Safety Assessment of Squalane and Squalene as Used in Cosmetics

Status:	Re-Review for Panel Review
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Panel Meeting Date:	April 8-9, 2019

The 2019 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D., Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Monice M. Fiume, Senior Director.

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Cosmetic Ingredient Review

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Monice M. Fiume *MMF*
Senior Director
Date: March 15, 2019
Subject: Re-Review of the Safety Assessment of Squalane and Squalene

The CIR Expert Panel first reviewed the safety of Squalane and Squalene in 1982. The Panel concluded that "both Squalane and Squalene are safe as cosmetic ingredients in the present practices of use and concentration," as described in that report (identified as *squal042019orig* in the pdf). In 2001, after considering new studies and updated use data on these two ingredients, the Panel determined to not re-open the safety assessment (*squal042019RR1sum*). The minutes from the Panel deliberations of that re-review are included (*squal042019min_RR1*). Minutes from the deliberations of the original review are unavailable.

Because it has been at least 15 years since the first re-review summary was published, in accord with CIR Procedures, the Panel should again consider whether the safety assessment of Squalane and Squalene should be re-opened. An exhaustive search of the world's literature was performed for studies dated 1995 forward. A brief synopsis of the relevant data is enclosed (*squal042019new data*).

Also included for your review are current and historical use data (*squal042019use tbl*). The frequency of use has increased significantly for both ingredients since the initial re-review was considered. According to VCRP data, Squalane and Squalene were reported to be used in 595 and 29 formulations, respectively, in 2001. In 2019, the VCRP indicates that Squalane is used in 2785 formulations, and Squalene is used in 527 formulations (*squal042019FDA*). For Squalane, the current maximum concentration of use (96.8%) is the same as that reported in 2001 (97%); however, the maximum concentrations of use by exposure type (e.g., eye area, nails) have increased for some categories. The opposite is true for Squalene; the maximum concentration of use has decreased since the previous re-review. In 2001, Squalene was used at up to 10%; data received in 2018 report that the maximum concentration of use is 1.2% (*squal042019conc*).

A data profile is included for the original (1982) report (*squal042019prof_orig rpt*). Also included are the FDA VCRP data (*squal042019FDA*) and the concentration of use data that were submitted in response to a Council survey (*squal042019conc*)

If, upon review of the new studies and updated use data, the Panel determines that a re-review is warranted, a full draft amended report will be presented at an upcoming meeting.

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Original (1982) Squalane and Squalene Report Data Profile* – April 2019 – Monice Fiume

				Toxicokinetics			Acute Tox			Repeated Dose Tox			DART		Genotox		Carci		Dermal Irritation			Dermal Sensitization				Ocular Irritation		Clinical Studies	
	Reported Use	Method of Mfg	Impurities	log P/log K_{ow}	Dermal Penetration	ADME	Dermal	Oral	Inhalation	Dermal	Oral	Inhalation	Dermal	Oral	In Vitro	In Vivo	Dermal	Oral	In Vitro	Animal	Human	In Vitro	Animal	Human	Phototoxicity	In Vitro	Animal	Retrospective/ Multicenter	Case Reports
Squalane	X	X	X		X	X		X	X			X								X	X			X			X		
Squalene	X	X	X			X		X									X				X								

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

Squalene & Squalene RR

Ingredient	CAS #	SciFin	PubMed	FDA	EU	ECHA	SIDS	ECETOC	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	NIOSH	Web
Squalane	111-01-3	similar to PubMed results	results below	---	noR	dossier – but no info			---	---	---	---				
Squalene	111-02-4 7683-64-9			---	noR	---				---	---	1990 genotox				

Squalene & Squalane – published in 1982 (safe as used); RR not reopened in 2001

Search Strategy/PubMed – 2/13/19 - from 1995 on

((((((Squalane) OR 111-01-3[EC/RN Number]) OR squalene) OR 111-02-4[EC/RN Number]) OR 7683-64-9[EC/RN Number])) AND ("1995"[Date - Publication] : "3000"[Date - Publication]) – 3245 hits

(((((((Squalane) OR 111-01-3[EC/RN Number]) OR squalene) OR 111-02-4[EC/RN Number]) OR 7683-64-9[EC/RN Number])) AND ("1995"[Date - Publication] : "3000"[Date - Publication])) AND toxic* - 239 hits

(((((((Squalane) OR 111-01-3[EC/RN Number]) OR squalene) OR 111-02-4[EC/RN Number]) OR 7683-64-9[EC/RN Number])) AND ("1995"[Date - Publication] : "3000"[Date - Publication])) AND (dermal* OR irrita* OR sensitiz* OR cancer OR carcinogen* OR muatgen* OR genotoxic*) – 318 hits

(((((((Squalane) OR 111-01-3[EC/RN Number]) OR squalene) OR 111-02-4[EC/RN Number]) OR 7683-64-9[EC/RN Number])) AND ("1995"[Date - Publication] : "3000"[Date - Publication])) AND ((toxicokinetic* OR metabolism OR metabolite OR absorp* OR absorb* OR excret*) AND dermal) – 6 hits

