last induction exposure. Abraded and intact sites were scored for signs of irritation at 24 and 48 h postapplication. The product did not induce sensitization in any of the animals[109] (Table 11).

TABLE 11. Skin Sensitization

Ingredient	*Alcohol concentration and vehicle*	*No. of animals*	*Procedure*	*Results*	*Reference*
Isostearyl Alcohol	5.0% in propylene glycol	20 guinea pigs	48-h induction patches; 24-h challenge	No sensitization	107
Isostearyl Alcohol	5.0% in Freund's complete adjuvant	20 guinea pigs	48-h induction patches; 24-h challenge	No sensitization	107
Isostearyl Alcohol	0.2% in ethanol	10 guinea pigs	5-h induction patches; 24-h challenge	No sensitization	109

Mutagenicity

Mutagenicity tests for Cetyl Alcohol were conducted with five mutant strains of *Salmonella typhimurium* LT2. These mutant strains were selected because of their ability to revert to prototrophy in the presence of a broad spectrum of mutagens and their sensitivity to mutagens. Spot tests were performed according to the methods described by Ames et al.[110] Results indicate that Cetyl Alcohol was not mutagenic to any of the strains in the presence or absence of metabolic activation.[111]

CLINICAL ASSESSMENT OF SAFETY

Skin Irritation

Cetyl Alcohol

The skin irritation potential of Cetyl Alcohol (100.0%) was evaluated in 20 subjects (18–65 years old). One-tenth milliliter of the test substance was applied via an occlusive patch to the volar surface of the forearm of each subject; each patch remained for 24 or 48 h. Skin reactions were scored 2 and 24 h after patch removal according to the scale 0.5 (barely perceptible irritation) to 4.0 (severe irritation). No erythematous reactions were elicited by the test substance[112] (Table 12). The same finding was reported in a similar study of Cetyl Alcohol[113] (Table 12).

A topical tolerance study involving an 11.5% Cetyl Alcohol cream base was conducted with 80 male subjects, ranging in age from 21 to 52 years and in weight from 120 to 220 pounds[62] (Table 12). The 80 subjects were assigned at random to eight treatment groups of 10 each. The cream base was applied (gentle rubbing) to the left forearm (700 mg/202 cm^2 area) in four groups and to the left lower facial region (250 mg/70 cm^2 area), including the left side of the lips, in the other four groups. The preparations were applied five times daily (every 3 hours) for 10 days. One subject had erythema, folliculitis, and pustule formation (forearm site).

A formulation containing 6.0% Cetyl Alcohol was tested for its skin irritation potential in 20 subjects according to the protocol stated above. The product did not induce skin irritation[114] (Table 12). In another study, the skin irritation potential of a cream containing 6.0% Cetyl Alcohol was evaluated in 12 female subjects ($\leq 18 - \geq 60$ years old). An occlusive patch containing 0.3 ml of the product was applied to the back of each subject. Patches were removed 23 h after application, and sites were bathed immediately. Reactions were scored 1 h after patch removal. The product was applied to the same test site for 21 consecutive days. The grading scale for cumulative irritation ranged from 0 to 630 (primary irritation). The total irritation score (all panelists) for the 21 applications was 418, indicating mild cumulative irritation[115] (Table 12).

The skin irritation potential of a cream containing 5.0% Cetyl Alcohol was evaluated in 9 female subjects (30–65 years old). A closed patch containing the

product (amount sufficient to cover patch) was applied to the back of each subject. Patches were removed 23 h after application, and sites were bathed immediately. Reactions were scored 1 h after patch removal. The product was applied to the same site for 21 consecutive days. The grading scale for cumulative irritation ranged from 0 to 630 (primary irritation). The total irritation score (9 subjects) was 1, interpreted as no evidence of cumulative irritation. The product was classified as a mild material[116] (Table 12). In another study (same protocol), 0.2–0.3 ml of a cream containing 4.0% Cetyl Alcohol was applied to 12 male and female subjects (10–>60 years old) via semiocclusive patches. The total irritation score (12 subjects) was 211, and the product was classified as a slight irritant[117] (Table 12).

A lipstick product containing 4.0% Cetyl Alcohol was applied to the face and lips of 52 subjects over a period of 4 weeks. The detailed experimental procedure was not stated. Reactions were graded according to the scale by Wilkinson et al.[161]: 1 (weak nonvesicular reaction) to 3 (bullous or ulcerative reaction). None of the subjects had signs of skin irritation[118] (Table 12).

The irritation potential of a hair conditioner containing 3.25% Cetyl Alcohol was evaluated in 75 female subjects (15–30 years old) during a 30-day home use study. Subjects were instructed to shampoo and condition their hair daily. Scalp irritation was evaluated by a dermatologist before the beginning of the study and after 2 and 4 weeks of product use according to the scale 0 to 4 (erythema and excoriations). There were no significant irritation reactions that were attributed to 4 weeks of use of the conditioner[119] (Table 12). In another study, two conditioners containing 3.25% Cetyl Alcohol were applied to the back of each of 15 adult subjects (21–65 years old). Each patch (0.2 ml of product) was removed after 24 h, and sites were then scored according to the scale 0 to 4 (intense erythema, edema, and vesicles). Fresh applications were then made to the same sites, and scoring occurred 24 h after patch removal. Patches applied on Friday were removed on the following Monday. This procedure was repeated for a total of 21 days. A cumulative score of less than 90 was interpreted as an insignificant level of irritation. Cumulative scores ranging from 91 to 180 were interpreted as very mild irritation. A cumulative (21 days) irritation score of 95 was reported for one of the products and 80 for the other[120] (Table 12).

In three separate studies, three different products containing 2.0% Cetyl Alcohol were tested according to the protocol stated immediately above. In one of the studies, 0.3 ml of a lotion was applied to 9 subjects (18–>60 years old) via closed patches. The total irritation score (9 subjects) was 9, interpreted as essentially no evidence of cumulative irritation. The product was classified as a mild material[121] (Table 12). In the second study, approximately 0.2 ml of a cream was applied to 11 female subjects (18–59 years old) via closed patches. The total irritation score was 105, indicating that the product was slightly irritating[122] (Table 12). In the third study, 0.2 ml of a cream was applied to 11 male and female subjects (18–>60 years old) via closed patches. A total irritation score of 55 was reported, indicating evidence of a slight potential for very mild cumulative irritation[123] (Table 12).

TABLE 12. Clinical Assessment of Safety

Type of study	*Ingredient*	*Alcohol concentration and vehicle*	*No. of subjects*	*Procedure*	*Results*	*Reference*
Skin irritation	Cetyl Alcohol	100%	20	24–48 h occlusive patch test	No irritation	112
Skin irritation	Cetyl Alcohol	100%	20	24–48 h occlusive patch test	No irritation	113
Skin irritation	Cetyl Alcohol	11.5% in cream base	80	10-day cumulative irritation test	Erythema, folliculitis, pustules (1 subject)	62
Skin irritation	Cetyl Alcohol	6.0% in formulation	20	24–48 h occlusive patch test	No irritation	114
Skin irritation	Cetyl Alcohol	6.0% in cream	12	21-day cumulative irritation test	Potential for mild cumulative irritation	115
Skin irritation	Cetyl Alcohol	5.0% in cream	9	21-day cumulative irritation test	No cumulative irritation	116
Skin irritation	Cetyl Alcohol	4.0% in cream	12	21-day cumulative irritation test	Slight irritation	117
Skin irritation	Cetyl Alcohol	4.0% in lipstick	52	4-week application period	No irritation	118
Skin irritation	Cetyl Alcohol	3.25% in hair conditioner	75	30-day home use test	No significant irritation	119
Skin irritation	Cetyl Alcohol	3.25% in conditioner	15	24-h patch test	Mild irritation	120
Skin irritation	Cetyl Alcohol	3.25% in conditioner	15	21-day cumulative irritation test	No significant irritation	120
Skin irritation	Cetyl Alcohol	2.0% in lotion	9	21-day cumulative irritation test	No cumulative irritation	121
Skin irritation	Cetyl Alcohol	2.0% in cream	11	21-day cumulative irritation test	Slight irritation	122
Skin irritation	Cetyl Alcohol	2.0% in cream	11	21-day cumulative irritation test	Potential for mild cumulative irritation	123
Skin irritation	Myristyl Alcohol	0.8% in moisturizing lotion	53	4-week application period	No irritation	124
Skin irritation	Myristyl Alcohol	0.25% in moisturizing lotion	51	1-month home use test	No irritation	125
Skin irritation	Isostearyl Alcohol	100%	20	24–48 h application	No irritation	126
Skin irritation	Isostearyl Alcohol	28.0% in lipstick	20	24–48 h application	No irritation	127

Skin irritation	Isostearyl Alcohol	27.0% in lipstick	19	24–48 h application	No irritation	128
Skin irritation	Isostearyl Alcohol	25.0% in lipstick	19	24–48 h application	No irritation	129
Skin irritation	Isostearyl Alcohol	5.0% in antiperspirant	11	21-day cumulative irritation test	Severe irritation	130
Skin irritation and sensitization	Cetyl Alcohol	8.4% in formulation	110	10 48-h induction patches; 1 48-h challenge	No irritation or sensitization	131
Skin irritation and sensitization	Cetyl Alcohol	6.36% in moisturizing cream	229	10 24-h induction patches; 2 48-h challenges	No irritation or sensitization	132
Skin irritation and sensitization	Cetyl Alcohol	6.0% in cream	52	9 24-h induction patches; 1 48-h challenge	Barely perceptible to mild erythema during induction (33 subjects); no sensitization	133
Skin irritation and sensitization	Cetyl Alcohol	4.0% in lipstick	103	24-h induction patch; 24-h challenge	No irritation or sensitization	134
Skin irritation and sensitization	Cetyl Alcohol	4.0% in skin cleanser	200	10 24-h induction patches; 2 48-h challenges	No irritation or sensitization	135
Skin irritation and sensitization	Cetyl Alcohol	4.0% in skin cleanser	200	10 24-h induction patches; 2 48-h challenges	No irritation or sensitization	136
Skin irritation and sensitization	Cetyl Alcohol	3.3% in lipstick	78	9 24-h induction patches; 1 24-h challenge	Mild erythema during induction (2 subjects); no sensitization	137
Skin irritation and sensitization	Cetyl Alcohol	3.25% in conditioner	53	10 48- to 72-h induction patches; 1 48-h challenge	Erythema during induction (6 subjects); no sensitization	138
Skin irritation and sensitization	Cetyl Alcohol	3.0% in hand cream	116	9 24-h induction patches; 1 24-h challenge	Mild to moderate erythema during induction (1 subject); no sensitization	139
Skin irritation and sensitization	Cetyl Alcohol	2.85% in cleansing cream	204	10 24-h induction patches; 2 48-h challenges	No irritation or sensitization	165
Skin irritation and sensitization	Cetyl Alcohol	2.7% in night cream	208	10 24-h induction patches; 2 48-h challenges	Mild to intense erythema during induction (1 subject); no sensitization	140

TABLE 12. (Continued)

Type of study	*Ingredient*	*Alcohol concentration and vehicle*	*No. of subjects*	*Procedure*	*Results*	*Reference*
Skin irritation and sensitization	Cetyl Alcohol	2.0% in moisturizer	239	10 24-h induction patches; 1 48-h challenge	No irritation or sensitization	166
Skin irritation and sensitization	Cetyl Alcohol	2.0% in formulation	210	10 24-h induction patches; 1 48-h challenge	No strong irritation or sensitization	142
Skin irritation and sensitization	Cetyl Alcohol	2.0% in cream	205	10 24-h induction patches; 1 48-h challenge	No strong irritation or sensitization	143
Skin irritation and sensitization	Cetyl Alcohol	2.0% in skin cream	90	9 24-h induction patches; 1 24-h challenge	Barely perceptible to mild erythema during induction (68 subjects); no sensitization	144
Skin irritation and sensitization	Cetyl Alcohol	1.0% in skin care preparation	804	24-h induction patch; 24-h challenge	Strong edematous reaction during induction (1 subject); no sensitization	145
Skin irritation and sensitization	Cetyl Alcohol	1.0% in skin care preparation	407	10 24-h induction patches; 1 48-h challenge	No irritation or sensitization	145
Skin irritation and sensitization	Myristyl Alcohol	0.25% in moisturizing lotion	229	10 24-h induction patches; 2 48-h challenges	No irritation or sensitization	146
Skin irritation and sensitization	Myristyl Alcohol	0.10% in moisturizing lotion	106	24-h induction patch; 24-h challenge	No irritation or sensitization	147
Skin irritation and sensitization	Myristyl Alcohol	0.10% in moisturizing lotion	52	10 24-h induction patches; 1 48-h challenge	No irritation or sensitization	147
Skin irritation and sensitization	Isostearyl Alcohol	25.0% in 95.0% isopropyl alcohol	12	9 24-h induction patches; 1 24-h challenge	Slight erythema during induction (3 subjects); no sensitization	148
Skin sensitization	Cetearyl Alcohol	3.0% in cream	25	5 48-h induction patches; 1 48-h challenge	No sensitization	149

Skin sensitization	Cetyl Alcohol	30.0% in white petrolatum	330	Method of Fregert et al., 1969	No sensitization	150
Skin sensitization	Cetyl Alcohol	5.0% in cream	25	5 48-h induction patches; 1 48-h challenge	No sensitization	151
Skin sensitization	Cetyl Alcohol	5.0% in facial makeup product	150	9 24-h induction patches; 2 48-h challenges	No sensitization	152
Skin sensitization	Cetyl Alcohol	4.78% in facial makeup product	150	9 24-h induction patches; 2 48-h challenges	No sensitization	141
Skin sensitization	Cetyl Alcohol	4.5% in facial makeup product	206	9 24-h induction patches; 2 48-h challenges	No sensitization	153
Skin sensitization	Cetyl Alcohol	2.59% in hand lotion	650	9 24-h induction patches; 4 24-h challenges	No sensitization	154
Skin sensitization	Cetyl Alcohol	2.0% in hand lotion	650	9 24-h induction patches; 4 24-h challenges	No sensitization	154
Skin sensitization	Isostearyl Alcohol	5.0% in antiperspirant	148	9 24-h induction patches; 1 24-h challenge	Sensitization in 6 subjects	155
Skin sensitization	Isostearyl Alcohol	5.0% in antiperspirant	60	9 24-h induction patches; 1 24-h challenge	Sensitization in 5 subjects	155
Skin sensitization	Isostearyl Alcohol	5.0% in antiperspirant	148	9 24-h induction patches; 4 24-h challenges	Reactions in 75, 65, 83, and 69 subjects after 1st, 2nd, 3rd, and 4th challenges, respectively	156
Skin sensitization	Isostearyl Alcohol	5.0% in antiperspirant	148	9 24-h induction patches; 1 24-h challenge	Sensitization in 4 subjects	157
Photosensitization	Cetyl Alcohol	4.0% in lipstick	52	–	No photosensitization	158
Photosensitization	Cetyl Alcohol	1.0% in skin care preparation	407	–	No photosensitization	159
Photosensitization	Myristyl Alcohol	0.10% in moisturizing lotion	52	–	No photosensitization	160

Myristyl Alcohol

A moisturizing lotion containing 0.80% Myristyl Alcohol was applied to the face of each of 53 subjects over a period of 4 weeks. The detailed experimental procedure was not stated. Reactions were graded according to the scale by Wilkinson et al.[16]: 1 (weak nonvesicular reaction) to 3 (bullous or ulcerative reaction). None of the subjects had signs of skin irritation[124] (Table 12).

In another study, the irritation potential of a moisturizing lotion containing 0.25% Myristyl Alcohol was evaluated in 51 subjects. The subjects used the product daily during a 1-month period. A burning sensation was experienced by 1 of the subjects 1 day after initial use of the product. None of the subjects had signs of skin irritation[125] (Table 12).

Isostearyl Alcohol

The skin irritation potential of Isostearyl Alcohol was evaluated in 19 male and female subjects (18–65 years old) at a concentration of 25.0% in petrolatum. One-tenth milliliter of the test substance was applied to the volar surface of the forearm of each subject and removed after 24 or 48 h. It was not stated whether or not patches were placed over the test sites. Skin reaction were scored 2 and 24 h after removal according to the scale: 0.5 (barely perceptible erythema) to 4.0 (severe erythema). The test substance did not induce skin irritation in any of the subjects (Primary Irritation Index = 0.05)[126] (Table 12). In three similar studies, three different lipstick products containing 25.0, 27.0, and 28.0% Isotearyl Alcohol, respectively, were tested according to the same protocol. The three products did not induce skin irritation[127–129] (Table 12).

An antiperspirant containing 5.0% Isostearyl Alcohol was applied to 11 subjects (21–60 years old) according to the procedure by Philips et al.[162] An occlusive patch containing 0.4 ml of the product was applied to the back of each subject and removed after 24 h. Sites were scored 30 min after removal, and fresh patches were then applied to the same sites. This procedure was repeated daily for 21 days. The product was classified as a severe irritant, based on a 21-day cumulative irritation score of 49.60 (scale: 0–60)[130] (Table 12).

Skin Irritation and Sensitization

Cetyl Alcohol

The skin irritation and sensitization potential of a product containing 8.4% Cetyl Alcohol was evaluated in 110 female subjects. The product was applied to the upper back of each subject, and sites were covered with a patch plaster. Patches remained in place for 48 h, after which sites were scored according to the scale 0 to 3 (vesiculation with edema). This procedure was repeated 10 times. Fourteen days after scoring of the tenth application site, a challenge patch was applied to each subject and removed after 48 h; sites were scored after patch removal. The product did not induce primary irritation or sensitization[131] (Table 12).

A moisturizing cream containing 6.36% Cetyl Alcohol was applied to the backs of 229 male and female subjects via occlusive patches. Patches remained for 24 h, after which reactions were scored according to the scale: 0 to 4 (in-

tense erythema with edema and vesicles). The product was applied to the same site for a total of 10 induction applications. After a 2-week nontreatment period, the product was again applied to each subject (first challenge). Challenge patches remained for 48 h, after which sites were scored. One week later, challenge patches were reapplied; sites were scored 48 and 72 h postapplication. The product did not induce irritation or sensitization in any of the subjects[132] (Table 12).

The skin irritation and sensitization potential of a cream containing 6.0% Cetyl Alcohol was evaluated in 52 male and female subjects. One-tenth milliliter of the product was applied to the upper back of each subject via a patch made of nonwoven cotton fabric. Patches were removed after 24 h, and sites were scored according to the scale 0 to 4 (deep red erythema with vesiculation). This procedure was repeated (same test sites) every Monday, Wednesday, and Friday for 3 consecutive weeks. The challenge phase was begun 2 weeks after scoring of the last induction site. Challenge patches were applied to new sites and removed after 24 h. Sites were scored 24 and 48 h after patch removal. Subjects having reactions that were indicative of possible sensitization underwent follow-up testing after a 1-week nontreatment period. During this procedure, the product was applied via an occlusive patch and removed after 24 h. Skin reactions were noted in 33 subjects during the induction phase and were limited to barely perceptible and mild erythema. Five subjects had barely perceptible to mild erythema during the challenge phase. Reactions were not observed in the 5 subjects during follow-up testing. The authors stated that the original challenge reactions were of a nonspecific (irritant) nature. It was concluded that the product did not have any potential for inducing allergic sensitization[133] (Table 12).