(((((((Squalane) OR 111-01-3[EC/RN Number]) OR squalene) OR 111-02-4[EC/RN Number]) OR 7683-64-9[EC/RN Number])) AND ("1995"[Date - Publication] : "3000"[Date - Publication])) AND ((toxicokinetic* OR metabolism OR metabolite OR absorp* OR absorb* OR excret*) AND oral) – 74 hits

(((((((Squalane) OR 111-01-3[EC/RN Number]) OR squalene) OR 111-02-4[EC/RN Number]) OR 7683-64-9[EC/RN Number])) AND ("1995"[Date - Publication] : "3000"[Date - Publication])) AND ((toxicokinetic* OR metabolism OR metabolite OR absorp* OR absorb* OR excret*) AND oral) – 24 hits

Squalane alone – 324 hits

(((squalene) OR 111-02-4[EC/RN Number]) OR 7683-64-9[EC/RN Number]) AND (dermal OR topical OR oral) – 191 hits

Minutes from the 1st Re-Review of Squalene and Squalane – September 10-11, 2001

Dr. Belsito noted that a CIR Final Report with the following conclusion on Squalene and Squalane was published in 1982: On the basis of the available information presented in this report, the Expert Panel concludes that both Squalane and Squalene are safe as cosmetic ingredients in the present practices of use and concentration.

After reviewing summaries of studies published since the Final Report was issued and considering that Squalene is a normal constituent of the skin, Dr. Belsito noted that his Team determined that the original safety assessment on Squalene and Squalane does not need to be reopened.

Dr. Bergfeld asked if the Panel has any concerns that need to be addressed in a discussion that would be included in the Annual Review.

Dr. Belsito stated that the results of one study indicated that UVB-peroxidated Squalene inhibited the induction of contact hypersensitivity to DNFB. However, he noted that emphasis should not be placed on this study in any discussion that is developed because Squalene is a normal constituent of the skin, and the inhibition of DNFB-induced contact hypersensitivity observed in the study was caused by UVB-peroxidated Squalene.

Dr. Belsito added that even if Squalene were peroxidated on the skin in the presence of UV light, the amount of Squalene normally in the skin would probably be greater than the amount of Squalene that would get into the skin.

Dr. Bergfeld noted that the re-review document contains a number of studies on the anti-tumor activity of Squalene. She then asked whether anti-inflammatory (inhibition of DNFB-induced contact hypersensitivity) and anti-tumor effects of Squalene should be addressed in a discussion.

Drs. Slaga and Snyder recommended that the case study on Gulf War Syndrome patients with antibodies to Squalene (Asa et al., 2000) be deleted from the re-review document because it is not considered relevant.

Dr. Andersen said that if information from the re-review document will be presented in an Annual Review, it would be difficult to justify deleting this study from the reference list. However, he noted that the reason why the study should not be discussed in the Annual Review is apparent.

The Panel agreed that a discussion does not need to be developed, and unanimously concluded that the Panel's original safety assessment on Squalene and Squalane does not need to be reopened and that the conclusion should not be changed.

Current and historical frequency and concentration of use of Squalane and Squalene according to duration and exposure

	# of Uses		*Max Conc of Use (%)*	
	SQUALANE			
	2019[1]	**2001[2]**	**2018[3]**	**2001[2]**
Totals*	**2785**	**595**	**0.0001-96.8**	**0.01 – 97**
Duration of Use				
Leave-On	*2608*	*541*	*0.0001 - 96.8*	*0.01 – 97*
Rinse-Off	*171*	*54*	*0.0001 - 34.9*	*0.1 – 5*
Diluted for (Bath) Use	*6*	*NR*	*0.14*	*NR*
Exposure Type				
Eye Area	366	42	0.0001 – 38	0.01 – 15
Incidental Ingestion	253	52	0.001 – 22.8	3 – 17
Incidental Inhalation-Spray	spray: 12 possible: 772[a]; 656[b]	spray: 12 possible: 170[a]; 68[b]	spray: 0.048 – 0.15 possible: 0.005 – 12[a]	possible: 0.3 – 36[a]; 0.1 – 97[b]
Incidental Inhalation-Powder	powder: 107 possible: 656[b]; 11[c]	powder: 28 possible: 68[b]; 2[c]	powder: 1 – 3.4 possible: 0.01 – 40.1	powder: 3 – 9 possible: 0.1 – 97[b]
Dermal Contact	2447	510	0.0001 – 85.4	0.1 – 97
Deodorant (underarm)	3[a]	NR	0.18 – 4	NR
Hair - Non-Coloring	69	17	0.001 – 2.3	0.8 – 5
Hair-Coloring	NR	NR	NR	NR
Nail	4	6	0.0001 – 96.8	NR
Mucous Membrane	277	63	0.001 – 22.8	0.1 – 17
Baby Products	11	2	0.03 - 2	NR

	SQUALENE			
	2019[1]	**2001[2]**	**2018[3]**	**2001[2]**
Totals*	**527**	**29**	**0.004 – 1.2**	**0.01 – 10**
Duration of Use				
Leave-On	*300*	*26*	*0.0045 – 0.7*	*0.02 – 10*
Rinse-Off	*215*	*2*	*0.004 – 1.2*	*0.01 – 0.5*
Diluted for (Bath) Use	*12*	*1*	*NR*	*0.2*
Exposure Type				
Eye Area	19	NR	0.0046 – 0.07	0.5 – 0.7
Incidental Ingestion	71	NR	0.0045 – 0.09	0.7
Incidental Inhalation-Spray	spray: 1 possible: 102[a]; 67[b]	possible: 9[a]; 13[b]	possible: 0.07[a]	possible: 0.06 – 0.5[a]; 0.08 – 0.5[b]
Incidental Inhalation-Powder	powder: 2 possible: 67[b]; 2[a]	possible: 13[b]	possible: 0.05 – 0.7	powder: 10 possible: 0.08 – 0.5[b]
Dermal Contact	453	29	0.004 – 0.7	0.02 – 10
Deodorant (underarm)	NR	NR	0.06	NR
Hair - Non-Coloring	3	NR	0.07 – 1.2	0.01
Hair-Coloring	NR	NR	0.2	NR
Nail	NR	NR	NR	NR
Mucous Membrane	288	1	0.004 – 0.09	0.2 – 0.7
Baby Products	2	NR	NR	NR

*Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.
[a] It is possible these products are sprays, but it is not specified whether the reported uses are sprays.
[b] Not specified whether a spray or a powder, but it is possible the use can be as a spray or a powder, there fore the information is captured in both categories
[c] It is possible these products are powders, but it is not specified whether the reported uses are powders.
NR – not reported

REFERENCES

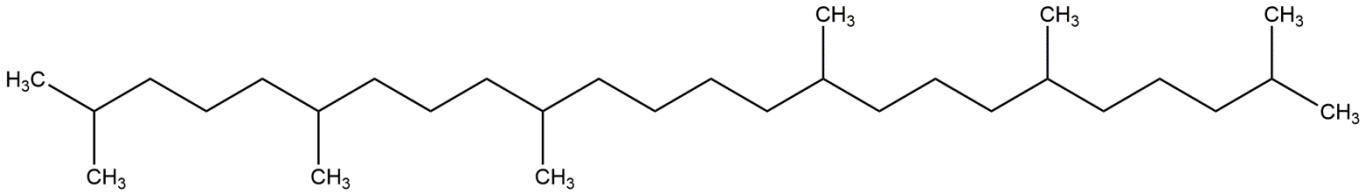
1. US Food and Drug Administration (FDA) Center for Food Safety & Applied Nutrition (CFSAN). 2019. Voluntary Cosmetic Registration Program (VCRP) - Frequency of Use of Cosmetic Ingredients. College Park, MD (Obtained under the Freedom of Information Act from CFSAN; requested as "Frequency of Use Data" January 3 2019; received February 13, 2019.)

2. Andersen F.A. (ed). Squalene and Squalane. *Int J Toxicol* 2003;22:27-31.

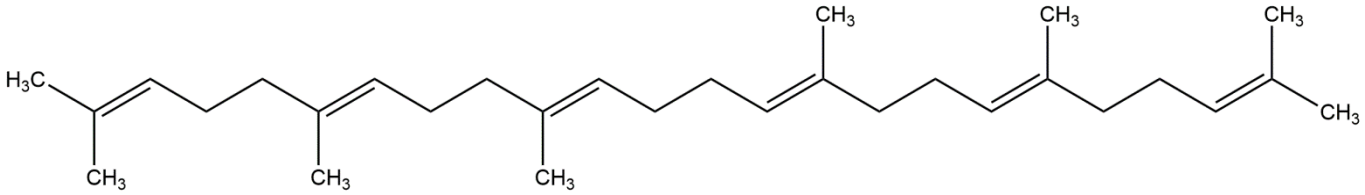
3. Personal Care Products Council. 2018. Council Concentration of Use by FDA Product Category: Squalande and Squalene. (Unpublished data submitted by the Personal Care Products Council on June 1, 2018.)

New Data – Squalane and Squalene

Structures



Squalane



Squalene

Method of Manufacture

Squalane

Squalane can be derived from fermentable sugars.[1] The process involves linear dimerization, hydrogenation, and purification.

Photooxidation

Squalene

Squalene is a major component of human sebum. When human skin is exposed to sunlight, photooxidation of skin surface lipids occurs, and it is believed that Squalene is the first target lipid and main source of skin lipid peroxides.[2] Squalene was oxidized efficiently by singlet oxygen derived from coproporphyrin under ultraviolet (UV) exposure, and the rate constant of Squalene peroxidation by singlet oxygen was ten-fold higher than that of other skin surface lipids examined.[3] The reaction was promoted more efficiently by long wavelength UV (UVA) than by mid-wavelength UV (UVB).

Genotoxicity

Squalene

The genotoxic potential of Squalene was assessed in vitro in a chromosomal aberration assay, sister chromatid exchange (SCE) assay, and micronucleus test in human lymphocytes, and in vitro and in vivo in a comet assay using human lymphocytes and lymphocytes from rats that were injected (route not specified) with Squalene, respectively.[4] (Rat lymphocytes were obtained 1 day and 14 days after injection.) Five different concentrations of Squalene (1250 – 20,000 µg/ml for human lymphocytes and 0.07 – 1.12 mg/kg for rat lymphocytes) were studied. Squalene was not genotoxic in the chromosomal aberration assay or micronucleus test. A significant increase in SCEs was observed with almost all concentrations at 24-h treatment. Squalene was not considered genotoxic in the comet assay in vitro; however, Squalene significantly increased comet tail length and comet tail intensity in lymphocytes taken 1 day, and especially in those taken 14 days, after injection.