A lipstick product containing 4.0% Cetyl Alcohol was applied to 103 subjects according to the procedure of Schwartz and Peck.[163] During the first phase of testing, patches (one open, one closed) were applied to each subject and removed after 24 h. Sites were then scored according to the scale by Wilkinson et al.[161]: 1 (weak nonvesicular reaction) to 3 (bullous ulcerative reaction). After a 10- to 14-day nontreatment period, the procedure was repeated (2nd phase). Two subjects had a weak vesicular reaction at the closed patch site during the first phase of testing. No reactions to the product were noted during the second phase[134] (Table 12). The same product was tested for its irritation and sensitization potential in another study, according to a modification of the procedure by Shelanski and Shelanski.[164] During the induction phase, the product was applied (one open and one closed patch) to the skin of each of 52 subjects; patches were removed after 24 h. Reactions were then scored according to the scale by Wilkinson et al.,[161] after which a 24-h nontreatment period was observed. This procedure was repeated for a total of 10 exposures. After a 2- to 3-week nontreatment period, the product was reapplied (open and closed patches) and removed after 48 h. Reactions were scored immediately after patch removal. A weak (nonvesicular) reaction was observed in 8 subjects after the first induction and in 1 subject after the tenth induction. One subject had a strong vesicular reaction after the ninth induction. After the 48-h challenge, a weak (nonvesicular) reaction (1 subject) and a strong vesicular reaction (1 subject) were observed. It was concluded that the product was neither an irritant nor a sensitizer[134] (Table 12).

A skin cleanser containing 4.0% Cetyl Alcohol was applied to the back of each of 200 male and female subjects (18–65 years old) via open patches. During induction, applications were made every Monday, Wednesday, and Friday for 3½ weeks (total of 10 applications); patches were removed after 24 h. Sites were graded immediately after patch removal according to the scale: 0 to 4 (marked edema and vesicles). The challenge phase was begun 10 to 14 days after scoring of the tenth induction site. An open challenge patch was applied to each subject and removed after 48 h. Sites were then scored according to the same grading scale. Patches were reapplied 7–10 days later, and sites were scored 48 and 72 h after patch removal. None of the subjects had reactions to the product during the study. Within the limits imposed by the sample size and test procedure, it was concluded that the product was neither a strong irritant nor an allergic sensitizer[135] (Table 12). Identical results were reported in another study in which a different skin cleanser containing 4.0% Cetyl Alcohol was applied to 200 subjects according to the same protocol[136] (Table 12).

The irritation and sensitization potential of a lipstick product containing 3.3% Cetyl Alcohol was evaluated in 78 subjects (21–70 years old). During induction, 0.1 ml of the product was applied to the back of each subject via an occlusive patch every Monday, Wednesday, and Friday for 3 consecutive weeks; patches were removed after 24 h. Reactions were scored 24 h after patch removal according to the scale 0 to 4 (severe erythema with vesiculation). The challenge phase was initiated 2 weeks after scoring of the last induction sites. Challenge patches were applied to new test sites and removed after 24 h. Reactions were scored immediately after patch removal and 48 h later. Mild erythema was noted in 1 subject after the second induction, and in another subject, after the sixth, seventh, and ninth inductions. None of the subjects had reactions to the product during the challenge phase[137] (Table 12).

Five-hundredths milliliter of a conditioner containing 3.25% Cetyl Alcohol was applied to the back of each of 53 male and female subjects (12 years old and older) via occlusive patches. During the induction phase, patches applied on Mondays and Wednesdays remained for 48 h. Patches applied on Fridays remained for 72 h. Sites were graded within 15 min after patch removal according to the scale: 0 to 3 (erythema, edema, and vesiculation). This procedure was repeated for a total of 10 applications. Challenge applications of the product were made after a 2-week nontreatment period. Occlusive patches were applied to new test sites and removed after 48 h. Sites were scored at 48 and 72 h postapplication. Six subjects had erythema during the induction phase. Three subjects had erythema 72 h after challenge patch application, two of whom did not have reactions during induction. One of these two subjects was rechallenged with the product and had no evidence of sensitization. The authors concluded that there was definite evidence of the product causing skin irritation but no evidence of sensitization[138] (Table 12).

The skin irritation and sensitization potential of a hand cream containing 3.0% Cetyl Alcohol was evaluated in 116 subjects (18–70 years old). During induction, 0.1 ml of the product was applied to the back of each subject via an occlusive patch every Monday, Wednesday, and Friday for 3 consecutive weeks; patches remained for 24 h. Reactions to the product were scored 24 h after patch removal according to the scale 0 to 4 (severe erythema and vesicula-

tion). The challenge phase was initiated 3 weeks after grading of the last induction sites. Challenge patches were applied to new test sites and removed after 24 h. Reactions were scored immediately after patch removal and 48 h later. One subject had mild to moderate erythema during the induction phase. None of the subjects had reactions during the challenge phase[139] (Table 12).

An irritation and sensitization study of a cleansing cream containing 2.85% Cetyl Alcohol was conducted with 204 male and female subjects (18–65 years old). The product was applied to each subject via an occlusive patch every other day for 10 days. Patches remained for 24 h, after which sites were scored according to the scale 0 to 4 (intense erythema with edema and vesicles). After a 13-day nontreatment period, a challenge patch was applied to the back of each subject and removed after 48 h. A second challenge patch was applied 7 days after application of the first. Sites were graded immediately after patch removal and 1 h later. Mild erythema was noted in 16 subjects: 6 subjects (induction phase), 7 subjects (challenge phase), and 3 subjects (induction and challenge phase). One subject had mild to intense erythema during the induction phase. It was concluded that the product was neither an irritant nor an allergen.[165] The irritation and sensitization potential of a night cream containing 2.7% Cetyl Alcohol was evaluated in 208 subjects (18–64 years old) according to the same protocol. One subject had mild erythema and intense erythema with edema during induction. Mild erythema was also noted in this subject during the challenge phase. It was concluded that the product was neither an irritant nor an allergen[140] (Table 12).

A moisturizer containing 2.0% Cetyl Alcohol was tested for its irritation and sensitization potential in a study involving 239 male and female subjects (18–65 years old). One-tenth gram of the product was applied to the back of each subject via an occlusive patch on Mondays, Wednesdays, and Fridays during a 4-week induction period. Patches were removed after 24 h, after which sites were graded according to the scale 0 to 4 (erythema, edema/induration, blisters). The tenth (final) induction site was scored 24 and 48 h after patch application. The 48-h reading was followed by an 11-day nontreatment period. Challenge patches were then applied to new test sites and removed after 48 h. Sites were scored 48 and 72 h postapplication. One subject had erythema during induction. None of the subjects had reactions during the challenge phase. Within the limits imposed by the population size and test procedure, it was concluded that the product was neither a primary irritant nor an allergic sensitizer [166] (Table 12).

In another study, the irritation and sensitization potential of a product (type not stated) containing 2.0% Cetyl Alcohol was evaluated in 210 male and female subjects (18–65 years old). The product was applied via an occlusive patch every Monday, Wednesday, and Friday during a 3½ week induction period (total of 10 applications). Patches were removed after 24 h and sites were then scored according to the scale 0 to 4 (marked edema and vesicles). The challenge phase was begun 10–14 days after scoring of the tenth insult. Patches remained for 48 h, after which sites were immediately scored. Patches were again applied 7 to 10 days after scoring of the first challenge and removed after 48 h. Sites were scored immediately after patch removal and 24 h later. Two subjects had erythema and papules during induction. One of the two also had these reactions during the challenge phase. Within the limits imposed by the population

size and test procedure, the product was neither a strong irritant nor a strong contact sensitizer[142] (Table 12). In a similar study (same protocol), a cream containing 2.0% Cetyl Alcohol was applied to 205 male and female subjects (18–65 years old). The following observations were made during the induction phase: erythema (2 subjects), erythema and papules (1 subject), and erythema, papules, and vesicles (1 subject). Reactions were also noted during the challenge phase: erythema (4 subjects), erythema and papules (1 subject), erythema, papules, and vesicles (1 subject). None of the subjects with reactions during the challenge phase had them during induction. It was concluded that the product was neither a strong irritant nor a gross allergic sensitizer[143] (Table 12).

The skin irritation and sensitization potential of a skin cream containing 2.0% Cetyl Alcohol was evaluated in 90 male and female subjects (18–70 years old). One-tenth milliliter of the product was applied to the back of each subject via an occlusive patch. During induction, applications were made every Monday, Wednesday, and Friday for 3 consecutive weeks. Patch removals occurred 24 h postapplication, after which sites were scored according to the scale 0 to 4 (severe erythema with vesiculation). Reactions of barely perceptible and mild erythema were observed in 68 subjects during the induction phase. Because of the fairly large number of irritant responses observed during induction, a 50.0% aqueous solution of the product was applied during the challenge phase. A 2-week nontreatment period preceded the challenge phase. Challenge patches were applied to new sites and remained for 24 h. Reactions were scored 24 and 48 h after patch removal. Twenty-two of the subjects with reactions during induction also had these reactions during the challenge phase. Within the limits imposed by the sample size and test procedure, the product did not exhibit any potential for inducing allergic sensitization[144] (Table 12).

A skin care preparation containing 1.0% Cetyl Alcohol was applied to 804 subjects according to the procedure of Schwartz and Peck.[163] Patches (one open, one closed) were applied to each subject and removed after 24 h. Sites were then scored according to the scale of Wilkinson et al.[161]: 1 (weak nonvesicular reaction) to 3 (bullous or ulcerative reaction). Patches were reapplied after a 10–14 day nontreatment period and remained for 24 h; sites were then scored. One subject had a strong edematous reaction at the closed patch site during the first phase of testing. None of the subjects had reactions during the second phase. The product was neither an irritant nor a sensitizer[145] (Table 12). The same product was tested for its irritation and sensitization potential according to a modification of the procedure by Shelanski and Shelanski.[164] During the induction phase, patches (one open, one closed) were applied to 407 subjects. Patches remained for 24 h, after which sites were scored according to the scale by Wilkinson et al.[161] mentioned above. Scoring was followed by a 24-h nontreatment period. This procedure was repeated for a total of 10 applications. After a 2–3-week nontreatment period, the product was reapplied (open and closed patches) and remained for 48 h. Challenge sites were scored immediately after patch removal. One subject had a strong edematous reaction (closed patch site) during the induction phase. Reactions were not observed in subjects during the challenge phase. The product was neither an irritant nor a sensitizer[145] (Table 12).

Myristyl Alcohol

A moisturizing lotion containing 0.25% Myristyl Alcohol was applied to the backs of 229 male and female subjects via occlusive patches. Patches remained for 24 h, after which sites were scored according to the scale 0 to 4 (intense erythema with edema and vesicles). The product was reapplied to the same sites following a 24-h nontreatment period. This procedure was repeated Monday through Friday for a total of 10 induction applications. After a 2-week nontreatment period, two 48-h challenge patches were applied. The two applications were separated by a 1-week nontreatment period. Sites were scored 48 h after patch application (first challenge) and 48 and 72 h postapplication (second challenge). None of the subjects had reactions to the product. The product was considered neither an irritant nor an allergen[146] (Table 12).

A moisturizing lotion containing 0.10% Myristyl Alcohol was applied to 106 subjects according to the procedure of Schwartz and Peck.[163] During the first phase of testing, patches (one open, one closed) were applied to each subject and removed after 24 h. Sites were then scored according to the scale of Wilkinson et al.[161]: 1 (weak nonvesicular reaction) to 3 (bullous, ulcerative reaction). This procedure was repeated after a 10–14-day nontreatment period (second phase). Five subjects had a weak vesicular reaction at the closed patch site during the first phase of testing. Two subjects had this reaction during the second phase. The product was neither an irritant nor a sensitizer.[147] The same product was tested for its irritation and sensitization potential in another study according to a modification of the procedure by Shelanski and Shelanski.[164] During induction, the product was applied (one open and one closed patch) to the skin of each of 52 subjects; patches remained for 24 h. Reactions were then scored according to the scale by Wilkinson et al.,[161] after which a 24-h nontreatment period was observed. This procedure was repeated for a total of 10 exposures. After a 2–3-week nontreatment period, the product was reapplied (open and closed patches) and removed after 48 h. Reactions were scored immediately after patch removal. Weak nonvesicular reactions were observed at closed patch sites during the fifth (2 subjects) and sixth (2 subjects) inductions. A strong vesicular reaction at the closed patch site was noted in 1 subject during the seventh induction. None of the subjects had reactions to the product during the challenge phase. It was concluded that the product was neither an irritant nor a sensitizer[147] (Table 12).

Isostearyl Alcohol

The irritation and sensitization potential of Isostearyl Alcohol (25% V/V in 95.0% isopropyl alcohol) was evaluated in 12 male subjects (21–>60 years old). Each patch (type not stated, moistened with 0.5 ml of the solution, was applied to the upper arm of each subject and remained for 24 h. Applications were made to the same site for a total of 9 days. The third, sixth, and ninth induction sites were scored 48 h after patch removal, and the remaining sites were scored 24 h after removal. The grading scale ranged from 0 to 6 (strong reaction, spreading beyond test site). Challenge applications were made to original and adjacent sites 2 weeks after removal of the last induction patch. Patches re-

mained for 24 h, and sites were scored 24 and 48 h after removal. Three of the 12 subjects had slight erythema during induction, and there was no evidence of sensitization[148] (Table 12).

Skin Sensitization

Cetearyl Alcohol

The sensitization potential of a cream containing 3.0% Cetearyl Alcohol was evaluated in 25 subjects (18–25 years old). Three-tenths gram of the product was applied to the forearm (volar aspect) of each subject via an occlusive patch covered with a 15 mm aluminum chamber and removed after 48 h. Patches were reapplied after a 24-h nontreatment period. This procedure was repeated for a total of five applications. Since the product was nonirritating, 2.5% sodium lauryl sulfate was applied before each induction application. Following a 10-day nontreatment period, occlusive challenge patches were applied to new sites and removed after 48 h. A 5.0% aqueous solution of sodium lauryl sulfate was applied before application of the challenge patches. Sites were scored immediately after patch removal and 24 h later according to the scale 0 to 3 (strong sensitization). Sensitization reactions were not observed in any of the subjects[149] (Table 12).

Cetyl Alcohol

A total of 330 male and female patients (age range, 19–60 years) with eczematous lesions (88 suffered from leg ulcers and 242 had eczematous dermatitis) were tested with 30% Cetyl Alcohol in white petrolatum[150] (Table 12). This study contains the results of 3 years of patch tests in dermatological patients. More often, the tests were undertaken because of slow healing, aggravation, or recurrence of lesions. Patch tests were placed on the back and removed after 48 h. Results were read at 48 and 72 (or 96) h after application. All tests were in accordance with the technique described by Fregert et al.[167] Of the 330 patients, 11.2% had allergic reactions to Cetyl Alcohol (positive patch tests). The authors mentioned that the large number of allergic reactions reported in this study was not consistent with results from other studies in the literature. For example, Hjorth and Trolle-Lassen[168] identified only 2 positive reactions among 1664 consecutive patients. Fisher et al.[169] did not identify any positive reactions among 100 patients. The greater number of positive patch tests in the study by Blondeel et al.[150] may be attributed to the preferential choice of cream containing Cetyl Alcohol for the treatment of outpatients.

The sensitization potential of a cream containing 5.0% Cetyl Alcohol was evaluated in 25 male and female subjects (18–30 years old). Three-tenths gram of the product was applied to the forearm (volar aspect) of each subject via an occlusive dressing for a total of five 48-h exposures; the dressing remained for 48 h. The dressing was reapplied after a 24-h nontreatment period. This procedure was repeated for a total of five applications. Since the product was nonirritating, 1.5% sodium lauryl sulfate was applied before each induction application. After a 10-day nontreatment period, occlusive challenge patches were

applied to new sites and removed after 48 h. A 10.0% aqueous solution of sodium lauryl sulfate was applied before application of the challenge patches. Sites were scored immediately after patch removal and 24 h later according to the scale 0 to 3 (strong sensitization). None of the subjects had sensitization reactions[151] (Table 12).

The sensitization potential of a facial makeup product containing 5.0% Cetyl Alcohol was evaluated in 150 male and female subjects (18–65 years old). The product was applied to the back of each subject via an occlusive patch on Monday, Wednesday, and Friday for 3 consecutive weeks. Patches remained for 24 h, after which sites were scored according to the scale 0 to 4 (bullae or extensive erosions). The challenge phase was preceded by a 2-week nontreatment period. Two consecutive 48-h challenge patches were applied to the back of each subject. Sites were scored at 48 and 96 h postapplication. Faint erythema was noted in 2 subjects during the induction phase. None of the subjects had positive reactions during the challenge phase[152] (Table 12). A facial makeup product containing 4.78% Cetyl Alcohol was applied to 154 male and female subjects (18–65 years old) according to the same protocol. Faint erythema was observed in 1 subject during the induction phase. None of the subjects had positive responses during the challenge phase[141] (Table 12). In another study (same protocol), the sensitization potential of a facial makeup product containing 4.5% Cetyl Alcohol was evaluated in 206 male and female subjects (18–65 years old). Two subjects had equivocal reactions during the challenge phase. The product was not a sensitizer[153] (Table 12).

The sensitization potential of two hand lotions, one containing 25.9% Cetyl Alcohol and the other 2.0% Cetyl Alcohol, was evaluated in 650 male and female subjects (18–60 years old). Three-tenths milliliter of both products was applied to the arm of each subject via an occlusive patch for a total of nine induction applications (3 days/week for 3 weeks). Patches remained for 24 h, after which sites were scored according to the scale 0 to 7 (strong reaction spreading beyond test site). The challenge phase was preceded by a 10–14-day nontreatment period. A total of four applications were made to original and adjacent sites: first challenge (original), second challenge (adjacent), third challenge (original), and fourth challenge (adjacent). Patches remained for 24 h, after which sites were scored. After applications of both products, reactions of minimal erythema predominated throughout the induction phase. Reactions to the 2.59% product were noted in 3 subjects (minimal erythema) and in 1 subject (definite erythema) after the first challenge. None of the subjects had reactions to the 2.0% product during the challenge phase. The products were not sensitizers[154] (Table 12).

Isostearyl Alcohol

The sensitization potential of a pump spray antiperspirant containing 5.0% Isostearyl Alcohol was evaluated using 148 male and female subjects. The product was applied via an occlusive patch to the upper arm for a total of nine induction applications (3 times/week for 3 weeks). Each patch remained for 24 h, and sites were scored immediately before subsequent applications. During the

challenge phase, a patch was applied to the induction site and to a new site on the opposite arm of each subject. Reactions were scored 48 and 96 h after application. Ten of the twelve subjects with reactions suggestive of sensitization were rechallenged with the product 2 months later. Patches remained for 24 h, and sites were scored at 48 and 96 h postapplication. Six subjects had reactions during the rechallenge. Four of the six subjects were then tested with 5.0% Isostearyl Alcohol in solution with ethanol 6 weeks after scoring of the first rechallenge; all had positive responses. Negative responses were reported when the product (without Isostearyl Alcohol) and 100.0% ethanol each were tested[155] (Table 12). In a second study, the same product was applied to 60 male and female subjects (same protocol). Five of the subjects had positive responses after the first challenge. One of the five was rechallenged with 5.0% Isostearyl Alcohol in ethanol solution, and a positive reaction was observed[155] (Table 12).

The sensitization potential of another pump spray antiperspirant containing 5.0% Isostearyl Alcohol was evaluated in 148 male and female subjects (21–60 years old). The product contained 10 times the normal concentration of perfume. Four-tenths milliliter of the product was applied to the upper arm of each subject via a topical patch for a total of nine induction applications (3 days/week for 3 weeks). Patches remained for 24 h, after which sites were scored according to the scale 0 to 7 (strong reaction spreading beyond test site). The challenge phase was preceded by a 10–14-day nontreatment period. A total of four applications were made to original and adjacent sites: first challenge (original), second challenge (adjacent), third challenge (original), and fourth challenge (adjacent). Patches remained for 24 h, after which reactions were scored. Following the first and ninth inductions, 27 and 63 subjects, respectively, had reactions ranging from minimal erythema to erythema, edema, and papules. Reactions ranging from minimal erythema to a strong reaction spreading beyond the test site were observed after each of the four challenges: first challenge (75 subjects), second challenge (65 subjects), third challenge (83 subjects), and fourth challenge (69 subjects). The authors stated that the exaggerated amount of perfume in the product may have induced sensitization[156] (Table 12). The validity of this assumption was tested in a subsequent study involving 148 subjects (same protocol). Subjects were rechallenged with the following substances: pump spray antiperspirant containing 5.0% Isostearyl Alcohol (week of 1/10/77), pump spray without perfume (week of 2/21/77), pump spray without perfume or Isostearyl Alcohol (week of 5/9/77) and 5.0% Isostearyl Alcohol (week of 6/13/77). Sites were scored 48 and 96 h after patch application. The incidence of sensitization reactions was as follows: 4 subjects (pump spray antiperspirant), 2 subjects (pump spray without perfume), 1 subject (pump spray without perfume or Isostearyl Alcohol), and 4 subjects (5.0% Isostearyl Alcohol). The most severe reactions were observed when samples containing Isostearyl Alcohol were applied. The sensitization reactions resulting from application of the antiperspirant were suspected of being due to its Isostearyl Alcohol content[157] (Table 12).

Photosensitization

Cetyl Alcohol

The photosensitization potential of a lipstick product containing 4.0% Cetyl

Alcohol was evaluated in 52 subjects. The experimental procedure was not stated. Photosensitization reactions were not noted in any of the subjects[158] (Table 12). In another study, a skin care preparation containing 1.0% Cetyl Alcohol did not induce photosensitization in the 407 subjects tested. The experimental procedure was not stated[159] (Table 12).

Myristyl Alcohol

A moisturizing lotion containing 0.10% Myristyl Alcohol was evaluated for its photosensitization potential in a study involving 52 subjects. The experimental procedure was not stated. The product did not induce photosensitization in any of the subjects[160] (Table 12).

SUMMARY

The long-chain aliphatic alcohols are alcohols resulting from the reduction of corresponding fatty acids.

Noncosmetic uses of long-chain aliphatic alcohols include emulsifying agents in textile soaps, components of synthetic fibers and lubricants, and food additives. Data submitted to the FDA by cosmetic firms participating in the voluntary cosmetic registration program indicate that long-chain aliphatic alcohols were used in at least 63 cosmetic products during 1982, ranging in concentration from $\leq$0.1% to 50%. These cosmetic formulations are applied to the skin and may come in contact with the eyes.

The inhalation of Cetyl Alcohol vapor (26 ppm) by mice, rats, and guinea pigs caused slight irritation of the mucous membranes of the eyes, nose, throat, and respiratory passages. There were no signs of systemic toxicity, and no deaths were reported. Alternatively, exposure to a Cetyl Alcohol concentration of 2220 mg/m^3 resulted in death of all animals. Ataxia and moderate nasal irritation were observed in albino rats exposed to bursts of a 3.0% Myristyl Alcohol aerosol. No deaths were reported.

The oral LD_{50} of Cetyl Alcohol in fasted rats was >8.2 g/kg. The animals had signs of central nervous system depression and labored respiration. In acute oral toxicity studies (rats) of formulations containing 2.0, 3.25, and 4.0% Cetyl Alcohol, there were predominantly no toxic effects.

The oral administration of Myristyl Alcohol and a product containing 0.8% Myristyl Alcohol to albino rats resulted in LD_{50}s of >8.0 and >5.0 g/kg, respectively.

The oral administration of up to 20.0 g/kg of Isostearyl Alcohol to rats failed to cause a significant number of deaths that would have permitted calculation of an LD_{50}.

No mortalities were noted following the intragastric administration of a heated mixture of 1.0% Behenyl Alcohol in olive oil (dose, 10.0 g/kg).

In acute dermal toxicity studies (rabbits), doses of up to 2.6 g/kg of Cetyl Alcohol and 2.0 g/kg of a product containing 4.0% Cetyl Alcohol induced little toxicity, as did 2.0 g/kg of a product containing 0.8% Myristyl Alcohol.

Following the subchronic dermal administration of Cetyl Alcohol (30.0% in methyl alcohol and propylene glycol) to albino rabbits, dermal infiltrates of histiocytes were observed. Exfoliative dermatitis, parakeratosis, and hyperkeratosis were observed in New Zealand white rabbits after the subchronic dermal administration of 11.5% Cetyl Alcohol cream bases. In another subchronic dermal toxicity study, mild inflammation was observed at application sites after the administration of a 2.0% Cetyl Alcohol moisturizer.

Mild irritation was observed when a cream containing 3.0% Cetearyl Alcohol was applied to the skin of New Zealand albino rabbits. Following the administration of Cetyl Alcohol (50.0% in petrolatum) to abraded and intact skin of albino rabbits, minimal to slight skin irritation was observed. Slight to well-defined erythema and slight desquamation were observed in albino rabbits after application of a cream containing 4.0% Cetyl Alcohol. A lipstick product containing 4.,0% Cetyl Alcohol was nonirritating to abraded and intact skin of albino rabbits. Slight erythema and edema (abraded and intact skin) were observed in New Zealand white rabbits receiving cutaneous applications of a conditioner containing 3.25% Cetyl Alcohol. In a skin irritation study of a product containing 2.0% Cetyl Alcohol, observations of slight erythema predominated. Applications of a cream containing 2.0% Cetyl Alcohol resulted in well-defined erythema and mild edema.

A moisturizing lotion containing 0.8% Myristyl Alcohol was nonirritating to abraded and intact skin of albino rabbits.

Observations of barely perceptible erythema predominated in skin irritation studies of lipstick products containing 27.0 and 25.0% Isostearyl Alcohol. Following the cutaneous administration of a pump spray antiperspirant containing 5.0% Isostearyl Alcohol to New Zealand white rabbits, mild skin irritation was observed.

A product formulation containing 2.0% Cetyl Alcohol was nonirritating to the genital mucosa of albino rabbits.

A cream containing 3.0% Cetearyl Alcohol was considered to be a nonirritant when instilled into the eyes of albino rabbits.

Product formulations containing 6.36, 5.0, 4.0, 3.25, 2.85, 2.7, and 2.0% Cetyl Alcohol were instilled into the eyes of albino rabbits. The products were nonirritating in most of the studies.

The instillation of an aerosol antiperspirant containing 3.0% Myristyl Alcohol into the eyes of albino rabbits induced mild to moderate irritation. A moisturizing lotion containing 0.8% induced mild to moderate irritation. A moisturizing lotion containing 0.8% Myristyl Alcohol was nonirritating when instilled into the eyes of albino rabbits.

Reactions of minimal to mild irritation were observed after the ocular administration of lipstick products containing 27.0 and 25.0% Isostearyl Alcohol into the eyes of albino rabbits. Transient iridial and conjunctival irritation was observed in albino rabbits during ocular irritation studies of two pump spray antiperspirants (5.0 and 10.0% Isostearyl Alcohol). Corneal irritation was noted at the conclusion of the study involving the 5.0% Isostearyl Alcohol antiperspirant

Conjunctival irritation was observed 2 and 6 hours after instillation of a 1.0% Behenyl Alcohol in oil mixture into the eyes of New Zealand rabbits. Reactions had cleared by 24 h postinstillation. Irritation was not noted in the cornea or iris.

Applications of Isostearyl Alcohol (5.0% in propylene glycol) and an antiperspirant containing 5.0% Isostearyl Alcohol to albino guinea pigs resulted in no skin sensitization reactions.

Cetyl Alcohol was not mutagenic in *Salmonella typhimurium* LT2 mutant strains in the spot test. In human skin irritation studies, Cetyl Alcohol produced no erythematous reactions. Product formulations containing 11.5%, 6.0%, 5.0%, 4.0%, 3.25%, and 2.0% Cetyl Alcohol were, at most, mild irritants.

The results of human skin irritation studies of two moisturizing lotions (0.25% and 0.8% Myristyl Alcohol) indicated no signs of irritation.

No signs of skin irritation were observed in humans when Isostearyl Alcohol (25.0% in petrolatum) was applied. Results of clinical skin irritation studies of lipstick products containing 28.0%, 27.0%, and 25.0% Isostearyl Alcohol were negative, whereas an antiperspirant containing 5.0% Isostearyl Alcohol was classified as a severe irritant.

Clinical skin irritation and sensitization studies of product formulations containing 8.4%, 6.36%, 6.0%, 4.0%, 3.3%, 3.25%, 3.0%, 2.85%, 2.0%, and 1.0% Cetyl Alcohol produced no substantial evidence of irritation or sensitization.

Moisturizing lotions containing 0.10 and 0.25% Myristyl Alcohol were found to be neither irritants nor sensitizers in human skin irritation and sensitization studies.

The application of Isostearyl Alcohol (25.0% in Isopropyl Alcohol) to human subjects produced no substantial evidence of skin irritation or sensitization.

In a human skin sensitization study of a cream containing 3.0% Cetearyl Alcohol, none of the subjects had positive reactions. In a human skin sensitization study of Cetyl Alcohol (30.0% in petrolatum), sensitization reactions were observed in 11.0% of the subjects. Human sensitization studies of product formulations containing 5.0%, 4.78%, 4.5%, 2.59%, and 2.0% Cetyl Alcohol revealed no positive reactions in any of the subjects.

Positive reactions were observed in the four human sensitization studies of pump spray antiperspirants containing 5.0% Isostearyl Alcohol.

Clinical photosensitization studies of a lipstick product containing 4.0% Cetyl Alcohol and a skin care preparation containing 1.0% Cetyl Alcohol resulted in no positive reactions. Identical results were reported in a study of a moisturizing lotion containing 0.10% Myristyl Alcohol.

ANALYSIS

The toxicity of long-chain aliphatic alcohols, esters of fatty acids and alcohols, and a fatty acid (Isostearic Acid) has been reviewed. Long-chain aliphatic alcohols (C_{18} and C_{20}) induced minimal ocular and skin irritation but no sensitization or comedogenicity in rabbits; no mutagenic effects were noted in the Ames assay. In a subchronic percutaneous toxicity study, a product formulation (C_{18}-alcohol content) induced erythema and mild desquamation. Clinical studies of long-chain alcohols (C_{18} and C_{20}) indicated a low order of skin irritation and sensitization. Also, results were negative in clinical phototoxicity and photosensitization studies of products containing these alcohols.[4] Esters of stearic acid

(C_{21}–C_{34}) were essentially nonirritating to rabbit eyes when tested at and above concentrations used in cosmetic products. Cosmetic use concentrations were, at most, minimally irritating to rabbit skin. In clinical studies, the stearates and cosmetic products containing them were, at most, minimally to mildly irritating to the skin. Comedogenicity is a potential health effect that should be considered when stearates are used in cosmetic formulations.[4] Isopropyl palmitate (C_{19}), octyl palmitate (C_{24}), and cetyl palmitate (C_{32}), esters of palmitic acid, did not induce subchronic oral toxicity in rats (C_{32}) or subchronic dermal toxicity in rabbits (C_{19} and C_{24}). In rabbit skin irritation studies, the palmitates were neither sensitizing nor irritating but induced ocular irritation (none to slight) in Draize rabbit eye irritation tests. In clinical studies, formulations containing the palmitates induced minimal skin irritation but no sensitization, phototoxicity, or photocontact allergenicity.[1]

In most of the Draize tests, cetyl lactate (C_{19}) and myristyl lactate (C_{17}), esters of Cetyl Alcohol and Myristyl Alcohol, respectively, were minimally irritating to rabbit skin. Cetyl lactate was either nonirritating or slightly irritating and myristyl lactate was nonirritating in Draize ocular irritation tests. In clinical studies, minimal and no skin irritation were induced by cetyl lactate and myristyl lactate, respectively. Neither of the two were sensitizers.[1] Myristyl myristate (C_{28}), ester of myristic acid, induced minimal to mild skin irritation and minimal ocular irritation in rabbits; results were negative in a guinea pig sensitization study. A product formulation containing myristyl myristate did not induce sensitization in humans.[2] Cetearyl octanoate (C_{24}–C_{26}), ester of Cetearyl Alcohol, induced, at most, mild ocular irritation and no skin irritation in rabbits. Subchronic dermal toxic effects were not noted. Formulations containing cetearyl octanoate did not induce phototoxicity or sensitization in guinea pigs. A low incidence of moderate irritation was noted in a human skin irritation study of cetearyl octanoate. Also, product formulations containing this ingredient did not induce skin sensitization, photocontact allergenicity, or phototoxicity.[2]

Isostearyl neopentanoate (C_{23}), ester of Isostearyl Alcohol, was not toxic to rats in a subchronic oral toxicity study. It was a mild eye irritant but not a skin irritant in rabbits; sensitization was not induced in guinea pigs. Low level sensitization was induced by cosmetic formulations containing Isostearyl Alcohol. However, this was not considered to be due to the alcohol but to other ingredients in the formulation. Also, this ingredient was not considered to be a significant comedogenic agent in rabbits. In a clinical study, isostearyl neopentanoate induced a very low incidence of slight noninflammatory skin changes. At most, mild skin irritation was noted in subjects tested with formulations containing this ingredient.[5] Isostearic acid (C_{18}) induced no significant skin or ocular irritation in rabbits in Draize irritation tests. In a clinical study, isostearic acid was not irritating to the skin. Also, product formulations containing this ingredient did not cause skin irritation.[3]

Generically, much is known about the biological activities of fatty acids and long-chain aliphatic alcohols and esters. For the long-chain aliphatic alcohols, there is little information on their subchronic or chronic toxicities, genotoxicity, or photosensitization potential. However, based on their close structural similarities to fatty acids and long-chain aliphatic esters, the long-chain aliphatic alcohols are expected to have similar biological activities. Therefore, further tox-

icity testing of these long-chain aliphatic alcohols is not necessary for judging their safety as ingredients in cosmetics.

DISCUSSION

The toxicological data for the five long-chain aliphatic alcohols included in this report revealed no significant toxicity. Assuming that the five ingredients are of the same grade of purity, the similar chemical structure permits extrapolation of data for one of the alcohols to the remaining four alcohols. Based on these factors, the Expert Panel considered it reasonable to assume that the alcohols reviewed in this report have equivalent biological activity.

CONCLUSION

Based on the available data included in this report, the Expert Panel concludes that Cetearyl Alcohol, Cetyl Alcohol, Isostearyl Alcohol, Myristyl Alcohol, and Behenyl Alcohol are safe as cosmetic ingredients in the present practices of use.

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Final Report on the Safety Assessment of Stearyl Alcohol, Oleyl Alcohol, and Octyl Dodecanol

Stearyl Alcohol, Oleyl Alcohol, and Octyl Dodecanol are long-chain saturated or unsaturated (Oleyl) fatty alcohols. They are used in numerous cosmetic product categories at concentrations of less than 0.1 percent to greater than 50 percent.

The metabolism of Stearyl Alcohol and Oleyl Alcohol in rats is described. The results of acute oral toxicity studies indicate a very low order of toxicity. In rabbit irritation tests, these alcohols produced minimal ocular irritation and minimal to mild cutaneous irritation. Stearyl Alcohol produced no evidence of contact sensitization or comedogenicity.

Clinical patch testing indicates a very low order of skin irritation potential and sensitization. Photoreactivity studies on products containing these ingredients were negative for phototoxicity or photosensitization.

Based on the available data, it is concluded that Stearyl Alcohol, Oleyl Alcohol, and Octyl Dodecanol are safe as currently used in cosmetics.

INTRODUCTION

Stearyl Alcohol, Oleyl Alcohol, and Octyl Dodecanol are long-chain fatty alcohols used in a variety of cosmetic products. The materials of commerce are mixtures of fatty alcohols, and the terms Stearyl Alcohol, Oleyl Alcohol, and Octyl Dodecanol refer to these mixtures for the purposes of this report. If data pertain to the pure compound rather than the cosmetic ingredient, the distinction is noted.

CHEMICAL AND PHYSICAL PROPERTIES

Composition

Stearyl Alcohol

Stearyl Alcohol is a mixture of solid fatty alcohols that consists predominantly of n-octadecanol (90 percent minimum assay) with varying amounts of n-hexa-

decanol, n-tetradecanol, n-eriosanol, and n-dodecanol along with unspecified uneven and branched-chain alcohols. The predominant component conforms to the formula:[1-3]

$$CH_3(CH_2)_{16}CH_2OH$$

CAS Number: 112-92-5

Synonyms include Octadecanol, n-Octadecanol, Octa Decyl Alcohol, n-Octadecyl Alcohol, Stearol, USP XIII Stearyl Alcohol, and n-1-Octadecanol.

Oleyl Alcohol

Oleyl Alcohol is a mixture of fatty alcohols that consists predominantly of the straight-chain unsaturated 9-n-octadecenol (55 percent minimum assay) with varying amounts of 8-n-hexadecenol, 6-n-dodecenol, n-hexadecanol, n-octadecanol, n-tetradecanol, and 7-n-tetradecenol. The predominant component conforms to the formula:[2,4,5]

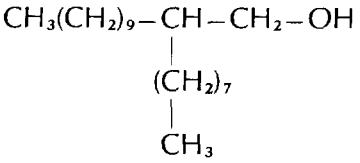
$$CH_3(CH_2)_7CH{=}CH(CH_2)_7CH_2OH$$

CAS Number: 143-28-2

Synonyms include cis-9-Octadecen-1-OL and Oleol.

Octyl Dodecanol

Octyl Dodecanol is an aliphatic alcohol with the structural formula:



Additional information concerning the composition of the material of commerce is unavailable.[2,6]

CAS Number: 5333-42-6

Synonyms include 2-Octyl Dodecanol.

Production and Occurrence

Stearyl Alcohol may be produced via Ziegler aluminum alkyl hydrolysis or the catalytic, high-pressure hydrogenation of stearic acid, followed by filtration and distillation. It may also be derived from natural fats and oils.[1,5,7-10]

Oleyl Alcohol is produced by catalytic, high-pressure hydrogenation of oleic acid followed by filtration and distillation.[4,5,7] It may also be prepared from butyl oleate by Bouveault-Blanc reduction with sodium and butyl alcohol or from triolein by hydrogenation in the presence of zinc chromite. Purification in these processes is obtained through fractional crystallization at $-40°C$ from acetone followed by distillation.[10]

Octyl Dodecanol is produced by the condensation of 2 molecules of decyl alcohol.[11] Further detail concerning the method of manufacture is unavailable.

Fatty alcohols occur in small quantities as components of wax esters in plants and animals. For example, Oleyl Alcohol has been found in the epidermis of many plants, and Stearyl Alcohol has been isolated from plants and insects. In both cases, the alcohols probably serve as components of the organisms' protective layers against water loss. Stearyl Alcohol has also been isolated from human sebaceous lipids and has been found in mammalian glands and organs. Oleyl Alcohol is found in fish oils.[10,12-23]

Properties

Stearyl Alcohol is a white, waxy, practically inert solid with a faint odor.[1,5,10,11,15] Oleyl Alcohol is a clear, odorless, viscous liquid.[4,5,11] Octyl Dodecanol is a clear, odorless, free-flowing liquid.[6,11] Other physical and chemical properties are listed in Table 1.