Anit-Mutagenicity

Squalene

Squalene demonstrated a protective effect against doxorubicin-induced genotoxicity in vivo in the mouse micronucleus assay and comet test.[5] Squalene alone was not genotoxic in either of these tests.

Anti-Carcinogenicity

Squalene

Squalene had an inhibitory effect on 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK; a tobacco specific nitrosamine)-induced lung tumorigenesis in female A/J mice.[6] When rats were fed a diet containing 2% Squalene 3 wks prior to a single intraperitoneal (i.p.) dose of NNK, and maintained on that diet throughout the study, lung tumor multiplicity was decreased by 5%, and lung hyperplasia was decreased by 70%.

Squalene also inhibited the formation of azoxymethane (AOM)-induced colonic aberrant crypt foci (ACF) formation in rats.[7] Feeding 1% Squalene to F34 rats for 2 wks prior to a subcutaneous injection of azoxymethane (AOM) inhibited total ACF induction and crypt multiplicity by > 46%.

Dermal Irritation and Sensitization

Squalene

A 24-h occlusive patch with a cream containing 1% Squalene was applied to the volar forearm of 16 female subjects.[8] No erythema was reported. Additionally, no erythema was induced when 36 female subjects applied the cream 2x/day for 21 days.

The sensitization potential of Squalene was assessed in both a local lymph node assay (LLNA) and a guinea pig maximization test (GPMT).[9] In the LLNA, 5 mice/group were used, and 25 µl of Squalene (10, 25, and 50% in acetone/olive oil (3:1)) was applied 1x/day for 3 days to the dorsal surface of the ear. In the GPMT, which used a test group of 10 animals, 5% Squalene was used for intradermal induction, and undiluted test material was used for topical induction and at challenge. The LLNA gave clear positive results, with a dose-response relationship. In the GPMT, two animals had sensitization reactions to Squalene.

Data on Squalene Peroxides

Hyperpigmentation

Using pigmented reconstructed human skin equivalents constructed with primary keratinocytes and melanocytes, there was an increase in pigmentation following 3-day continuous exposure to 3.4 nmol/cm^2 squalene monohydroperoxides.[10]

Squalene peroxide was applied to the shaved dorsal skin of four guinea pigs (24 nmol squalene peroxide/cm^2/day, 5 d/wk, for 3 wks).[3] Sub-erythematic redness was observed 7 - 9 days after application; this faded within 3 - 7 days. The gradual appearance of pigmentation on day 18 - 22 was observed in all four animals. Epidermal thickness and the amount of melanin were increased.

Comedogenicity

The comedogenicity of squalene peroxides was examined on rabbit ear skin after topical application of squalene-monohydroperoxide, which was obtained by irradiation of Squalene for 1 - 3 h with UVA, followed by extraction with methanol.[2] Application of the monohydroperoxide- to the ear of 3 - 4 rabbits, 3x/wk for 2 wks, produced comedogenic reactions in an irradiation time-dependent manner. Comedo formation was induced at a concentration of approximately 2 mM squalene-monohydroperoxide (which was equivalent to approximately 39 µg squalene-monohydroperoxide per cm^2 skin). However, the comedogenicity of reduced squalene-hydroxide and Squalene itself was lower than that of squalene-monohydroperoxide.

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2. Chiba K, Yoshizawa K, Makino I, Kawakami K, Onoue M. Comedogenicity of squalene monohydroperoxide in the skin after topical application. *J Toxicol Sci* 2000;25(2):77-83.

3. Ryu A, Arakane K, Koide C, Arai H, Nagano T. Squalene as a target molecule in skin hyperpigmentation caused by singlet oxygen. *Biol Pharm Bull* 2009;32(9):1504-1509.

4. Yuzbasioglu D, Unal F, Koc F, et al. Genotoxicity assessment of vaccine adjuvant squalene. *Food Chem Toxicol* 2013;56:240-246.

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3

Final Report on the Safety Assessment of Squalane and Squalene

Squalane and Squalene have been identified as natural components of human sebum. Both ingredients are used in a variety of cosmetics at concentrations ranging from ≤0.1 to > 50%.

Animal studies indicate Squalene is slowly absorbed through the skin, while both compounds are poorly absorbed from the gastrointestinal tract. The acute animal toxicity of these ingredients by all routes is low. Both compounds are nonirritants to rabbit skin and eye at 100% concentration. Formulations containing Squalene indicate it is not a significant human skin irritant or sensitizer. Limited contact sensitization tests indicate Squalene is not a significant contact allergen or irritant.

It is concluded that both Squalane and Squalene are safe as cosmetic ingredients in the present practices of use and concentration.

INTRODUCTION

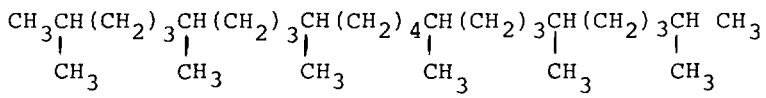
Squalane may be obtained by complete hydrogenation of shark liver oil, Squalene, or other natural oils. This material also exists as a normal constituent of human sebum in amounts up to 2.6%; next to Squalene, it is the most common hydrocarbon in these lipids. Because the human is capable of saturating Squalene, Squalane can be a biogenic product.[1-6]

The triterpene Squalene is a polyunsaturated aliphatic hydrocarbon which is widely distributed in nature. It is found in large quantities in shark liver oil, other fish oils, and in smaller amounts in olive oil, wheat germ oil, rice bran oil, yeast, and in various other foodstuffs. According to a USDA survey taken in 1965, the daily intake of Squalene in the average U.S. diet ranged from 24 to 38 mg per 2,000 calories. The principal hydrocarbon of human surface lipids, it constitutes up to 11% of total surface fat and approximately 5% of adult skin surface sebum. It has also been reported to occur in dermoid cysts, cerumen, and hair fat. In higher vertebrates and humans, it is a precursor of cholesterol. Moderate amounts are found in sites of active cholesterol synthesis, namely the liver (75 μg/g) and the small intestine (42 μg/g).[1,3,5,7-10]

CHEMICAL AND PHYSICAL PROPERTIES

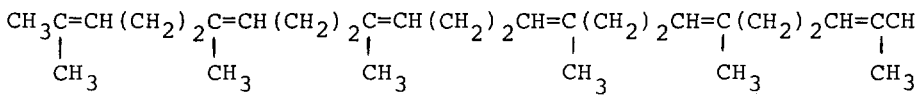
Structure

Squalane: Squalane, (2,6,10,15,19,23-hexamethyltetracosane) is the saturated branched chain hydrocarbon that conforms to the formula:



It has a molecular formula of $C_{30}H_{62}$ and a molecular weight of 422.80. Squalane is also known as dodecahydrosqualene, perhydrosqualene and spinacane.[1-3,6]

Squalene: Squalene (2,6,10,15,19,23-hexamethyl-2,6,10,14,18,22-tetracosahexaene) is a branched-chain isoprenoid hydrocarbon with six unconjugated double bonds. It conforms to the formula:



Squalene has a molecular formula of $C_{30}H_{50}$ and a molecular weight of 410.70. It is also known as spinacene.[1,3,6]

Properties

Squalane: Squalane is a colorless, odorless, tasteless, transparent oil, stable to air and oxygen. It is readily soluble in ether, gasoline, petroleum ether, benzene, chloroform, and oils. It is slightly soluble in methanol, ethanol, acetone, and glacial acetic acid. It is insoluble in water.[2,3]

Squalene: Squalene is an oil with a faint agreeable odor. It is practically insoluble in water, and freely soluble in ether, petroleum ether, carbon tetrachloride, acetone, and other lipophilic solvents. It is only sparingly soluble in alcohol and glacial acetic acid.[3]

Additional chemical and physical properties for both Squalane and Squalene are presented in Table 1.[2,3,6,11,12]

Reactivity

Squalane: No information was presented to the Panel regarding the reactivity of Squalane. Since Squalane is a saturated compound, it is not as easily oxidized as Squalene.[13]

Squalene: Squalene has the propensity towards instability, ready oxidation, and darkening, and towards becoming viscous and taking on an odor. When Squalene is exposed to air, oxygen is taken up permitting the formation of peroxides.[5,8]

TABLE 1. Chemical and Physical Properties.

	Squalane		*Squalene*	
Properties	*Reported values*	*Ref.*	*Reported values*	*Ref.*
Specific gravity at 20°C	0.805–0.812	11	0.855–0.865	11
Boiling point	approx. 350°C	3,6,11,12	approx. 335°C	11
Melting point	−38°C	3,6,12	−75°C	3
			−60°C	6
			< −20°C	12
Refractive index at 20°C	1.452–1.453	11	1.495–1.500	6,11
Flash point	approx. 230°C	11	approx. 200°C	3,11
Specific heat at 20°C	0.62 cps	3		
Viscosity at 20°C	34 cps			
Viscosity at 25°C			12 cps	3
Acid value	5.0 max.	2,11	5 max.	11
Saponification value	7.5 max.	2,11	0–5.0 max.	6,11
Iodine value	3.0 max.	11	360–380	3,6,11
Iodine no.			360–380	

In a study conducted by Rao and Achaya,[14] Squalene isolated from olive oil initially showed antioxidant properties for methyl oleate and methyl linoleate, but subsequently behaved as an oxidizing agent. Methyl oleate and linoleate solutions with initial peroxide values of 2 and 11, respectively, were incubated at 63 °C for 10 days with and without the incorporation of 0.02% Squalene and tocopherols. During the first four days, Squalene showed "good protective action" with respect to stability. For methyl oleate, the daily peroxide value increases were 7 and 22 units in the presence and absence, respectively, of 0.02% Squalene. For methyl linoleate, the corresponding figures were 11 and 50 units. Within this four-day period, Squalene had a better protective action than the same quantity of mixed tocopherols. In the subsequent six-day storage period the tocopherols continued to exert their protective effect; Squalene did not so continue. The rate of peroxide value increase for Squalene became greater than that for the control. According to the authors, "The oxidation of products of Squalene may perhaps be pro-oxidant, as has also been suggested for other polyene materials, such as carotene. Thus Squalene per se is initially an antioxidant but subsequently behaves as a pro-oxidant."