TABLE 1. Properties of Stearyl Alcohol, Oleyl Alcohol, and Octyl Dodecanol

Properties	*Stearyl Alcohol*[1,3,5,7,11]	*Oleyl Alcohol*[4,5,10,11,28]	*Octyl Dodecanol*[6-11]
Molecular weight (pure compound)	270.5	268.5	298.56
State	Flakes, granules	Viscous liquid	Liquid
Color	White	Clear colorless to light yellow	Colorless to pale yellow
Odor	Faint fatty	Faint	Odorless
Specific gravity	0.8124 (59°/4°C) 0.811 (35°/25°C)	0.850–0.966 (20°/20°C)	0.830–0.850 (20°/20°C)
Melting point	51–60°C 55–60°C	−7.5°C	–
Boiling point	210.5°C (15 mm)	333°C	–
Refractive index	1.4388 60°C	1.458–1.460	1.453–1.547 n_D^{20}
Acid value	1.0 max 2.0 max	1.0 max	1.0 max
Saponification value	2.0 max 3.0 max	2.0 max	10 max
Iodine value	2.0 max 5.0 max	45–98 85–95	10 max
Hydroxyl value	195–220 200–220	195–220 205–215	165–180 175–190
Soluble in	Alcohol Acetone Ether Benzene Chloroform	Alcohol Ether Acetone Light mineral oil	–
Insoluble in	Water	Water	–

Analytical Methods

Analytical methods used to detect and identify fatty alcohols include gas-liquid chromatography, thin-layer chromatography, differential scanning calorimetry, and gas chromatography.[24-27]

Impurities

Stearyl Alcohol consists of not less than 90 percent stearyl alcohol. The remainder consists chiefly of cetyl alcohol,[3] oleyl alcohol, palmityl alcohol, and other alcohols.[9] The known major constituents and minor impurities are:[1]

n-Octadecanol	90 percent minimum
n-Hexadecanol	Variable
n-Tetradecanol	Variable
n-Eriosanol	Variable
n-Dodecanol	Variable
Stearyl stearate	2 percent maximum
Octadecane	1 percent maximum
Stearic acid	0.5 percent maximum
Total hydrocarbons	1.8 percent (approx.)

Oleyl Alcohol consists of 9-n-octadecenol, but may contain some such unsaturated and saturated high molecular weight fatty alcohols as linoleyl, myristyl, and cetyl alcohols.[5,28] The known major components and minor impurities are:[4]

9-n-Octadecenol	55 percent minimum
8-n-Hexadecenol	Variable
6-n-Dodecenol	Variable
n-Hexadecanol	Variable
n-Octadecanol	Variable
n-Tetradecanol	Variable
7-n-Tetradecenol	Variable
Oleyl oleate	1.9 percent maximum
Oleic acid	0.5 percent maximum

Information on the impurities of Octyl Dodecanol is unavailable.

USES

Noncosmetic Uses

Stearyl Alcohol is used in surface-active agents, lubricants, emulsions, resins, and USP ointments and as a substitute for cetyl alcohol and antifoaming agents.[5,10,29]

Stearyl Alcohol (synthetic) has been approved as a direct food additive (DFA) ingredient, to be used under the same manufacturing practices as the natrual alcohol product. It also has indirect food additive (IFA) status for use in food con-

tainers and coatings (21 CFR 172.864; 175.300; 176.200; 176.210; 177.1200; 178.3910).[30]

Stearyl Alcohol is also used as an ingredient in over-the-counter (OTC) drugs of the miscellaneous external drug product category. It is considered to be safe at a concentration of 8 percent or less.[31]

Oleyl Alcohol is used in chemical and polymer synthesis, as a petroleum additive, and as a surfactant, plasticizer, and antifoaming agent. It is also used as an ingredient in pharmaceuticals, as a metal-machining lubricant, as a component of carbon paper, stencil paper, and ink, as an emulsifying agent, and as an emollient.[5,10,28]

Oleyl Alcohol has been approved as an IFA ingredient for use in paperboard components, as a defoaming agent, and as a lubricant (21 CFR 176.170; 176.210; 177.1210; 178.3910).[30]

Uses for Octyl Dodecanol, other than cosmetic, were not found in the review of the available literature.

Cosmetic Uses

Purpose in Cosmetic Products

The fatty alcohols, in general, are used primarily as emulsifiers, emollients, antifoaming agents, and surfactants.[5,7,32,33]

Stearyl Alcohol is used in cosmetics as an emollient, stabilizer, antifoaming agent, emulsifier, and carrier. It is used as a water in oil (w/o) emulsifier to produce firm cosmetic products at ordinary temperatures.[1,5,7,33] A personal communication from the Society of Cosmetic Chemists to the Cosmetic, Toiletry and Fragrance Association[34] states:

> Stearyl Alcohol is used in creams and lotions as an emollient, auxiliary emulsifier, bodying and pearlizing agent, thickener, and emulsion stabilizer. Stearyl Alcohol is hydrophobic in nature and will, therefore, produce a semiocclusive film on the skin that aids in inducing hydration. When used in sufficient concentrations, in the absence of liquid fats, Stearyl Alcohol emulsions leave a matte finish on the skin. In addition, Stearyl Alcohol has a sufficiently high melting point to deposit nongreasy films on the skin. When used in powders, Stearyl Alcohol improves adhesion and imparts a soft feel to the skin. Stearyl Alcohol is stable in high pH formulations, such as hair straighteners, depilatories, and cuticle removers. It is also used in shampoos and bubble baths as an opacifier.

Oleyl Alcohol is used as an emollient, emulsion stabilizer, surfactant, lubricant, and antifoaming agent.[4,7] A personal communication from the Society of Cosmetic Chemists to the Cosmetic, Toiletry and Fragrance Association[34] states:

> Oleyl Alcohol is used in a variety of cosmetic preparations as an emollient, superfatting agent, emulsion stabilizer, and pigment suspending agent. Oleyl Alcohol is miscible with fats, oils, and wax mixtures and will blend well with the oil phase of a cosmetic emulsion. Oleyl Alcohol is easily emulsified and aids in the hydration of other ingredients in a cosmetic formulation. In lipsticks, Oleyl Alcohol has excellent solvent properties, improves glide and slip, and leaves a thin film on the lips. Oleyl Alcohol has an appreciable hydroalcohol solubility and is easily incorporated into a wide variety of such lotions.

In regard to Octyl Dodecanol, the same communication[34] states:

> Octyl Dodecanol is a saturated liquid fatty alcohol with a total carbon length of 20. It is odorless, colorless, and has an indefinite shelf life. Octyl Dodecanol spreads easily when applied to the skin and leaves no visible trace of greasiness. It can be used as a carrier for oil soluble active ingredients, as an emollient, as a dispersant for pigments, and as a coupling agent for waxes and other fatty materials. Octyl Dodecanol is also used as a superfatting agent in shampoos, hair conditioners, and soaps.

Extent of Use in Cosmetic Products

The Food and Drug Administration (FDA), in voluntary cooperation with cosmetic ingredient manufacturers and formulators, compiles a list of cosmetic ingredients and the types of products and concentrations in which they are used. Filing of product formulation data with the FDA conforms to the prescribed format of preset concentration ranges and product categories as described in Title 21 part 720.4 of the Code of Federal Regulations.[30] Since certain cosmetic ingredients are supplied by the manufacturer at less than 100 percent concentration, the concentration reported by the cosmetic formulator may not necessarily reflect the true concentration found in the finished product; the actual concentration in such a case would be a fraction of that reported to the FDA. Since data are only submitted within the framework of preset concentration ranges, the opportunity exists for a 2- to 10-fold overestimation of the actual concentration of an ingredient in a particular product.

In 1981, Stearyl Alcohol was reported to be used in 425 cosmetic formulations at concentrations ranging from less than 0.1 percent to 50 percent. Oleyl Alcohol was present in 1018 different formulations at concentrations of less than 0.1 percent to greater than 50 percent. Octyl Dodecanol was listed in 371 products at concentrations of less than 0.1 percent to greater than 50 percent. Very few products contain these ingredients in the highest concentration ranges[35] (Table 2).

These compounds are found in a wide variety of cosmetic products and may, therefore, contact and enter the body through numerous routes. Some products may be applied several times daily and may remain in contact for extended periods (Table 2).

BIOLOGICAL PROPERTIES

Absorption, Metabolism, and Excretion

Stearyl Alcohol is found naturally in various mammalian tissues. This fatty alcohol is readily converted to stearic acid, another common constituent of mammalian tissues. Results from several studies indicate that Stearyl Alcohol is poorly absorbed from the gastrointestinal tract. For a review of the literature written from the years 1933 to 1978 on the absorption, metabolism, and excretion of Stearyl Alcohol, see the Evaluation of the Health Aspects of Stearyl Alcohol as a Food Ingredient, prepared for the Food and Drug Administration by The Federation of American Societies for Experimental Biology.[36]

Sieber et al.[37] studied the entry of octadecanol-1-^{14}C (Stearyl Alcohol) into

the thoracic duct lympho of the rat. The thoracic duct, abdominal aorta, and the duodenum below the pyloric valve were cannulated in male Sprague-Dawley rats. The common bile duct of some animals was also cannulated. Lymph flows were monitored, and 24 hours after surgery the radiolabeled compound (25 mCi/mmol) was administered via either the duodenal or aortic cannula. Blood and lymph were monitored for radioactivity after dosing at 0.25, 0.5, 0.75, 1, 2, 4, 6, and 24-hour intervals. Intestinal radioactivity was determined by quantifying the ^{14}C or ^{3}H of the homogenate of the intestines, which showed the percent absorbed radioactivity in the lymph was 56.6 ± 14.0. Of this, more than half was found in the triglycerides of the lymph, 6 to 13 percent in the phospholipids, 2 to 8 percent as the cholesterol esters, and 4 to 10 percent unchanged octadecanol. Ninety percent of octadecanol was carried in the chylomicron fraction. The absorption of the compound appeared to be a function of its lipid solubility.

The metabolism of Oleyl Alcohol was studied in 1 adult sheep. The rumen was cannulated and the animal received 66.0 g per day of Oleyl Alcohol in the diet for 12 days. Continuous measurement showed increased excretion of lipids (9 g/day fatty acids and 30 g/day unsaponifiables) and increased excretion of stearic and oleic acid. Oleyl Alcohol had no effect on either methane or heat production.[38]

Cis-9-octadecanol (Oleyl Alcohol) was reported to be a prominent constituent of long-chain alcohols in rat tissue. Ethanol (0.1 ml) containing 1.85 mEq cis-9-octadecanol-1-^{14}C was injected into the tail veins of rats, and the animals were sacrificed at 1, 24, 48, or 76 hours after injection. After 1 hour, the highest amount of radioactivity was found in the lungs, less in the liver, and the lowest amount in the brain. At 24, 48, and 96 hours, the rate of decline of radioactivity was greatest in the lungs and liver and least in the heart and brain. The radioactivity was incorporated mainly in glycerophosphocholines, glycerophosphoethanolamines, and neutral lipids. It was rapidly used for biosynthesis of lipids in the rat.[39]

The permeability of the blood–brain barrier to long-chain alcohols in plasma was studied using Oleyl Alcohol. Four groups of 4 male Wistar rats were fed either a standard diet (control) or the standard diet plus 160 mg of Oleyl Alcohol (available ad lib) for 7 or 14 days. The entire supplement was consumed every day by the individually caged rats. At the end of the specified times, the animals were fasted for 24 hours and killed, and the organs were analyzed. No differences in growth rates were found between experimental and control groups. The addition of Oleyl Alcohol to the diet for 7 days increased the free and esterified long-chain alcohols in the liver. After 14 days, there was a 3-fold increase in free and esterified alcohols when compared to control animals. The hepatic alk-1-enyl acyl and alkyl acyl phosphoglycerides increased 2- to 8-fold over control values during the 14-day feedings. No quantifiable changes were noted in brain lipids after 7 or 14 days.[40]

The fate of dietary Oleyl Alcohol was studied using 8 weanling male rats. For the first 5 days after weaning, the animals were fed a standard diet; then 4 rats received a mixture of 85:15 lab diet:oleyl palmitate, and the other 4 received 96:4 lab diet:Oleyl Alcohol. Two weeks after commencement of feeding of the experimental diet, tha animals were killed, and the liver and intestines were removed. Growth on the Oleyl Alcohol diet was poor when compared to the oleyl palmitate diet. The fecal distribution of ingested Oleyl Alcohol was 46 percent wax es-

TABLE 2. Product Formulation Data[35]

Product Category*	Total Formulations in Category	Total No. Containing Ingredient	No. Product Formulations Within Each Concentration Range (%)*							
			Unreported Concentration	>50	>25-50	>10-25	>5-10	>1-5	>0.1-1	≤0.1
Stearyl Alcohol										
Baby lotions, oils, powders, and creams	56	2	–	–	–	–	–	–	2	–
Eyebrow pencil	145	1	–	–	–	–	–	1	–	–
Eye shadow	2582	24	–	–	–	–	–	–	23	1
Mascara	3097	2	–	–	–	–	–	–	2	–
Other eye makeup preparations	230	2	–	–	–	–	–	–	1	1
Sachets	119	26	–	–	–	4	4	4	14	–
Hair conditioners	478	46	–	–	–	–	1	14	22	9
Hair straighteners	64	2	–	–	–	–	1	–	1	–
Permanent waves	474	5	–	–	–	–	–	–	2	3
Hair rinses (noncoloring)	158	21	–	–	–	–	–	5	10	6
Hair shampoos (noncoloring)	909	1	–	–	–	–	–	–	1	–
Hair dyes and color (all types requiring caution statement and patch test)	811	1	–	–	–	–	–	–	1	–
Hair bleaches	111	5	–	–	–	–	–	2	3	–
Other hair coloring preparations	49	2	–	–	–	–	–	2	–	–
Blushers (all types)	819	15	–	–	–	–	–	–	14	1
Makeup foundations	740	8	–	–	–	–	–	–	8	–
Leg and body paints	4	3	–	–	–	–	–	–	3	–
Lipstick	3319	3	–	–	–	–	–	–	1	2
Makeup bases	831	63	–	–	–	–	–	2	38	23
Rouges	211	1	–	–	–	–	–	–	–	1
Makeup fixatives	22	1	–	–	–	–	–	–	–	1
Other makeup preparations (not eye)	530	2	–	–	–	–	–	–	1	1
Cuticle softeners	32	2	–	–	–	–	–	–	2	–
Nail creams and lotions	25	1	–	–	–	–	–	1	–	–
Deodorants (underarm)	239	3	–	–	3	–	–	–	–	–

Other personal cleanliness products	227	10	–	–	–	9	–	1	–	–
Beard softeners	4	1	–	–	–	–	1	–	–	–
Shaving cream (aerosol, brushless, and lather)	114	6	–	–	–	–	–	1	5	–
Other shaving preparation products	29	2	–	–	–	–	–	–	1	1
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	680	39	–	–	–	–	4	15	17	3
Depilatories	32	6	–	–	–	–	–	6	–	–
Face, body, and hand skin care preparations (excluding shaving preparations	823	36	–	–	–	–	1	14	19	2
Moisturizing skin care preparations	747	49	–	–	–	–	1	22	24	2
Night skin care preparations	219	12	–	–	–	–	–	6	4	2
Paste masks (mudpacks)	171	2	–	–	–	–	–	1	1	–
Skin lighteners	44	6	–	–	–	–	1	4	1	–
Skin fresheners	260	1	–	–	–	–	–	–	1	–
Wrinkle smoothers (removers)	38	1	–	–	–	–	–	1	–	–
Other skin care preparations	349	9	–	–	–	–	1	6	1	1
Suntan gels, creams, and liquids	164	2	–	–	–	–	1	–	1	–
Indoor tanning preparations	15	1	–	–	–	–	–	1	–	–
TOTAL 1981 DATA		425	–	–	3	13	16	109	224	60
TOTAL 1979 DATA		414	23	–	–	12	16	101	208	54
Oleyl Alcohol										
Bath oils, tablets, and salts	237	17	–	–	–	5	2	8	1	1
Bubble baths	475	1	–	–	–	–	–	1	–	–
Bath capsules	3	1	–	–	–	–	1	–	–	–
Other bath preparations	132	3	–	–	–	–	–	3	–	–
Eyebrow pencil	145	1	–	–	–	–	1	–	–	–
Eyeliner	369	15	–	–	–	7	7	1	–	–
Eye shadow	2582	124	–	–	–	36	60	19	7	2
Mascara	397	26	–	–	–	–	–	26	–	–
Other eye makeup preparations	230	8	–	–	–	3	2	2	1	–

TABLE 2. (Continued)

Product Category*	Total Formulations in Category	Total No. Containing Ingredient	No. Product Formulations Within Each Concentration Range (%)*							
			Unreported Concentration	>50	>25–50	>10–25	>5–10	>1–5	>0.1–1	≤0.1
Colognes and toilet waters	1120	2	–	–	–	–	–	–	2	–
Perfumes	657	5	–	–	–	3	–	1	–	1
Sachets	119	2	–	–	–	–	–	2	–	–
Other fragrance preparations	191	9	–	–	–	–	–	8	1	–
Hair conditioners	478	9	–	–	–	–	–	3	6	–
Hair straighteners	64	4	–	–	–	–	–	4	–	–
Tonics, dressings, and other hair grooming aids	290	4	–	–	–	–	–	1	3	–
Other hair preparations (noncoloring)	177	1	–	–	–	–	–	1	–	–
Hair dyes and colors (all types requiring caution statement and patch test)	811	63	–	–	–	13	–	50	–	–
Hair tints	15	13	–	–	–	13	–	–	–	–
Hair bleaches	111	2	–	–	–	–	–	2	–	–
Blushers (all types)	819	13	–	1	2	1	7	2	–	–
Face powders	555	1	–	–	–	–	–	1	–	–
Makeup foundations	740	5	–	–	–	–	–	3	2	–
Lipstick	3319	633	–	2	6	236	225	138	19	7
Makeup bases	831	2	–	–	–	1	–	1	–	–
Rouges	211	3	–	–	–	2	–	1	–	–
Other makeup preparations (not eye)	530	10	–	–	–	7	3	–	–	–
Nail polish and enamel remover	41	1	–	–	–	–	–	1	–	–
Deodorants (underarm)	239	2	–	–	–	–	–	2	–	–
Feminine hygiene deodorants	21	1	–	–	1	–	–	–	–	–
Other personal cleanliness products	227	2	–	–	–	–	–	1	1	–
Aftershave lotions	282	2	–	–	–	–	–	2	–	–
Preshave lotions (all types)	29	1	–	–	–	–	–	–	1	–
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	680	2	–	–	–	–	–	2	–	–

Face, body, and hand skin care preparations (excluding shaving preparations)	823	6	–	–	–	–	1	4	–	1
Hormone skin care preparations	10	1	–	–	–	1	–	–	–	–
Moisturizing skin care preparations	747	8	–	–	–	1	–	4	2	1
Night skin care preparations	219	2	–	–	–	1	–	1	–	–
Paste masks (mudpacks)	171	2	–	–	–	–	–	1	–	1
Skin fresheners	260	2	–	–	–	–	–	–	1	1
Other skin care preparations	349	4	–	–	–	1	–	2	–	1
Suntan gels, creams, and liquids	164	5	–	–	–	–	1	3	1	–
TOTAL 1981 DATA		1018	–	3	9	331	310	301	48	16
TOTAL 1979 DATA		1069	138	1	11	267	313	294	32	13
Octyl Dodecanol										
Bath oils, tablets, and salts	237	4	–	–	–	–	4	–	–	–
Eyebrow pencil	145	1	–	–	–	–	1	–	–	–
Eyeliner	369	14	–	–	–	–	11	1	2	–
Eye shadow	2582	82	–	–	–	6	60	16	–	–
Eye lotion	13	1	–	–	1	–	–	–	–	–
Eye makeup remover	81	3	–	–	–	2	–	1	–	–
Mascara	397	1	–	–	–	–	–	1	–	–
Other eye makeup preparations	230	4	–	–	–	2	2	–	–	–
Perfumes	657	3	–	–	3	–	–	–	–	–
Fragrance powders (dusting and talcum, excluding aftershave talc)	483	4	–	–	–	–	–	–	4	–
Sachets	119	6	–	–	6	–	–	–	–	–
Other fragrance preparations	191	1	–	–	–	–	1	–	–	–
Hair conditioners	478	3	–	–	–	–	–	2	1	–
Hair sprays (aerosol fixatives)	265	2	–	–	–	–	–	1	1	–
Hair rinse (noncoloring)	158	2	–	–	–	–	–	–	2	–
Hair dyes and colors (all types requiring caution statement and patch test)	811	41	–	–	–	1	40	–	–	–
Blushers (all types)	819	6	–	–	–	3	2	1	–	–
Face powders	555	6	–	–	–	–	3	1	2	–