Squalene reacts exothermically at 185 °C as it begins to polymerize. This exothermic reaction increases suddenly at 300 °C. During thermal cracking, Squalene first undergoes a polymerization and then breaks down into smaller volatile molecules.[15]

Analytical Methods

Squalane: Squalane may be determined by gas chromatographic analysis.[16,17]

Squalene: Squalene may be determined by thin-layer, ion-exchange, gas, and gas–liquid chromatography.[18-22]

An early method involving the formation and isolation of squalene hexahydrochloride proved to be a very "delicate" test for the detection of Squalene.[23]

Tsukida[24] described a procedure that is particularly effective for estimating natural Squalene in the presence of other unsaturated polyenes. This involves

chromatographic separation of the dehydrogenated reaction product of Squalene with N-bromosuccinimide followed by spectrophotometric determination at 395 nm.

A method was reported by Wheatley[25] for estimating Squalene in small amounts of sebum (5 mg) and other lipids; this procedure gives an average recovery of 80% of added Squalene. Following saponification, the hydrocarbon fraction is isolated chromatographically and the unsaturated material in it is determined iodometrically.

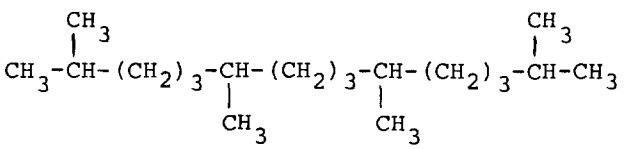
Liu and coworkers[7] described a method for measuring Squalene in human tissues and plasma; this depends on mild saponfication, extraction with petroleum ether, isolation by alumina column chromatography, and measurement by gas-liquid chromatography. Recoveries from all tissues by this technique exceeded 80%, while recoverles from plasma exceeded 96%. Losses were accurately accounted for by appropriate additions of Squalene. The lowest practical detection limit was reported to be approximately 10 ng/mg plasma.

A colorimetric method was reported by Mendelsohn and Mendelsohn[26] for the determination of Squalene in plasma. The plasma is saponified and the Squalene extracted with petroleum ether. The Squalene is then separated and purified by gel chromatography. Color is developed with o-phthalaldehyde in acetic acid + H_2SO_4 heated at 90 °C for three minutes. The color is read at 440 nm. Recovery of added Squalene by this method is 88 ± 5%.

Other reported analytical techniques include: an infrared method for the estimation of Squalene in olive oil; a quantitative colorimetric assay for Squalene eluted from silicic acid columns; a color test for the detection of Squalene on paper chromatograms; a color test for the detection of Squalene using Bezssonoff's Reagent; and a more recent method for measuring Squalene synthesis in man that involves isotope kinetics.[27-30]

Method of Manufacture and Impurities

Squalane: Squalane is obtained by molecular distillation of shark liver oil, hydrogenation of the distillate, and redistillation. This process yields a purity of at least 96% Squalane. Impurities include approximately 1% neutral fat and about 3% pristane. The latter, a stable liquid, is the saturated branched chain hyrocarbon ($C_{19}H_{40}$) that conforms to the formula:[11]



According to older sources, Squalane prepared from direct hydrogenation of shark liver oil may contain some batyl alcohol.[3,31] The latter, another cosmetic ingredient, is the monooctadecyl ether of glycerol.[1]

Squalene: Squalene is obtained by the molecular distillation of shark liver oil, which yields a purity of at least 96% Squalene. Impurities include approximately 1% neutral fat and 3% pristane.[11]

USE

Purpose and Frequency of Use in Cosmetics

Squalane: This ingredient has been in commercial use for over 25 years. Primarily, it functions as an emollient for topical application in creams, lotions, ointments, lipsticks, and other cosmetics. It is also used as a perfume fixative, as a skin lubricant, and as a base or vehicle in the production of creams and other cosmetics.[3,5,6,32,33]

Squalane is reported to be used in 294 cosmetic formulations in concentrations ranging from ≤0.1 to > 50%. It is employed in a wide variety of products including bath oils, eye makeups, hair preparations, makeup bases, lipsticks, suntan preparations, body powders, and nail products, and in cleansing, moisturizing and skin-care preparations.[34]

Squalene: Squalene has also been in use for more than 25 years, primarily as a vehicle for topical application.[5,33]

Squalene is reported to be used in 19 cosmetic formulations in concentrations ranging from ≤0.1 to > 25 to 50%. It is employed in a wide variety of products including bath preparations, eye makeup removers, blushers, and suntan preparations, and in moisturizing and skin-care products.[34]

Detailed cosmetic product formulation data for both Squalane and Squalene are presented in Table 2. Voluntary filing of product formulation data with FDA by cosmetic manufacturers and formulators 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 (1979). 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, effective concentration found in the finished product; the effective 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 two- to ten-fold error in the assumed ingredient concentration.

The presence of Squalane and Squalene in a wide variety of product types provides the opportunity for contact with most body surfaces including skin, eye, hair, nails, mucous membrane, and respiratory eipthelium; small amounts of Squalene may be ingested from lipstick.[34]

Product formulations containing Squalane or Squalene may be used from once a week to several times per day. Many of the products may be expected to remain in contact with the body for as briefly as a few minutes to as long as a few days. Each product could potentially be applied hundreds of times over the course of several years.

Noncosmetic Use

Squalane: Squalane is used as a high-grade lubricating oil and as an ingredient of watch and chronometer oils. Pharmaceutical applications include use as

TABLE 2. Product Formulation Data.[a]

Ingredient *Cosmetic product type*	*Concentration (%)*	*No. of product formulations*
Squalane		
Lotions, oils, powders, and creams	>0.1-1	2
Bath oils, tablets, and salts	>5-10	1
	>1-5	5
	>0.1-1	3
Other bath preparations	≤0.1	1
Eyeliner	>1-5	1
	>0.1-1	6
Eyeshadow	>10-25	1
	>5-10	4
	>0.1-1	3
Eye makeup remover	>1-5	1
	>0.1-1	1
Mascara	>5-10	2
	>1-5	1
Perfumes	>1-5	2
Powders (dusting and talcum) (excluding aftershave talc)	>0.1-1	1
Other fragrance preparations	>5-10	1
Hair conditioners	>1-5	2
	>0.1-1	2
Hair sprays (aerosol fixatives)	>0.1-1	2
	≤0.1	2
Permanent waves	>0.1-1	15
Rinses (noncoloring)	>0.1-1	1
Shampoos (noncoloring)	≤0.1	2
Other hair preparations	>1-5	1
Blushers (all types)	>10-25	1
	>5-10	2
	>1-5	5
	≤0.1	5
Face powders	>0.1-1	12
Foundations	>5-10	2
	>1-5	4
	≤0.1	1
Lipstick	>25-50	1
	>10-15	1
Makeup bases	>50	2
	>10-25	1
	>1-5	12
	>0.1-1	4
Rouges	>5-10	4
	>1-5	1
Other makeup preparations	>10-25	1
	>5-10	1
	>1-5	9
Cuticle softeners	>5-10	1
Nail creams and lotions	>10-25	1
Nail polish and enamel removers	>1-5	1
Other manufacturing preparations	>0.1-1	1
Other personal cleanliness products	>5-10	3
	>0.1-1	1
Cleansing (cold creams, cleansing lotions, liquids,	>25-50	1
	>10-25	1

TABLE 2. (Continued.)

Ingredient Cosmetic product type	*Concentration (%)*	*No. of product formulations*
and pads)	>5-10	2
	>0.1-1	2
Face, body and hand (excluding shaving preparations)	>25-50	4
	>5-10	4
	>1-5	1
	>0.1-1	6
Foot powders and sprays	>0.1-1	1
Moisturizing	>10-25	2
	>5-10	6
	>1-5	46
	>0.1-1	16
	≤0.1	1
Night	>25-50	4
	>10-25	2
	>5-10	7
	>1-5	11
	>0.1-1	5
Paste masks (mud packs)	>5-10	1
	>1-5	1
	≤0.1	1
Skin lighteners	>1-5	2
	>0.1-1	1
Skin fresheners	≤0.1	2
Wrinkle smoothing (removers)	>1-5	1
	≤0.1	1
Other skin care preparations	>10-25	1
	>5-10	2
	>1-5	10
	>0.1-1	3
Suntan gels, creams, and liquids	>10-25	1
	>5-10	2
	>1-5	1
	>0.1-1	1
Indoor tanning preparations	> 1-5	1
Squalene		
Other bath preparations	>0.1-1	1
Eye makeup remover	>1-5	1
Blushers (all types)	>25-50	1
Foundations	>0.1-1	1
Face, body and hand (excluding shaving preparations)	>1-5	2
	≤0.1	1
Moisturizing	>5-10	1
	>0.1-1	2
	≤0.1	3
Night	>1-5	1
Skin fresheners	≤0.1	1
Wrinkle smoothing (removers)	≤0.1	1
Other skin preparations	>1-5	1
	≤0.1	1
Suntan gels, creams, and liquids	>0.1-1	1

[a]Data from Ref. 34.

a skin lubricant, as an ingredient of suppositories, and as a carrier of lipid-soluble drugs.[3,6]

Squalene: Squalene has found use as an intermediate in the manufacture of pharmaceuticals, aromatics, organic coloring agents, rubber chemicals, and surface-active agents. It has been reported that Squalene is also employed as a bactericide. Synthetic squalene derivatives have been reported to be effective as antiulcer agents in clinical practices; however, they failed to show efficacy in large-scale clinical trials.[3,35]

BIOLOGICAL PROPERTIES

General Effects

Squalene: Sobel et al.[36] reported that undiluted Squalene on the surface of Sabourand's agar prevented multiplication of stock cultures of *Microsporum mentagrophytes, M. audouini*, and *M. tonsurans*. Inhibition was sporadic with *M. gypseum* and absent with *Aspergillus terreus*. Squalene that had a high peroxide content as a result of exposure to air was found to be more effective than pure Squalene in inhibiting in-vitro growth.