TABLE 2. (Continued)

Product Category*	Total Formulations in Category	Total No. Containing Ingredient	No. Product Formulations Within Each Concentration Range (%)*							
			Unreported Concentration	>50	>25–50	>10–25	>5–10	>1–5	>0.1–1	≤0.1
Lipstick	3319	112	–	1	5	46	54	5	1	–
Makeup bases	831	1	–	–	–	–	–	–	1	–
Rouges	211	1	–	–	–	1	–	–	–	–
Makeup fixatives	22	1	–	–	–	–	1	–	–	–
Other makeup preparations (not eye)	530	2	–	–	–	–	1	1	–	–
Bath soaps and detergents	148	1	–	–	–	–	–	–	–	1
Deodorants (underarm)	239	1	–	–	–	1	–	–	–	–
Other personal cleaniness products	227	1	–	–	–	–	–	1	–	–
Preshave lotions (all types)	29	1	–	–	–	–	–	–	1	–
Shaving cream (aerosol, brushless, and lather)	114	1	–	–	–	–	–	–	1	–
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	680	9	–	–	–	–	3	5	–	1
Face, body, and hand skin care preparations (excluding shaving preparations)	823	23	–	–	3	2	7	9	2	–
Moisturizing skin care preparations	747	14	–	–	–	1	1	6	4	2
Night skin care preparations	219	3	–	–	–	2	–	1	–	–
Skin lighteners	44	4	–	–	–	–	–	3	1	–
Wrinkle smoothers (removers)	38	1	–	–	–	–	–	1	–	–
Other skin care preparations	349	7	–	–	–	2	2	3	–	–
Suntan gels, creams, and liquids	164	3	–	–	–	1	2	–	–	–
Other suntan preparations	28	1	–	–	–	–	–	1	–	–
TOTAL 1981 DATA		371	–	1	18	70	195	60	23	4
TOTAL 1979 DATA		295	294	–	–	–	–	1	–	–

*Preset product categories and concentration ranges in accordance with federal filing regulations (21 CFR 720.4); see Scope and Extent of Use in Cosmetics.

ter, 27 percent fatty alcohol, 16 percent monoglyceride, 6 percent free fatty acid, and 5 percent diglyceride. Oleyl Alcohol deposition in liver was manifested as 7 percent wax ester, 11 percent triglyceride, 3 percent free fatty acid, 6 percent free fatty alcohol, and 72 percent phospholipid.[41]

Two additional studies investigated the metabolism of orally administered Oleyl Alcohol in rats. The intragastric administration to rats of 200 mg/day of Oleyl Alcohol for 14 days increased the relative concentration of alkyl and alky-1-enyl moieties in alkoxylipids in the small intestine.[42] In another study, the incoporation of long-chain alcohols and acyl glycerols into hepatic tissues of rat was studied. A group of 4 rats were fed a basic diet (control), and a second group of 4 were fed the basic diet plus 100 mg/day of cis-9-octadecenyl alcohol (Oleyl Alcohol) for 28 days. Experimental compounds were fed by stomach tube, and the animals were killed 10 hours after the last feeding. The alcohol produced no abnormalities in the rats and did not effect the distribution of lipid classes or fatty acid composition of the phosphoglycerides in the liver. Pronounced changes did occur in both the alkyl and alkyl-1-enyl moieties of the phosphoglycerides of the liver. Metabolites of long-chain alcohols become incorporated into the phosphoglycerides of the liver.[43]

Miscellaneous Effects

Microbial Effects

Yanagi and Onishi[44] found that Oleyl and Stearyl Alcohol can be utilized as the sole source of carbon by some species of *Penicillium, Candida,* and *Pseudomonas.*

Cellular and Subcelluar Effects

Stearyl Alcohol, a known tobacco smoke constituent, was studied for its effect on the plasma membrane of cultured human lung fibroblasts. The fibroblasts, labeled with ^{3}H-uridine, were incubated for 30 minutes at 37°C with 25 mM alcohol in Tris-buffered saline. The leakage of radiolabeled intracellular substances was used to indicate plasma membrane damage. Stearyl Alcohol was inactive in inducing significant cellular damage.[45]

The differential effects of Oleyl Alcohol on the osmotic fragility of erythrocytes were studied using heparinized adult male human blood. The erythrocytes from venous blood were washed, prepared as a 50 percent cell suspension, and then mixed with varying concentrations of saline solution. The alcohol was dissolved in methanol and added to the cells for 10 minutes. The cells were then centrifuged, and hemolysis was determined by measuring the supernatant hemoglobin absorbance at 540 nm. At high saline concentrations, those at which hemolytic activity was greatest, the alcohol did not stabilize the erythrocytes against hypotonic hemolysis.[46]

Raz and Goldman[47] studied the effect of Oleyl Alcohol on the osmotic fragility of lysosomes. Rat livers were removed and homogenized, and their lysosomal fraction was extracted. To this fraction, Oleyl Alcohol was added in varying concentrations. Damage to lysosomes was determined by using the extent of leakage of lysosomal acid phosphatase. At 2×10^{-5} M, Oleyl Alcohol had significant stabilizing effect, and 5×10^{-5} M caused extensive damage to the lyso-

somes. The interaction of Oleyl Alcohol with lysosomes was biphasic; it was stabilizing at low concentrations and labilizing at high concentrations.

Animal Toxicology

Oral Toxicity

Acute Studies

Egan and Portwood[7] reported the LD_{50} of Stearyl Alcohol was not reached even at doses of 8 g/kg given orally to male and female Holtzman albino rats. Stearyl Alcohol is classified as "nontoxic" by the Federal Hazardous Substances Labelling Act (FHSLA) and "practically non-toxic" by the criteria of Hodge and Sterner. Other sources reported that Stearyl Alcohol had a low order of toxicity.[29,48]

Undiluted Octyl Dodecanol was administered orally as a single dose to 5 rats at 5 g/kg, with no evident toxicity.,[49]

Product formulations containing Oleyl Alcohol or Octyl Dodecanol have been tested for acute oral toxicity in rats. Products containing 8.0 percent or 20 percent Oleyl Alcohol administered by gastric intubation at doses up to 10 g/kg caused no deaths and no toxic effects.[50-52] A lipstick containing 10.2 percent Octyl Dodecanol was diluted to 50 percent and administered to 10 rats at a dose of 25 g/kg. The total dose of Octyl Dodecanol was 1.28 g/kg. There were no deaths.[53]

Percutaneous Toxicity

Acute Studies

An acute percutaneous toxicity study was conducted with 100 percent Octyl Dodecanol on 6 guinea pigs. A single dose of 3.0 g/kg was applied under occlusion to each animal on abraded and intact skin. No deaths occurred, all animals appeared normal throughout the study, and there were no gross lesions at necropsy on the seventh day.[54]

Subchronic Studies

A subchronic percutaneous toxicity study was conducted for 3 months on a cream product formulation containing 8.0 percent Stearyl Alcohol. In 2 groups of 10 rabbits each, animals received topical applications of the product at doses of 8.8 mg/cm^2 per 8.4 percent body surface area (BSA) or 13.2 mg/cm^2 per 11.2 percent BSA 3 days a week during a 3-month period. A third group of 10 rabbits served as an untreated control. The product caused very slight to well-defined erythema and mild desquamation during the first month of treatment, and mild inflammation at the site of application was noted at necropsy. The results of hematological and blood chemistry determinations, urinalyses, organ weight measurements, and necropsy indicated no treatment-related effects. No evidence of systemic toxicity attributable to topical application of the product was found.[55]

Ocular Irritation

Studies of irritation to the rabbit eye were conducted on samples of undiluted Stearyl Alcohol from 4 separate commercial sources. Each of the samples

was instilled full strength into 1 eye of each of 6 rabbits. Minimal irritation was noted on Day 1 for 3 of the samples (maximum score of 5, scale 0 to 110), and there was no irritation from the remaining sample. Scores decreased to 0 by Day 4 in all cases.[56]

An irritation test of 100 percent Oleyl Alcohol using 6 rabbits gave an ocular irritation score of 1 (max, 110) on Day 1; all scores were 0 by the second day.[57] The ocular toxicity of 4 lots of Oleyl Alcohol was tested in a modified version of the Official French Method.[58] The undiluted ingredient in a 0.1 ml volume was applied to 1 eye of each of 6 rabbits, and readings were made at 1, 24, and 48 hours. The scores were 7.17 (max, 110) at 1 hour, 0.33 at 24 hours, and 0.0 at 48 hours.[59]

In an ocular irritation test 100 percent Octyl Dodecanol with 6 rabbits had an average irritation score of 4 (max, 110) on Day 1, with a score of 0 by Day 4.[60] In an identical test, 100 percent Octyl Dodecanol had scores of 1 on Days 1 and 2 and 0 on Day 3.[61]

Several ocular irritation studies using rabbits were conducted on product formulations containing 8.0 to 20 percent Oleyl Alcohol or 3.0 to 10.2 percent Octyl Dodecanol. In every case, there was either no or only minimal, transient ocular irritation induced by these products.[52,62-67]

A Draize ocular irritation test was conducted on a hairdressing formulation containing 1.5 percent Oleyl Alcohol after several complaints of ocular irritation were reported from its use. A 0.1 ml volume of the undiluted product was instilled into the eyes of 3 albino rabbits both with and without tapwater rinse. The product was practically nonirritating. The product was also tested undiluted and in a 25 percent diluted form and caused no ocular irritation in squirrel monkeys. Furthermore, exposure of the hairdressing formulation to oxygen, UV irradiation, and 0.01 N sulfuric acid caused no increase in product-induced irritation. Instillation of the hairdressing did not potentiate the ocular irritancy of a saturated solution of NaCl, 4 percent Formosaline, or 15 percent Teepol. Irritation did occur after the instillation into the eyes of rabbits of rinsings taken from the human head after use of the hairdressing.[68]

Skin Irritation

Acute Studies

Cutaneous irritation tests using rabbits were conducted on 4 samples of Stearyl Alcohol obtained from separate commercial sources. When each sample was applied full strength under occlusion to the clipped skin of 9 rabbits for 24 hours, irritation scores of 0.4, 0.5, 1.42, and 1.5 were recorded (scale 0 to 4). These scores were indicative of minimal to mild primary skin irritation.[69]

Many studies on the irritant properties to the skin of Oleyl Alcohol have been reported. According to Drill and Lazar[70] 25 percent Oleyl Alcohol in mineral oil caused no to low skin irritation. Four lots of Oleyl Alcohol were tested for acute skin irritation according to a modified version of the Official French Method.[58] Samples were fixed for 24 hours under occlusion to the backs of rabbits. Irritation was evaluated according to a modification of the French Method scale of 0 to 8: nonirritant, less than 0.5; slight irritant, 0.5 to 2; moderate irritant, 2–5; severe irritant 5–8. The four lots were each tested in undiluted form and in a 10 percent aqueous dispersion, and 2 samples were assayed twice. Each assay was per-

formed on at least 6 animals. By this assay, Oleyl Alcohol was slightly irritating when undiluted and nonirritating when in a 10 percent aqueous dilution (Table 3).[59]

A skin irritation test with 9 rabbits gave an irritation index of 0.17 (scale 0 to 4) for 100 percent Oleyl Alcohol applied for 24 hours under occlusion. This score was indicative of minimal primary skin irritation.[71] When undiluted Oleyl Alcohol was applied to the skin of rabbits for 4 consecutive days, the greatest average irritation score was 2.33 (scale 0 to 4). This result was interpreted as mild primary skin irritation.[72]

Three separate cutaneous irritation tests using rabbits were conducted on 100 percent Octyl Dodecanol or a 30 percent aqueous dilution of Octyl Dodecanol in which the test material was applied under occlusion to the backs of 9 rabbits for 24 hours. The ingredient produced skin irritation indices (scale 0 to 4) of 1.13,[73] 0.5,[74] and zero[75] for the alcohol full strength and zero[75] for the 30 percent aqueous dilution.

Technical grade Oleyl Alcohol and 2-octyl dodecanol were tested for skin irritation using rabbits, guinea pigs, rats, miniature swine, and man.[76] In the rabbit studies, the hair on 6 areas of each of 6 albino rabbits was shaved, and test materials were applied 24 hours later. Undiluted samples were applied in 0.1 g amounts to the test areas for 24 hours. The sites were graded for irritation, and the compounds were reapplied 30 minutes later. Second gradings were made 48 hours later (72 hours after the initial application), after which Evans blue solution was injected intravenously into each animal. One hour after injection, the animals were killed and the skin sampled. In guinea pig and rat studies, 2 dorsal areas of each of 6 male Hartley guinea pigs and 6 Wistar rats were clipped free of hair, and testing began 24 hours later. One site received a dose of 0.1 g of the test compound, and the other site was left untreated. Other test parameters were identical to the rabbit test procedure. In the swine test, the entire dorsal area of groups of 6 miniature Pitman-Moore improved strain swine was clipped free of

TABLE 3. Oleyl Alcohol, Acute Skin Irritation[59]

		Irritation		
Lot	*Compound Concentration*	*Assay No.*	*Score*	*Interpretation*
1	Undiluted	1	1.71	Slight irritant
		2	1.58	Slight irritant
	10%	1	0.17	Nonirritant
		2	0.33	Nonirritant
2	Undiluted	1	1.67	Slight irritant
		2	1.75	Slight irritant
	10%	1	0.04	Nonirritant
		2	0.25	Nonirritant
3	Undiluted	1	1.50	Slight irritant
	10%	1	0.29	Nonirritant
4	Undiluted	1	1.33	Slight irritant
	10%	1	0.42	Nonirritant

hair, and testing began 24 hours later. The test compounds (0.05 g) were applied under occlusion for 48 hours and scored on a scale of (−), no reddening, to (+++), severe reddening. The results of these assays were expressed as scores of 0 (negative) to 3 (severely irritating) and compared to the results of human skin patch testing of these compounds by the same investigators. Although irritation was moderate to severe in the rabbit, guinea pig, and rat, no irritation occurred in swine or human skin. The two compounds were comparable in their ability to produce irritation (Table 4). Skin samples from the rabbit, guinea pig, and rat following exposure to the 2 alcohols had changes of acanthosis, hyperkeratinization, swelling of cells, and proliferation of basal cells. Vasodilatation, edema, alteration of collagenous fibers, and mononuclear and polymorphonuclear leukocyte infiltration were observed in the dermis. In the case of Oleyl Alcohol, edema of the epidermis developed into spongiosis, causing an "eruption" of the epidermis and "crust and ulcer" formation. Both the erupted epidermis and the infundibulum of the hair follicles were infiltrated by inflammatory cells.

Several primary skin irritation studies have been conducted on product formulations containing various concentrations of Oleyl Alcohol or Octyl Dodecanol.[52,62,58,77–80] Single applications under occlusion for 24 hours of products containing 8.0 to 20 percent Oleyl Alcohol or 4.0 percent Octyl Dodecanol produced no to mild irritation with primary irritation indices (scale 0 to 4) of 0.0 to 1.08.[52,77–79] Product formulations containing 12.7 percent Oleyl Alcohol or 10.2 percent Octyl Dodecanol applied to the skin of rabbits for 3 to 4 consecutive days produced minimal to mild irritation.[62,80] A product containing 1.5 percent Oleyl Alcohol was tested for primary skin irritation undiluted and diluted 1:4 with water. Test materials were applied to the intact and abraded skin of rabbits and to the ears of female CF/1 mice, for 4 daily 0.01 ml applications. The product, both diluted and undiluted, was irritating to the skin of rabbits and mice.[68] The degree of irritation in these studies did not correlate with the concentration of Oleyl Alcohol or Octyl Dodecanol present.

Subchronic Studies

A 60-day modified cumulative irritation test as outlined in *Journal Officiel de la Republique Francaise*[58] was conducted on 4 lots of Oleyl Alcohol in undiluted form and in 10 percent dilutions. Materials were applied every day. Scoring

TABLE 4. Comparative Irritation of Oleyl Alcohol and 2-Octyl Dodecanol in Several Species[76]

Species	Concentration (%)	Dose (g)	Irritation Score*	
			Oleyl Alcohol	2-Octyl Dodecanol
Rabbit	100	0.1	3	3
Guinea pig	100	0.1	3	2
Rat	100	0.1	2	2
Swine	100	0.05	0	0
Human	100	0.05	0	0

*0, negative; 2, moderately irritating; 3, severely irritating.

was expressed as a weekly average of daily observations. After 8 weeks, microscopic examinations of 2 samples of skin were conducted. A study of recovery from cutaneous injury was performed by interrupting application for 7 days and examining the skin thereafter. The results indicated that undiluted Oleyl Alcohol was poorly tolerated, with thickening and drying of skin and eschar formation. Microscopic changes were thinning of stratum corneum, acanthosis, and orthokeratosis. The 10 percent dilutions were "relatively well tolerated," with only slight exfoliation. Hyperplasia, moderate hypercanthosis, vascular congestion of superficial dermis, and slight erythema and edema were present.[59]

Guinea Pig Skin Sensitization

Two guinea pig sensitization studies were conducted on a deodorant containing 24.0 percent Stearyl Alcohol using the Draize repeated topical application method.[81,82] In one study,[81] 25 animals received 9 induction applications of the deodorant, diluted to 50 percent in petrolatum, under occlusion for 24 hours on abraded skin sites. This was followed by a 2-week nontreatment period and then challenge applications to both intact and abraded untreated sites. Groups of 5 animals served as petrolatum and untreated controls. At challenge, 1 of 25 treated animals and 1 of 5 petrolatum controls gave a ± (equivocal) score at 24 hours on the intact skin sites; all other test sites were nonreactive. In the second similar experiment,[82] no evidence of reaction at challenge was noted, although 2 of the 10 test animals died during the experiment. Under these test conditions, Stearyl Alcohol was not a contact sensitizer.

Comedogenicity

Stearyl Alcohol was not comedogenic when applied to the ear canal of 2 rabbits 5 days per week, for 2 weeks.[83]

Special Studies

Mutagenicity

Stearyl Alcohol was tested for mutagenic activity in an Ames assay using 4-histidine-requiring mutants of *Salmonella typhimurium* (TA98, TA100, TA1535, TA1537). The compound was tested both with and without metabolic activating S-9 fractions from the livers of rats pretreated with Aroclor 1254 or methylcholanthrene. Stearyl Alcohol was not mutagenic.[84]

Tumorigenicity

Sice[85] studied the tumor-promoting activity of alkanes and 1-alkanols. Thirty female Swiss strain mice received an initiating dose of 7,12-dimethylbenz[a]anthracene to the shaved skin of the back. Beginning 1 week after the initiating dose, 1 drop (20 μl) of a solution of Stearyl Alcohol in cyclohexane (20 g/100 ml) was applied 3 times weekly for 60 weeks over the initiated area. Twenty-three of the 30 mice survived the study, and 1 tumor appeared on the initiated area of one mouse at 30 weeks.[85]

Clinical Assessment of Safety

Eye Irritation

Ten human volunteers used 3 ml of a hairdressing product containing 1.5 percent Oleyl Alcohol daily for 5 days. The head was rinsed daily with 50 ml of water. One drop of the rinse water was instilled 4 times daily for 5 days into the same eye. No irritation occurred in any volunteers.[68]

Skin Irritation and Sensitization

Patch Testing

In 24-hour single insult occlusive patch tests, mild irritation was produced by 100 percent Stearyl Alcohol in 1 of 80 subjects[86] and by 100 percent Octyl Dodecanol in 1 of 40 subjects (Table 5).[87]

Occlusive 48-hour patches using undiluted technical grade Oleyl Alcohol and Octyl Dodecanol in 0.05 g amounts were applied to randomized sites on the skin of the back of 50 adult male volunteers.[76] The patches were removed, and 30 minutes later the sites were evaluated. Observations also were made at 72 and 96 hours and, if necessary, at 120 hours. There were no signs of skin irritation.

The North American Contact Dermatitis Group reported results of 48- and 96-hour screening patch tests of 30 percent Stearyl Alcohol in petrolatum from several 1-year intervals. Allergic reactions occurred in 2 of 172 individuals tested during the year ending in June 1976,[88] 1 of 446 during the year ending June 1977,[89] 6 of 824 during the year ending June 1979,[90] and 6 of 634 during the year ending June 1980[91] (Table 5).

Hjorth and Trolle-Lassen[92] studied allergic skin reactions to ointment bases. Out of a test population of 1664 panelists, each tested with all 3 ingredients, Stearyl Alcohol (30 percent in liquid paraffin) caused 4 positive reactions, Oleyl Alcohol (30 percent in petrolatum) produced 10 positive reactions, and Octyl Dodecanol (30 percent in petrolatum) caused 6 positive reactions (Table 5). Of the 10 patients sensitive to Oleyl Alcohol, 3 were also sensitive to Stearyl Alcohol, and the investigators suggest that cross-sensitization may have occurred.

Lanette-0 (20 percent in petrolatum) is a mixture of Cetyl and Stearyl Alcohols. Lanette-0 was patch tested on 21 patients, and Stearyl Alcohol (50 percent in petrolatum) was tested on those patients who were sensitive to the Lanette-0. Of 7 individuals who were sensitive to the Lanette-0, 4 were sensitive to the Stearyl Alcohol.[93]

Calnan and Connor[94] reported 4 positive reactions to carbon paper among 40,000 subjects tested. One of the four had dermatitis and a positive reaction to Oleyl Alcohol.

A number of product formulations containing various alcohols at concentrations of 2.5 to 24 percent have also been tested for human skin irritation (Table 6). Single insult occlusive patch tests on lipstick formulations containing 20 percent Oleyl Alcohol and a moisturizing cream containing 4.0 percent Octyl Dodecanol produced no or only minimal irritation.[95-97] Daily patch testing of 5 product formulations containing 8.0 to 24 percent Stearyl Alcohol, 2.5 percent Oleyl Alcohol, or 3.0 percent Octyl Dodecanol for 21 days produced ratings of "essentially nonirritating" or "slightly irritating."[98-102] Controlled use of a lipstick containing 8.0 percent Oleyl Alcohol for 4 weeks produced no irritation.[103] Re-

TABLE 5. Clinical Skin Patch Tests with Stearyl Alcohol, Oleyl Alcohol, or Octyl Dodecanol

Test Method	*Material Tested*	*Concentration of Alcohol (%)*	*No. of Subjects*	*Results*	*Reference*
24-hour single insult occlusive patch	Stearyl Alcohol	100	80	Mild irritation in 1 subject	86
	Octyl Dodecanol	100	40	Mild irritation in 1 subject	87
Single insult screening patch for contact sensitization	Stearyl Alcohol	30 in petrolatum	172	2 positive reactions; 1.2 %	88
	Stearyl Alcohol	30 in petrolatum	446	1 positive reaction; 0.22 %	89
	Stearyl Alcohol	30 in petrolatum	824	6 positive reactions; 0.73 %	90
	Stearyl Alcohol	30 in petrolatum	634	6 positive reactions; 0.95 %	91
Single insult screening patch for contact sensitization	Stearyl Alcohol	30 in liquid paraffin	1664	4 positive reactions; 0.24 %	92
	Oleyl Alcohol	30 in petrolatum	1664	10 positive reactions; 0.60 %	92
	Oleyl Dodecanol	30 in petrolatum	1664	6 positive reactions; 0.36 %	92

TABLE 6. Clinical Skin Patch Tests with Product Formulations Containing Stearyl Alcohol, Oleyl Alcohol, or Octyl Dodecanol

Test Method	*Material Tested*	*Concentration of Alcohol (%)*	*No. of Subjects*	*Results*	*Reference*
24-hour single insult occlusive patch	Lipstick	20 Oleyl Alcohol	19	No signs of irritation	95
	Lipstick	20 Oleyl Alcohol	16	No signs of irritation	96
	Moisturizing cream	4.0 Octyl Dodecanol	20	PII, 0.03 (max 4.0); minimal irritation in 1 subject	97
21-day cumulative irritancy (23-hour occlusive patch for 21 consecutive days)	Deodorant	24 Stearyl Alcohol	12	Slightly irritating; total composite score was 128/630 max	98
	Antiperspirant	17 Stearyl Alcohol	27	Essentially nonirritating	99
	Cream	8.0 Stearyl Alcohol	9	Essentially nonirritating; total composite score was 36/630 max	100
	Moisturizer	2.5 Oleyl Alcohol	10	Slightly irritating; total composite score was 59/630 max	101
	Eye pencil	3.0 Octyl Dodecanol	16	Essentially nonirritating; total composite score was 7.5/630. Patches applied 5 days/week for 21 total patches	102
Controlled use (4 weeks of daily use)	Lipstick	8.0 Oleyl Alcohol	52	No irritation	103
Schwartz-Peck prophetic patch test (open and closed 48-hour patches, repeated after 2 weeks)	Lipstick	8.0 Oleyl Alcohol	308	Mild irritation with closed patch in 3 subjects at first exposure; no evidence of sensitization. Supplemental UV exposure after second insult produced no reactions	104
Modified repeated insult patch test (12- or 24-hour patches 4 days/week for 8 induction patches; challenge patch after 2-week rest)	Antiperspirant	17 Stearyl Alcohol	52	Minimal irritation; no sensitization	105
	Antiperspirant	17 Stearyl Alcohol	45	Minimal to mild irritation with evidence of fatigue; no evidence of sensitization	106
	Antiperspirant	14 Stearyl Alcohol	50	No irritation; no sensitization	107

TABLE 6. (Continued)

Test Method	*Material Tested*	*Concentration of Alcohol (%)*	*No. of Subjects*	*Results*	*Reference*
Draize-Shelanski repeated insult patch test (24- or 48-hour patches 3 days/ week for 10 induction patches; challenge after 2-week rest)	Deodorant	24 Stearyl Alcohol	176	Minimal irritation; no sensitization	108
	Deodorant	24 Stearyl Alcohol	150	Minimal irritation; no sensitization	109
	Antiperspirant	17 Stearyl Alcohol	50	Minimal irritation; 1 subject demonstrated reaction indicative of allergic contact dermatitis at challenge; however, rechallenge at untreated site was negative	110
	Antiperspirant	14 Stearyl Alcohol	100	No irritation; no sensitization	111
	Hand cream	12 Stearyl Alcohol	205	Minimal irritation; no sensitization	112
	Deodorant	12 Stearyl Alcohol	48	Mild irritation; no sensitization	113
	Deodorant	12 Stearyl Alcohol	154	Minimal irritation; no sensitization	114
	Cream	8.0 Stearyl Alcohol	213	Minimal irritation; no sensitization	115
	Cream	12.7 Oleyl Alcohol	102	No irritation; no sensitization	116
	Lipstick	8.0 Oleyl Alcohol	154	Minimal irritation; no sensitization. Supplemental UV exposure after induction patches 1, 4, 7, and 10 and after challenge showed no photosensitization	104
	Cream	2.5 Oleyl Alcohol	210	Mild irritation in 1 subject during induction and 1 at challenge; none thought to be indicative of sensitization	117
	Cream	2.5 Oleyl Alcohol	205	Minimal to mild irritation during induction and at challenge; none were thought to be indicative of sensitization	118
	Lipstick	10.2 Octyl Dodecanol	197	No irritation; no sensitization	119
	Unspecified product formulation	3.0 Octyl Dodecanol	210	Isolated mild induction reactions in 2 subjects; no reactions at challenge	120

sults indicative of irritation from product formulations are difficult to interpret with respect to a single ingredient.

Several product formulations containing the alcohols have been tested for skin sensitization on a total of 2629 subjects using a variety of test methods. These studies included: 1 Schwarz-Peck prophetic patch test on a product formulation containing 8.0 percent Oleyl Alcohol, 3 modified repeated insult patch tests on antiperspirant formulations containing 14 or 17 percent Stearyl Alcohol, and 14 Draize-Shelanski repeated insult patch tests on products containing 8.0 to 24 percent Stearyl Alcohol, 2.5 to 12.7 percent Oleyl Alcohol, or 3.0 or 10.2 percent Octyl Dodecanol. Of the 2629 subjects in these studies, there were no reactions indicative of sensitization (Table 6).

Case Reports

Contact sensitization to Stearyl Alcohol has been reported in 3 individuals: 2 had an urticarial-type reaction, and 1 of these reactions was thought to be due to impurities in the Stearyl Alcohol sample.[9,121,122]

Photoreactivity

A phototoxicity study was conducted on a cream product formulation containing 2.5 percent Oleyl Alcohol using 10 subjects. A single 24-hour skin patch of the product with 1X Minimal Erythema Dose (MED) exposure to a Krohmeyer Hot Quartz Lamp produced no reactions.[123] The same product was tested for photoallergenicity with 25 subjects. Five daily 24-hour induction patches with exposure for 30 seconds to a windowglass-filtered Krohmeyer Hot Quartz Lamp were followed by a 12-day nonexposure period and then a single 24-hour challenge with the same UV light exposure. No signs of photosensitivity were present.[123]

A repeated insult photosensitization test using 23 subjects was conducted on a lipstick formulation containing 10.2 percent Octyl Dodecanol. Each subject had applied a 24-hour occlusive patch of the test material followed by UV irradiation of the test site with 3 times the individual's MED. The light source was a filtered 150W Xenon Arc Solar Simulator that produced a continuous emission spectrum in the UVA and UVB region (290 to 400 nm). Patches and irradiation were repeated twice weekly for a total of 6 exposures. Following a 10-day nonexposure period, patches and irradiation were repeated on a previously untreated site. There were no reactions and thus no evidence of phototoxicity or photoallergenicity.[124]

Schwartz-Peck and Draize-Shelanski skin sensitization tests on a lipstick formulation containing 8.0 percent Oleyl Alcohol (summarized in Table 6) also included supplemental UV light exposure, with no resultant reactions.[104]

SUMMARY

Stearyl Alcohol, Oleyl Alcohol, and Octyl Dodecanol are long-chain saturated or unsaturated (Oleyl) fatty alcohols. The materials of commerce are mixtures of fatty acids, with the predominant species being the named compound.

These alcohols have a wide variety of uses in pharmaceutical, food, and other industries. Stearyl Alcohol is approved for use in certain over-the-counter drugs, and Stearyl and Oleyl Alcohols are approved for some food additive appli-

cations. They are used in numerous cosmetic product categories at concentrations of less than 0.1 percent to greater than 50 percent. They are chiefly used at concentrations less than 25 percent.

The metabolism of Stearyl Alcohol and Oleyl Alcohol in rats is well described. They are used in the biosynthesis of lipids and other naturally occurring cellular constituents or enter metabolic pathways for energy production.

Stearyl Alcohol was not mutagenic in the Ames Assay, and it did not promote tumor formation when tested with DMBA. Oleyl Alcohol and Octyl Dodecanol were not tested in these assays. Due to the chemical nature and benign biological activity of these compounds, they are not suspected of significant potential for carcinogenesis.

The results of acute oral toxicity studies in rats of undiluted Stearyl Alcohol and Octyl Dodecanol and of products containing Oleyl Alcohol and Octyl Dodecanol at concentrations up to 20 percent indicate a very low order of toxicity. Results of percutaneous toxicity studies with 100 percent Octyl Dodecanol and with products containing 8.0 percent Stearyl Alcohol or 8.0 percent Oleyl Alcohol also indicate a low order of toxicity. In rabbit irritation tests, these alcohols produced minimal ocular irritation and minimal to mild primary cutaneous irritation. In 1 assay system, the skin irritancy of technical grade Oleyl Alcohol and Octyl Dodecanol was moderate to severe in rabbits, guinea pigs, and rats, whereas no irritation was seen in swine and human skin. Observations made in a subchronic skin irritation study indicated that 100 percent Oleyl Alcohol was "poorly tolerated" when applied to the skin of rabbits daily for 60 days, whereas 10 percent dilutions were "relatively well tolerated." A product containing 24 percent Stearyl Alcohol produced no evidence of contact sensitization in the guinea pig. A rabbit ear comedogenicity test on Stearyl Alcohol was negative.

The results of single insult clinical patch testing indicate a very low order of skin irritation potential for undiluted Stearyl Alcohol and Octyl Dodecanol. Several studies of screening patch testing for contact sensitization in large populations had rates of 19 of 3740 (0.51 percent) for Stearyl Alcohol, 10 of 1664 (0.60 percent) for Oleyl Alcohol, and 6 of 1664 (0.36 percent) for Octyl Dodecanol. Reports of isolated cases of contact dermatitis from Stearyl Alcohol are available. Tests of product formulations in humans demonstrated low potentials for significant skin irritation or sensitization from the alcohols in formulation. Photoreactivity studies on products containing 2.5 percent Oleyl Alcohol or 10.2 percent Octyl Dodecanol were negative for phototoxicity or photosensitization. A hairdressing product containing 1.5 percent Oleyl Alcohol was nonirritating to the human eye.

CONCLUSION

Based on the available data, Stearyl Alcohol, Oleyl Alcohol, and Octyl Dodecanol are safe as currently used in cosmetics.

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Final Report on the Safety Assessment of *Cocos nucifera* (Coconut) Oil and Related Ingredients

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Abstract

Cocos nucifera (coconut) oil, oil from the dried coconut fruit, is composed of 90% saturated triglycerides. It may function as a fragrance ingredient, hair conditioning agent, or skin-conditioning agent and is reported in 626 cosmetics at concentrations from 0.0001% to 70%. The related ingredients covered in this assessment are fatty acids, and their hydrogenated forms, corresponding fatty alcohols, simple esters, and inorganic and sulfated salts of coconut oil. The salts and esters are expected to have similar toxicological profiles as the oil, its hydrogenated forms, and its constituent fatty acids. Coconut oil and related ingredients are safe as cosmetic ingredients in the practices of use and concentration described in this safety assessment.

Keywords

Cocos nucifera (coconut) oil, cosmetics, safety

Introduction

Cocos nucifera (coconut) oil and its derivatives, coconut acid, hydrogenated coconut acid, and hydrogenated coconut oil, are used by industry as a convenient source of lower chain length fatty acids. A safety assessment for these ingredients was published in 1986 with the conclusion from the Cosmetic Ingredient Review (CIR) Expert Panel that these ingredients are "safe for use as cosmetic ingredients."[1]

A summary of the Expert Panel assessment is provided below:

> In cosmetic products, coconut oil is used as a cleanser, foaming agent, or stabilizer at concentrations up to 50%. Acute, chronic, and subchronic oral toxicity studies indicate that coconut oil and hydrogenated coconut oil are relatively nontoxic by ingestion. Neither compound produced significant skin or eye irritation in laboratory animals. No sensitization was reported. Clinical assessment of cosmetic products containing coconut oil produced very minimal skin irritation reactions. There was no indication that these ingredients were primary irritants, sensitizers, or phototoxic compounds following human testing. It is concluded that coconut oil, coconut acid, hydrogenated coconut oil, and hydrogenated coconut acid are safe for use as cosmetic ingredients.

This report summarizes only new information reviewed in considering if the safety of additional cosmetic ingredients could be supported.

The Panel determined that the available data in the original safety assessment on coconut oil, coconut acid, hydrogenated coconut oil, and hydrogenated coconut acid are sufficient to support the safety of an additional 21 cosmetic ingredients in the coconut oil and related fatty alcohols, fatty acid esters, and salts group: ammonium cocomonoglyceride sulfate, butylene glycol cocoate, caprylic/capric/coco glycerides, cocoglycerides, coconut alcohol, coconut oil decyl esters, decyl cocoate, ethylhexyl cocoate, hydrogenated coco-glycerides, isodecyl cocoate, lauryl cocoate, magnesium cocoate, methyl cocoate, octyldodecyl cocoate, pentaerythrityl cocoate, potassium cocoate, potassium hydrogenated cocoate, sodium cocoate, sodium cocomonoglyceride sulfate, sodium hydrogenated cocoate, and tridecyl cocoate. These ingredients consist of fatty acids derived from coconut oil, hydrogenated forms of these fatty acids, corresponding fatty alcohols, simple esters of these fatty acids, inorganic salts of these fatty acids, and sulfated salts of these fatty acids.

The CIR Expert Panel has also published safety assessments for components of some of the ingredients covered by this assessment, including butylene glycol, glyceryl cocoate, methyl alcohol, propylene glycol dicocoate, and sorbitan cocoate, finding

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Table 1. Previously Reviewed Ingredients

Ingredient	Uses	Use Concentrations (%)	Conclusion	Reference
Butylene glycol	165	<0.1->50	Safe as presently used in cosmetics	Elder[7]
	813	0.00007-89	Reaffirmed in 2006	Andersen[6]
Glyceryl cocoate	1	0.3-5	Safe as a cosmetic ingredient in the present practices of use and concentration	Andersen[5]
Methyl alcohol	4	0.1-5	Safe as used to denature alcohol used in cosmetic products	Andersen[3]
Propylene glycol dicocoate	Not in use[a]	Not in use[a]	Safe as a cosmetic ingredient in the present practices of use[a]	Andersen[2]
Sorbitan cocoate	Not in use[a]	Not in use[a]	Safe for use as a cosmetic ingredient under the present practices of use.[a]	Andersen[4]
Lanolin acid	51	>0.1-10	Safe for topical application to humans in the present practice of use and concentration	Elder[8]
	44	1-3	Reaffirmed in 2005	Andersen[6]
Lanolin alcohol	738	≤0.1->50	Safe for topical application to humans in the present practice of use and concentration	Elder[8]
	337	0.6-4	Reaffirmed in 2005	Andersen[6]

[a] Were ingredients not in current use to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to other related chemicals.

them safe for use as cosmetic ingredients.[2-7] Included in these safety assessments were dermal absorption, acute inhalation toxicity, acute oral toxicity, acute dermal toxicity, subchronic and chronic oral toxicity, comedogenicity, ocular irritation, dermal irritation, reproductive and developmental toxicity, genotoxicity, carcinogenicity, and photosensitization studies.

The CIR Expert Panel previously reviewed the safety of lanolin acid and lanolin alcohol, finding that the fatty acids and the corresponding fatty alcohols in lanolin are equivalently safe.[8] This safety assessment was rereviewed in 2003 and the conclusion was reaffirmed.[9]

Table 1 provides a listing of previously reviewed ingredients.

Chemistry

Definition

The definitions and structures of the coconut oil ingredients presented in this report as given in the International Cosmetic Ingredient Dictionary and Handbook are found in Table 2.[10]

The primary constituents of coconut oil are trimyristin, trilaurin, tripalmitin, tristearin, and various other triglycerides.[11] About 90% of the triglycerides are saturated.

Physical Properties

The Physical properties of coconut oil, including analytical methods used to determine its composition, have previously been published.[1] Table 3 describes the material specifications of butylene glycol cocoate, decyl cocoate, hydrogenated coco-glycerides, and potassium cocoate.

Method of Manufacture

Coconut oil is obtained from copra (the dried meat, or kernel, of the coconut), where it is present in quantities of 60% to 70%. The expressed material has a water content of 4% to 10%.[12] Crude coconut oil is obtained through mechanical expression of copra. The oil is then refined, bleached, and deodorized to remove free fatty acids, phospholipids, color, odor, flavor components, and other nonoil materials.[13] Hydrogenated coconut oil is prepared by the hydrogenation of coconut oil. Coconut acid is derived from coconut oil by hydrolysis and isolation of the fatty material, which is then distilled. Hydrogenated coconut acid is prepared by the hydrogenation of coconut acid.

Various processing parameters in expressing coconut oil from dried coconut gratings have been studied including pressing time, particle size, pressing pressure, moisture content, and temperature. This study found that coconut oil expression efficiency was significantly dependent on the moisture content of the coconut gratings.[14]

The different fatty acid fractions of coconut oil can be esterified with a mono-alcohol or a polyol to produce various esters. Alcohols of coconut fatty acids are manufactured by high pressure hydrogenation of coconut fatty acids or coconut fatty acid methyl esters. The coconut fatty alcohols can be further processed by sulfation, ethoxylation, amination, phosphatization, sulfitation, etc.[15]

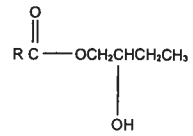
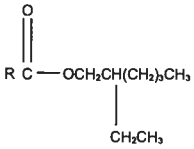
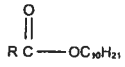
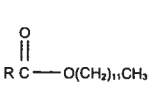
Hydrogenated coco-glycerides are produced by esterification of coconut fatty acids (C12-C18) with glycerol.[16]

Esterification of coconut fatty acids (C12-C18) with butylene glycol produces butylene glycol cocoate.[17] Potassium cocoate is produced in a trade name mixture by combining the fatty acids of coconut oil with potassium hydroxide.

Impurities

Coconut oil is usually quite low in color bodies, pigments, phosphatides, gums, and other nonglyceride substances commonly found in much larger quantities in other vegetable oils.

Table 2. Definitions, Structures, and Functions of *Cocos nucifera* (Coconut) Oil and Derivitives

Ingredient	Definition	Structure	Function(s)
Cocos nucifera (coconut) oil (CAS No. 8001-31-8)	A fixed oil obtained by expression from the kernels of the seeds of *Cocos nucifera*.	–	Fragrance ingredient; hair conditioning agent; skin-conditioning agent-miscellaneous; skin-conditioning agent-occlusive
Coconut acid (CAS No. 61788-47-4)	A mixture of fatty acids derived from *Cocos nucifera* (coconut) oil.	–	Surfactant-cleansing agent
Coconut alcohol (CAS No. 68425-37-6)	A mixture of fatty alcohols derived from coconut acid.	–	Emulsion stabilizer; surfactant-foam booster; viscosity increasing agent-aqueous; viscosity increasing agent-nonaqueous
Butylene glycol cocoate	The ester of butylene glycol and coconut acid that conforms generally to the structure on the right where RCO-represents the coconut acid moiety.		Emulsion stabilizer; viscosity increasing agent-nonaqueous
Caprylic/capric/coco glycerides	A mixture of mono, di, and triglycerides of caprylic, capric, and coconut acids.	–	Skin-conditioning agent-emollient
Cocoglycerides (CAS No. 68606-18-8)	A mixture of mono, di, and triglycerides derived from coconut oil.	–	Skin-conditioning agent-emollient
Coconut oil decyl esters	A product obtained by the transesterification of decyl alcohol and *Cocos nucifera* (coconut) oil.	–	Skin-conditioning agent-occlusive
Decyl cocoate	The ester of decyl alcohol and the fatty acids derived from *Cocos nucifera* (coconut) oil.	–	Skin-conditioning agent-occlusive
Ethylhexyl cocoate (CAS Nos. 91052-62-9, 92044-87-6)	The ester of 2-ethylhexanol and coconut acid that conforms to the structure to the right where RCO- represents the fatty acid radical derived from coconut oil.		Skin-conditioning agent-emollient
Isodecyl cocoate	The ester of branched chain decyl alcohols and coconut acid that conforms to the structure to the right where RCO- represents the fatty acids derived from coconut oil.		Skin-conditioning agent-emollient
Lauryl cocoate	The ester of lauryl alcohol and the fatty acids derived from coconut oil that conforms to the structure to the right where RCO- represents the fatty acids derived from coconut oil.		Skin-conditioning agent-emollient; skin-conditioning agent-occlusive

(continued)

Table 2 (continued)

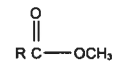
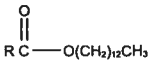
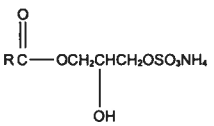
Ingredient	Definition	Structure	Function(s)
Methyl cocoate (CAS No. 61788-59-8)	The ester of methyl alcohol and coconut fatty acids. It conforms generally to the structure on the right where RCO- represents the fatty acids derived from coconut oil.		Skin-conditioning agent-emollient
Octyldodecyl cocoate	The ester of octyldodecanol and coconut acid.		Skin-conditioning agent-emollient
Pentaerythrityl cocoate	The ester of coconut acid and pentaerythritol.		Skin-conditioning agent-miscellaneous
Tridecyl cocoate	The ester of tridecyl alcohol and coconut acid. It conforms to the structure to the right where RCO- represents the fatty acids derived from coconut oil.		Skin-conditioning agent-occlusive
Magnesium cocoate	The magnesium salt of coconut acid.	–	Anticaking agent; slip modifier; viscosity increasing agent-nonaqueous
Potassium cocoate (CAS No. 61789-30-8)	The potassium salt of coconut acid.	–	Surfactant-cleansing agent; surfactant-emulsifying agent
Sodium cocoate (CAS No. 61789-31-9)	The sodium salt of coconut acid.	–	Surfactant-cleansing agent; surfactant-emulsifying agent
Ammonium cocomonoglyceride sulfate (CAS No. 61789-03-5)	Ammonium salt of sulfated fatty acids derived from coconut oil where RCO- represents the fatty acids derived from coconut oil.		Surfactant-cleansing agent

Table 3. Material Specifications for Butylenes Glycol Cocoate, Decyl Cocoate, Hydrogenated Coco-Glycerides, and Potassium Cocoate

Specification	Butylene Glycol Cocoate	Decyl Cocoate	Hydrogenated Coco-Glycerides	Hydrogenated Coco-Glycerides	Potassium Cocoate
Source	Gattefossé 2007	Evonik Industries 1999; Evonik Industries 2008	Gattefossé 2001	Sasol 2007	Nikko Chemical Co, Ltd. 2008
Trade name	Cocoate BG	Tegosoft DC	Lipocire NA-10	Witepsol; Massa Estarinum	Nikkol MNK-40 (mixed product)
Appearance	Oil limpid liquid at 20°C	Liquid	Waxy solid	Hard fats in pastill shape	White to yellow liquid
Odor	Characteristic	Almost odorless	Faint	Odorless	Faint characteristic
Color	<2.0 (Gardner Scale)	<125.0 (Hazen); light yellow	<3.0 (Gardner Scale)	White	200 max (APHA)
Flash point	NA	>100°C	NA	NA	NA
Melting point	NA	NA	33.0-36.0°C (capillary tube) 34.0-37.0°C (drop point)	30.0-44.0°C	NA
Specific gravity	0.900-0.920 at 20°C	0.85 g/cm^3 at 25°C	NA	NA	1.010-1.060 at 20°C
Refractive index	1.440-1.460 at 20°C	NA	NA	NA	NA
Acid value	<3.0 mg KOH/g	<1.00 mg KOH/g	<0.5 mg KOH/g	0.2-1.3 mg KOH/g	NA
Free butylene glycol	<4.0%	NA	NA	NA	NA
Monoesters content	45.0-70.0%	NA	NA	NA	NA
Diesters content	30.0-55.0%	NA	NA	NA	NA
Water content	<0.20%	<0.100 %	<0.50%	NA	NA
Saponification value	NA	155.0-170.0 mg KOH/g	230-250 mg KOH/g	215-255 mg KOH/g	NA
Iodine value	NA	<10.00 g I_2/100 g	<2.0 g I_2/100 g	2-8 g I_2/100 g	NA
Hydroxyl value	NA	<5.0 mg KOH/g	<15 mg KOH/g	2-70 mg KOH/g	NA
Peroxide value	NA	<2.0 meq O_2/kg	<1.2 meq O_2/kg	1-4 meq O_2/kg	NA
Alkaline impurities	NA	NA	<30 ppm NaOH	max. 0.15 mL HCL/2 g	NA
Unsaponifiable matter content	NA	NA	<0.6%	0.3-3.0%	NA
Evaporation Residue (105°C, 90 min)	NA	NA	NA	NA	38.0-42.0%
Total ashes content	NA	NA	<0.05%	max. 0.05%	NA
Heavy metals content	NA	max. 20 ppm	<10 ppm	max. 10 ppm	20 ppm max (arsenic 2 ppm max)
Hg; As; Cd; Ni respective	NA	<1 ppm	NA	NA	NA
pH (10%)	NA	NA	NA	NA	10.0-11.0

It may contain free fatty acids, low concentrations of sterols, tocopherol, and squalene.[12] It is the presence of lactones at approximately 150 ppm that provides the characteristic coconut flavor. They are present as a series of d-lactones with 6, 8, 10, 12, or 14 carbon atoms.[18]

Other potential impurities, including polycyclic aromatic hydrocarbons (PAH) and aflatoxin contamination of raw and dried copra, have been reported and have previously been described.[1]

Use

Cosmetic

Table 4 presents the product use and concentration data for *Cocos nucifera* (coconut) oil, coconut acid, hydrogenated coconut oil, hydrogenated coconut acid, butylene glycol cocoate, caprylic/capric/coco glycerides, cocoglycerides, coconut alcohol, ethylhexyl cocoate, hydrogenated coco-glycerides, magnesium cocoate, methyl cocoate, pentaerythrityl cocoate, potassium cocoate, and sodium cocoate. The total uses of each ingredient were supplied to the Food and Drug Administration (FDA) by industry as part of the Voluntary Cosmetic Ingredient Reporting Program (VCRP). Total uses for coconut oil and coconut acid have increased significantly since the original safety assessment in 1986 in which coconut oil had 122 total uses and coconut acid had 36 uses.[1] The FDA reported that these ingredients had a total of 626 and 142 total uses, respectively, in 2007.[19]

A survey of current use concentrations was conducted by the Personal Care Products Council (Council), formerly known as the Cosmetic, Toiletry, and Fragrance Association (CTFA). No uses or concentrations were reported for the following coconut

Table 4. Cosmetic Product Uses and Concentrations for *Cocos nucifera* (Coconut) Oil and Its Derivatives

Product Category	2007 Uses (Total Number of Products in a Category)[19]	2006/2007/2008 Concentrations[32,33,34] (%)
Cocos nucifera (coconut) oil		
Baby products		
Shampoos	1 (55)	0.05
Lotions, oils, powders, and creams	5 (132)	0.3
Other	6 (138)	0.01[a]
Bath products		
Oils, tablets, and salts	–(257)	0.05-23
Soaps and detergents	130 (1329)	0.3-41
Bubble baths	1 (262)	0.04-1
Other	10 (239)	0.05-1
Eye makeup		
Eyebrow pencils	–(147)	0.4
Eyeliners	2 (684)	0.4-25
Eye shadow	1 (1196)	0.1-0.5
Eye lotion	2 (177)	0.3-80
Eye makeup remover	1 (131)	0.4
Mascara	1 (463)	0.01-0.4
Other	–(288)	0.4-43
Fragrance products		
Colognes and toilet waters	1 (1288)	0.1
Powders	1 (278)	0.1
Other	5 (399)	26
Noncoloring hair care products		
Conditioners	26 (1249)	0.0001-0.01
Sprays/aerosol fixatives	–(371)	0.3
Hair straighteners	17 (144)	2
Shampoos	22 (1403)	0.01-0.3
Tonics, dressings, etc.	22 (1097)	1-13
Other	10 (716)	–
Hair coloring products		
Dyes and colors	142 (2481)	–
Tints	1 (58)	–
Bleaches	2 (152)	–
Makeup		
Blushers	1 (539)	0.1-0.5
Face powders	–(613)	0.1
Foundations	1 (635)	0.1
Leg and body paint	1 (29)	–
Lipsticks	19 (1912)	0.2-51
Makeup bases	–(164)	0.1
Rouges	–(99)	0.4
Other	12 (406)	0.1-10
Nail care products		
Basecoats and undercoats	–(62)	2
Cuticle softeners	–(18)	0.1
Nail polishes and enamels	–(419)	0.005-0.1
Other	2 (124)	0.1-0.2[b]
Personal hygiene products		
Deodorants (underarm)	–(540)	0.1-16
Douches	–(12)	16
Feminine deodorants	–(21)	16
Other	12 (514)	0.0005-16[c]
Shaving products		
Shaving cream	10 (162)	2-9
Shaving soap	–(6)	16
Other	1 (107)	–
Skin care products		
Skin cleansing creams, lotions, liquids, and pads	16 (1368)	–
Face and neck creams, lotions, powders, and sprays	7 (1195)	0.3-10
Body and hand creams, lotions, powders, and sprays	59 (1513)	1-8[d]
Foot powders and sprays	–(48)	6
Moisturizers	43 (2039)	0.01-25
Night creams, lotions, powders, and sprays	3 (343)	2
Paste masks/mud packs	3 (418)	2
Skin fresheners	2 (285)	–
Other	10 (1244)	0.3-2[e]
Suntan products		
Suntan gels, creams, liquids, and sprays	12 (156)	0.1-50
Indoor tanning preparations	1 (200)	0.5
Other	2 (62)	0.5-2[f]
Total uses/ranges for *Cocos nucifera* (coconut) oil	626	0.0001-80
Coconut acid		
Baby products		
Other	1 (138)	–
Bath products		
Oils, tablets, and salts	–(257)	6
Soaps and detergents	93 (1329)	0.04-14
Other	–(239)	0.5
Eye makeup		
Eyeliner	1 (684)	–
Noncoloring hair care products		
Shampoos	2 (1403)	0.03-0.3
Makeup		
Face powders	2 (613)	–
Foundations	7 (635)	–
Personal hygiene products		
Other	1 (514)	0.04-2[g]
Shaving products		
Aftershave lotion	1 (395)	–
Shaving cream	23 (162)	6-9
Shaving soap	1 (6)	–
Skin care products		
Skin cleansing creams, lotions, liquids, and pads	4 (1368)	2-9
Face and neck creams, lotions, powders, and sprays	1 (1195)	–
Body and hand creams, lotions, powders, and sprays	1 (1513)	–
Moisturizers	1 (2039)	–
Paste masks (mud packs)	1 (418)	–
Other	2 (1244)	–
Total uses/ranges for coconut acid	142	0.03-14
Hydrogenated coconut acid		
Skin care products		

(continued)

Table 4 (continued)

Product Category	2007 Uses (Total Number of Products in a Category)[19]	2006/2007/2008 Concentrations[32,33,34] (%)
Skin cleansing creams, lotions, liquids, and pads	–(1368)	10
Moisturizers	–(2039)	6
Total uses/ranges for hydrogenated coconut acid	–	6-10
Hydrogenated coconut oil		
Baby products		
Other baby products	1 (138)	2-50
Bath products		
Soaps and detergents	1 (1329)	39
Bubble baths	–(262)	20
Other	–(239)	0.5
Eye makeup		
Eyebrow pencils	3 (147)	0.3-9
Eyeliners	5 (684)	0.8-22
Eye shadow	–(1196)	0.2-10
Eye lotion	–(177)	0.8-9
Eye makeup remover	–(131)	9
Mascara	–(463)	1-9
Other	1 (288)	1-11
Fragrance products		
Sachets	–(28)	0.3
Other	–(399)	0.3
Noncoloring hair care products		
Conditioners	2 (1249)	0.001-2
Rinses	–(47)	0.5
Shampoos	–(1403)	1
Tonics, dressings, etc.	–(1097)	0.001-0.9
Other	1 (716)	0.5
Hair coloring products		
Dyes and colors	–(2481)	0.6
Rinses	–(43)	0.5
Makeup		
Face powders	3 (613)	0.4
Foundations	4 (635)	0.6-7
Lipsticks	6 (1912)	0.7-29
Makeup bases	1 (164)	–
Other	1 (406)	0.5-2
Nail care products		
Cuticle softeners	–(18)	1
Nail creams and lotions	–(17)	0.8
Other	–(124)	2-25
Oral hygiene products		
Mouthwashes and breath fresheners	–(85)	17
Personal hygiene products		
Feminine hygiene deodorants	–(21)	1
Shaving products		
Aftershave lotions	–(395)	0.9
Shaving cream	–(162)	0.3
Shaving soap	1 (6)	–
Skin care products		
Skin cleansing creams, lotions, liquids, and pads	3 (1368)	0.06-2
Face and neck creams, lotions, powders, and sprays	4 (1195)	1-2
Body and hand creams, lotions, powders, and sprays	5 (1513)	0.7-3
Foot powders and sprays	–(48)	0.7
Moisturizers	9 (2039)	0.6
Night creams, lotions, powders, and sprays	2 (343)	0.5-2
Paste masks/mud packs	–(418)	0.5
Other	7 (1244)	1-50
Suntan products		
Suntan gels, creams, liquids, and sprays	1 (156)	–
Indoor tanning preparations	1 (200)	–
Total uses/ranges for hydrogenated coconut oil	62	0.001-50
Butylene Glycol Cocoate		
Makeup		
Foundations	–(635)	2
Skin care products		
Skin cleansing creams, lotions, liquids, and pads	1 (1368)	–
Moisturizers	–(2039)	1
Other	–(1244)	1[h]
Total uses/ranges for butylene glycol cocoate	1	1-2
Caprylic/capric/coco glycerides		
Skin care products		
Face and neck creams, lotions, powders, and sprays	–(1195)	4
Total uses/ranges for caprylic/capric/coco glycerides	–	4
Cocoglycerides		
Baby products		
Lotions, oils, powders, and creams	2 (132)	2
Bath products		
Other	1 (239)	–
Eye makeup		
Eyeliner	1 (684)	10
Eye lotion	1 (177)	5
Fragrance products		
Other	1 (399)	–
Makeup		
Foundations	1 (635)	–
Lipsticks	2 (1912)	6-14
Personal hygiene products		
Other	–(514)	3[i]
Skin care products		
Skin cleansing creams, lotions, liquids, and pads	8 (1368)	–
Face and neck creams, lotions, powders, and sprays	5 (1195)	1
Body and hand creams, lotions, powders, and sprays	5 (1513)	4-13
Moisturizers	2 (2039)	2

(continued)

Table 4 (continued)

Product Category	2007 Uses (Total Number of Products in a Category)[19]	2006/2007/2008 Concentrations[32,33,34] (%)
Night creams, lotions, powders, and sprays	3 (343)	0.2
Other	3 (1244)	–
Suntan products		
Suntan gels, creams, liquids, and sprays	1 (156)	5
Other	3 (62)	–
Total uses/ranges for cocoglycerides	39	0.2-14
Coconut alcohol		
Bath products		
Soaps and detergents	1 (1329)	–
Noncoloring hair care products		
Shampoos	2 (1403)	–
Personal hygiene products		
Other	–(514)	0.8[j]
Shaving products		
Shaving cream	1 (162)	–
Skin care products		
Face and neck creams, lotions, powders, and sprays	1 (1195)	0.9
Moisturizers	1 (2039)	–
Night creams, lotions, and powders	–(343)	0.8
Other	–(1244)	0.2[k]
Total uses/ranges for coconut alcohol	6	0.2-0.9
Ethylhexyl cocoate		
Baby products		
Baby lotions, oils, powders and creams	–(132)	5
Bath products		
Bath oils, tablets and salts	–(257)	6
Eye makeup		
Eye shadow	1 (1196)	0.2
Eye lotion	–(177)	0.02
Other eye makeup preparations	4 (288)	–
Noncoloring hair care products		
Conditioners	1 (1249)	–
Tonics, dressings, etc.	1 (1097)	–
Makeup		
Foundations	1 (635)	0.1-6
Lipsticks	–(1912)	0.01-19
Makeup bases	1 (164)	–
Personal hygiene products		
Underarm deodorants	–(540)	5
Shaving products		
Aftershave lotion	1 (395)	–
Skin care products		
Skin cleansing creams, lotions, liquids, and pads	–(1368)	3-5
Face and neck creams, lotions, powders, and sprays	2 (1195)	5-41
Body and hand creams, lotions, powders, and sprays	2 (1513)	7-39[l]
Moisturizers	3 (2039)	3-4
Night creams, lotions, powders, and sprays	–(343)	3-8
Suntan products		
Suntan gels, creams, liquids, and sprays	1 (156)	4-10
Total uses/ranges for ethylhexyl cocoate	18	0.01-41
Hydrogenated coco-glycerides		
Bath products		
Soaps and detergents	1 (1329)	–
Bath oils, tablets, and salts	1 (257)	–
Eye makeup		
Eyebrow pencil	11 (147)	–
Eyeliners	58 (684)	12-23
Eye shadow	14 (1196)	5-23
Eye lotion	–(177)	0.8
Eye makeup remover	–(131)	4
Other	10 (288)	0.01-31[m]
Makeup		
Blushers	3 (539)	0.3-2
Face powders	8 (613)	0.04-10
Foundations	9 (635)	0.4
Lipsticks	18 (1912)	0.5-24
Makeup bases	1 (164)	–
Other	10 (406)	0.3-12[n]
Nail care products		
Nail polish and enamel	–(419)	0.08
Personal hygiene products		
Other	1 (514)	2[o]
Shaving products		
Shaving cream	1 (162)	–
Skin care products		
Skin cleansing creams, lotions, liquids, and pads	1 (1368)	–
Face and neck creams, lotions, powders, and sprays	5 (1195)	6
Body and hand creams, lotions, powders, and sprays	8 (1513)	0.02-4
Moisturizers	15 (2039)	1-5
Night creams, lotions, powders, and sprays	5 (343)	3
Paste masks (mud packs)	–(418)	3
Other	9 (1244)	–
Suntan products		
Indoor tanning preparations	3 (200)	–
Total uses/ranges for hydrogenated coco-glycerides	192	0.01-31
Magnesium cocoate		
Bath products		
Soaps and detergents	11 (1329)	–
Total uses/ranges for magnesium cocoate	11	–
Methyl cocoate		
Bath products		
Soaps and detergents	–(1329)	0.04

(continued)

(continued)

Table 4 (continued)

Product Category	2007 Uses (Total Number of Products in a Category)[19]	2006/2007/2008 Concentrations[32,33,34] (%)
Noncoloring hair care products		
Shampoos	42 (1403)	0.05
Other hair preparations	5 (716)	–
Personal hygiene products		
Other personal cleanliness products	1 (514)	–
Skin care products		
Skin cleansing creams, lotions, liquids, and pads	–(1368)	0.06
Other skin care preparations	1 (1244)	–
Total uses/ranges for methyl cocoate	49	0.04-0.06
Pentaerythrityl cocoate		
Skin care products		
Face and neck creams, lotions, powders, and sprays	1 (1195)	–
Total uses/ranges for pentaerythrityl cocoate	1	–
Potassium cocoate		
Bath products		
Soaps and detergents	11 (1329)	0.3-40
Bubble baths	–(262)	0.2
Noncoloring hair care products		
Shampoos	2 (1403)	15
Hair coloring products		
Tints	–(58)	0.003
Other	–(166)	0.003
Personal hygiene products		
Deodorants (underarm)	–(540)	0.3
Douches	–(12)	0.3
Feminine hygiene deodorants	–(21)	0.3
Other	3 (514)	0.3
Shaving products		
Shaving cream	3 (162)	7
Shaving soap	1 (6)	–
Skin care products		
Skin cleansing creams, lotions, liquids, and pads	4 (1368)	28
Total uses/ranges for potassium cocoate	24	0.003-40
Sodium cocoate		
Baby products		
Other	2 (138)	–
Bath products		
Soaps and detergents	146 (1329)	1-52
Bubble baths	3 (262)	–
Fragrance products		
Other	1 (399)	–
Noncoloring hair care products		
Conditioners	1 (1249)	–
Shampoos	48 (1403)	2
Tonics, dressings, etc.	1 (1097)	–
Other	5 (716)	–
Personal hygiene products		
Other	1 (514)	1-2
Shaving products		
Aftershave lotion	1 (395)	–
Shaving cream	2 (162)	6
Shaving soap	1 (6)	24
Skin care products		
Skin cleansing creams, lotions, liquids, and pads	16 (1368)	–
Paste masks (mud packs)	1 (418)	–
Other skin care preparations	1 (1244)	–
Total uses/ranges for sodium cocoate	230	1-52

[a] 0.01% in baby wipes.
[b] 0.1% in a nail brightener.
[c] 0.0005% in a body wash.
[d] 1% in body and hand sprays.
[e] 0.3% in a body mousse.
[f] 2% in a tanning oil spray.
[g] 0.08% in a liquid hand soap; 2% in a body wash.
[h] 1% in a lip moisture cream.
[i_tbl4] 3% in a body scrub.
[i] 0.8% in a body wash.
[k] 0.2% in an exfoliating cream.
[l] 16% in a body and hand spray.
[m] 2% in a concealor; 8% in a brow powder wax.
[n] 0.5% in a lip cream; 8% and 12% in lip pencils.
[o] 2% in a body scrub.

oil-derived ingredients: ammonium cocomonoglyceride sulfate, coconut oil decyl esters, decyl cocoate, lauryl cocoate, octyldodecyl cocoate, potassium hydrogenated cocoate, sodium cocomonoglyceride sulfate, sodium hydrogenated cocoate, and tridecyl cocoate.

Because coconut oil and its related ingredients are used in sprays, the effects of aerosol on safety has to be considered. The potential adverse effects of inhaled aerosols depend on the specific chemical species, the concentration, the duration of the exposure, and the site of deposition within the respiratory system.[20] In general, the smaller the particle, the further into the respiratory tree the particle will deposit and the greater the impact on the respiratory system.

Anhydrous hair spray particle diameters of 60 to 80 μm have been reported, and pump hair sprays have particle diameters of ≥80 μm.[21,22] The mean particle diameter is around 38 μm in a typical aerosol spray. In practice, aerosols should have at least 99% of particle diameters in the 10 to 110 μm range. This means that most aerosol particles are deposited in the nasopharyngeal region and are not respirable. Cosmetics that contain coconut oil and related substances are applied to all areas of the skin, including mucous membranes. These cosmetics are frequently applied to the face and have the potential for coming into contact with the eyes or being ingested from the lips. Products containing these ingredients may be applied up to several times a day and can remain in contact with the skin for long periods of time.

Coconut oil and the derivatives discussed in this report are not included among the substances listed as prohibited, restricted, or provisionally allowed in the use of cosmetic products marketed in Japan.[23,24] In addition, coconut oil and its

derivatives are not restricted from use in any way under the rules governing cosmetic products in the European Union.[25]

Noncosmetic Use

Coconut oil is used in the manufacturing of soaps, edible fats, chocolate, candies, candles, and night lights.[11] It is also used in place of lard in baking, in cotton dyeing, and as a base for ointments. The FDA has determined that coconut oil is a food additive permitted for direct addition to food for human consumption as a substitute for cocoa butter.[26] Coconut oil is also listed as a substance generally recognized as safe (GRAS) by the FDA in food packing material.[27] Hydrogenated coco-glycerides are hard fats used in a pharmaceutical products as an excipient in suppositories.[28]

Absorption, Distribution, Metabolism, Excretion

No new bioavailability data relevant to cosmetic use of coconut oil was available.

Animal Toxicology

The previous safety assessment concluded that coconut oil and hydrogenated coconut oil are relatively nontoxic by ingestion and that hydrogenated coconut oil was nontoxic, nonirritating, and not a sensitizer.[1]

Genotoxicity

The genotoxic potential of saponified coconut oil (SCO) in several prokaryote systems has been studied.[29] A plasmid treated with SCO did not have DNA strand breaks. Treatment of wild-type and repair deficient CC104 with SCO resulted in moderate cytotoxicity in the wild-type strain. Saponified coconut oil was not able to induce SOS function in *Escherichia coli* strains PQ35 and PQ37. In an Ames test conducted without metabolic activation, SCO was not mutagenic for *Salmonella typhimurium* strain TA98, but it displayed mutagenic potential for strains TA100 and TA104. The authors concluded that the cytotoxic, antioxidant, and mutagenic effects of SCO can be influenced by the aggregational state.

Clinical Assessment of Safety

Skin Irritation

The skin irritation potential of potassium cocoate in participants with preexisting dermatitis was assessed.[30] The skin of 40 healthy volunteers and 480 participants with active skin diseases were patch tested with 15 μL of 5% aqueous potassium cocoate. Positive responses were observed in 5 participants (0.9%). Intensities of the positive responses were not reported; however, 2 participants had active psoriasis and 3 had active eczema.

Skin Sensitization

Coconut oil was not an allergen at 100% concentration in 12 participants in a double-blind randomized controlled pilot study.[31] The participants had known allergic reactions to cocamidopropyl betaine (CAPB) and were patch tested with several coconut oil derivatives to determine whether reactions were due to cross-reactivity and allergenicity to surfactants containing these ingredients.

Summary

Use concentrations were reported for the following: butylene glycol cocoate, caprylic/capric/coco glycerides, cocoglycerides, coconut acid, coconut alcohol, *Cocos nucifera* (coconut) oil, ethylhexyl cocoate, hydrogenated coco-glycerides, hydrogenated coconut acid, hydrogenated coconut oil, magnesium cocoate, methyl cocoate, pentaerythrityl cocoate, potassium cocoate, and sodium cocoate. Coconut oil had the greatest number of uses reported by the FDA with 626. The use concentration range for coconut oil was 0.0001% to 70%. Coconut oil and its derivatives are not restricted for use in the European Union or Japan.

Coconut oil is used in the manufacturing of soaps, edible fats, chocolate, candies, candles, and night lights. It is also used in place of lard in baking, in cotton dyeing, and as a base for ointments.

The genotoxic potential of SCO was evaluated in several prokaryote systems. This study found that the cytotoxic, antioxidant, and mutagenic effects of SCO can by influenced by the aggregational state.

The skin irritation potential of potassium cocoate in participants with preexisting dermatitis was assessed. Positive responses were observed in 0.9% of the participants. Coconut oil was not an allergen at 100% concentration in 12 participants in a double-blind randomized controlled pilot study. Coconut oil was evaluated for its therapeutic potential in several studies.

Discussion

The Expert Panel recognized that there are numerous animal and clinical studies on the health effects of dietary fats such as coconut oil and hydrogenated coconut oil. These dietary fat studies were not included in this safety assessment, however, because they have little relevance in regard to the use of coconut oil and hydrogenated coconut oil in cosmetic ingredients because of the lack of absorption via dermal application. The Expert Panel considered that the available acute, subchronic, chronic, ocular, dermal, and clinical toxicity data are adequate to support the safety of coconut acid, coconut oil, hydrogenated coconut acid, and hydrogenated coconut oil. The original safety assessment of the coconut oil group of ingredients did include oral toxicity studies that formed part of the basis for the determination of safety, along with animal and human dermal irritation and sensitization data. The

conclusion that the original group of ingredients is safe for use as cosmetic ingredients is reaffirmed.

While very few toxicity studies were identified specifically in the published literature for the additional salts and esters that were added to this safety assessment, there is no reason to expect the salts and esters to differ in toxicity from coconut oil, coconut acid, hydrogenated coconut oil, and hydrogenated coconut acid. The salts and esters of the expanded group of coconut ingredients are expected to have similar toxicological profiles as the regular and hydrogenated forms of the oil and the acid. In solution, the salts are expected to dissociate in any product formulation independent of whether the salt is sodium, ammonium, magnesium, or potassium. The esters likely will break down into their component parts, none of which present any safety issues, for example, lauryl alcohol and coconut fatty acids for lauryl cocoate. The coconut-derived ingredients that have been added to this safety assessment do not have any functional groups that pose any significant toxicity. Fatty alcohols of corresponding fatty acids present no safety issues in the experience of the CIR Expert Panel. Accordingly, the available data for coconut acid, coconut oil, hydrogenated coconut acid, and hydrogenated coconut oil are considered supportive of the safety of the expanded group of derivatives as used in cosmetics. Therefore, the Expert Panel determined that the toxicity data on coconut acid, coconut oil, hydrogenated coconut acid, and hydrogenated coconut oil could be extrapolated to include: ammonium cocomonoglyceride sulfate, butylene glycol cocoate, caprylic/capric/coco glycerides, cocoglycerides, coconut alcohol, coconut oil decyl esters, decyl cocoate, ethylhexyl cocoate, hydrogenated coco-glycerides, isodecyl cocoate, lauryl cocoate, magnesium cocoate, methyl cocoate, octyldodecyl cocoate, pentaerythrityl cocoate, potassium cocoate, potassium hydrogenated cocoate, sodium cocoate, sodium cocomonoglyceride sulfate, sodium hydrogenated cocoate, and tridecyl cocoate.

The Expert Panel recognizes that use concentration data are not available for all ingredients in this group and that some ingredients in this group are not in current use. The Panel considers that the use concentrations for the ingredients that are in use are not likely to be different from the use concentration for coconut oil, coconut acid, hydrogenated coconut acid, and hydrogenated coconut oil. Were those ingredients not in current use to be used in the future, the Panel expects that they would be used in products and at concentrations similar to those reported for the coconut oil and coconut acid ingredients.

While aflatoxin contamination of raw and dried copra has been reported, the Panel believes that aflatoxin should not be present in coconut oil and ingredients derived from *Cocos nucifera*; the Panel adopted the USDA designation of <15 ppb as corresponding to "negative" aflatoxin content.

In the absence of inhalation toxicity data, the Panel determined that coconut oil and its derivatives can be used safely in hair sprays, because the product particle size is not respirable. The Panel reasoned that the particle size of aerosol hair sprays ($\sim$38 μm) and pump hair sprays (>80 μm) is large compared to respirable particulate sizes ($\leq$10 μm).

The Expert Panel expressed concern regarding pesticide residues and heavy metals that may be present in botanical ingredients. They stressed that the cosmetics industry should continue to use the necessary procedures to limit these impurities in the ingredient before blending into cosmetic formulation.

Amended Conclusion

The CIR Expert Panel concludes that ammonium cocomonoglyceride sulfate, butylene glycol cocoate, caprylic/capric/coco glycerides, cocoglycerides, coconut acid, coconut alcohol, coconut oil decyl esters, *Cocos nucifera* (coconut) oil, decyl cocoate, ethylhexyl cocoate, hydrogenated coco-glycerides, hydrogenated coconut acid, hydrogenated coconut oil, isodecyl cocoate, lauryl cocoate, magnesium cocoate, methyl cocoate, octyldodecyl cocoate, pentaerythrityl cocoate, potassium cocoate, potassium hydrogenated cocoate, sodium cocoate, sodium cocomonoglyceride sulfate, sodium hydrogenated cocoate, and tridecyl cocoate are safe for use as cosmetic ingredients Were ingredients in this group not in current use to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in the group.

Authors Note

Unpublished sources cited in this report are available from the Director, Cosmetic Ingredient Review, 1101 17th St., Suite 412, Washington, DC 20036, USA.

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Conflict of Interest

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Memorandum

TO: F. Alan Andersen, Ph.D.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Halyna Breslawec, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: January 23, 2013

SUBJECT: Concentration of Use by FDA Product Category: Alkyl Sulfosuccinate Salts

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Concentration of use by FDA Product Category*

Ammonium Dinonyl Sulfosuccinate
Ammonium Lauryl Sulfosuccinate
Diammonium Lauryl Sulfosuccinate
Diamyl Sodium Sulfosuccinate
Dicapryl Sodium Sulfosuccinate
Diethylhexyl Sodium Sulfosuccinate
Diheptyl Sodium Sulfosuccinate
Dihexyl Sodium Sulfosuccinate
Diisobutyl Sodium Sulfosuccinate
Dipotassium Lauryl Sulfosuccinate
Disodium Cetearyl Sulfosuccinate
Disodium Cetyl Sulfosuccinate
Disodium Coco-Sulfosuccinate
Disodium Isodecyl Sulfosuccinate
Disodium Isostearyl Sulfosuccinate
Disodium Lauryl Sulfosuccinate
Disodium Oleyl Sulfosuccinate
Disodium Stearyl Sulfosuccinate
Disodium Tridecylsulfosuccinate
Ditridecyl Sodium Sulfosuccinate

Ingredient	**FDA Code†**	**Product Category**	**Maximum Concentration of Use**
Ammonium Lauryl Sulfosuccinate	05F	Shampoos	1.6%
Diethylhexyl Sodium Sulfosuccinate	03A	Eyebrow pencil	2.8-4.4%
Diethylhexyl Sodium Sulfosuccinate	03B	Eyeliner	0.06-4.2%
Diethylhexyl Sodium Sulfosuccinate	05B	Hair sprays aerosol pump spray	 0.15% 0.25%
Diethylhexyl Sodium Sulfosuccinate	05F	Shampoos (noncoloring)	0.75%
Diethylhexyl Sodium Sulfosuccinate	08E	Nail polish and enamel	1%
Diethylhexyl Sodium Sulfosuccinate	10B	Deodorants not spray	 0.0002%
Diethylhexyl Sodium Sulfosuccinate	12A	Skin cleansing (cleansing lotions, liquids and pads)	0.5-1.2%
Diethylhexyl Sodium Sulfosuccinate	12C	Face and neck products not spray	 0.2%
Diethylhexyl Sodium Sulfosuccinate	12F	Moisturizing products not spray	 0.1%
Diethylhexyl Sodium Sulfosuccinate	12H	Pastes masks and mud packs	0.1-0.5%
Diethylhexyl Sodium Sulfosuccinate	12J	Other skin care preparations	0.083%
Disodium Lauryl Sulfosuccinate	05F	Shampoos (noncoloring)	0.4-3.5%
Disodium Lauryl Sulfosuccinate	06A	Hair dyes and colors (all types requiring caution statement and	1.1%

		patch test)	
Disodium Lauryl Sulfosuccinate	06G	Hair bleaches	0.04%
Disodium Lauryl Sulfosuccinate	10A	Bath soaps and detergents	3%
Disodium Lauryl Sulfosuccinate	10E	Other personal cleanliness products	1.9%
Disodium Lauryl Sulfosuccinate	12A	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.00004-7%
Disodium Lauryl Sulfosuccinate	12J	Other skin care preparations	2-3%

*Ingredients included in the title of the table but not found in the table were included in the concentration of use survey, but no uses were reported.
†Product category codes used by FDA

Information collected in 2012
Table prepared January 23, 2013