Mihay and Zackheim[37] reported that both freshly purified or oxidized Squalene exhibited no in-vitro fungistatic properties against cultures of *Trichophyton mentagrophytes, T. sulfureum, Microsporum audouini,* or *M. lanosum. Trichophyton mentagrophytes* was not inhibited in a semi-in-vitro study.

When 21,21-dimethoxyprogesterone (a bacteriostatic and fungistatic compound) was added to growth media containing *Curvularia lunata* at a concentration of 100 μg/ml, a 75–85% inhibition of radial growth was observed. When a mixture of 21,21-dimethoxyprogesterone and Squalene was added to growth media containing the organism at concentrations of 100 μg/ml and 50 μg/ml, respectively, a 65–75% inhibition of growth resulted. According to the authors, addition of Squalene to the mixture did not modify the inhibition of radial growth. In shaken cultures, the inhibition of mycelial synthesis was reversed by Squalene at concentrations between 1 and 20 μg/ml. "No clear explanation can be given for this behavior but experimental evidence obtained so far indicates that under submerged conditions, the presence of Squalene increases the conversion rate of dimethoxyprogesterone to less toxic compounds".[38]

In a study conducted by Kritchevsky et al.,[39] four groups of rabbits were maintained on various diets for seven weeks, after which they were sacrificed and the aortae examined and graded for atherosclerotic plaques. The plaques were graded on a scale from 0–4, and any doubtful plaques were classified as a plus–minus (±). The results are presented in Table 3. The authors stated that unlike cholesterol, dietary Squalene did not induce a significant increase in atheroma, even though it is a precursor in the biosynthesis of the sterol. It was suggested that prolonged feeding of Squalene may produce more atheroma or that ". . . it may develop that under no conditions of Squalene feeding can enough cholesterol be synthesized to effect the appearance of atheroma."

El Ridi et al.[40] described a Squalene-deficient diet which was satisfactory for normal growth and reproduction but inefficient for maintaining successful lactation in the albino rat. The beneficial effect of Squalene on lactation perfor-

TABLE 3. Squalene Feeding in Experimental Atherosclerosis.[a]

Diet	No. of rabbits	Avg. wt. gain (g)	Avg. liver wt. (g)	Plaques 1–4	Plaques ±	Avg. atheroma
Normal	10	328	68	0/10	1/10	0.05
Normal + oil (9%)	9	214	62	0/9	2/9	0.11
Normal + cholesterol (3%) in oil (9%)	8	84	90	8/8	0/8	2.50
Normal + Squalene (3%) in oil (9%)	8	448	91	1/8	2/8	0.25

[a]Data from Ref. 39.

mance in the rat was demonstrated by a comparison of a record of lactation efficiency in animals kept on the purified diets (lactation index 34.9 percent) with a record in similar animals given oral supplementary doses of 0.1 grams of Squalene per day (lactation index 92.1 percent).

Absorption, Metabolism, and Excretion

Squalane: Tritiated Squalane was tested for percutaneous absorption on normal and denuded skin of mice. Over a period of 60 minutes, the average quantity absorbed through the normal skin of 12 mice was 0.12 nmol/cm^2/min (3.05 μg/cm^2) with a standard error of the mean of 0.94 μg/cm^2. Over 120 minutes, the average quantity absorbed through the normal skin of five mice was 0.103 nmol/cm^2/min (5.25 μg/cm^2) with a standard error of the mean of 1.65 μg/cm^2. On the denuded skin of nine mice, the average rate of absorption was 0.148 nmol/cm^2/min (3.75 μg/cm^2) over 60 minutes with a standard error of the mean of 1.2 μg/cm^2. To account for the slight percutaneous absorption, the authors concluded that the main barrier to penetration of Squalane resulted from failure to be removed from the dermis via circulation.[41]

Using an autoradiographic technique, Wepierre[42] showed that tritiated Squalene is able to penetrate mouse skin and migrate via hair follicles into the sebaceous glands. It was found that the compound is not systemically absorbed even when the epidermal barrier is removed.

When it was orally administered in bulk as a solution in corn oil, or fed as a mixture with the standard diet wafer, Squalane was not absorbed from the gastrointestinal tract of rats. Ninety-six to 100% of the Squalane administered to both fed and fasted animals was recovered in the feces collected over a four-day period. Squalane was not detected in the 72-hour urine of 400 g rats given 85 mg doses by stomach tube. Bile collected for eight hours and lymph collected for five hours after administration contained no detectable amounts of Squalane. Seventy-two hours after administration of Squalane, only 120 ± 10 μg (14% of the dose) was recovered from extracts of the gastrointestinal tract.[43,44]

Ingredients commonly used in cosmetic formulations (hydrocarbons of high molecular weight, alcohols, esters, fatty acids and silicones) were studied for possible assimilation by various microorganisms. The microorganisms used in the study were isolated from cosmetic products and included *Penicillum, Candida,* and *Pseudomonas*. These organisms had a strong ability to assimilate some of the ingredients noted; however, Squalane was classified with the ingredients which these organisms do not utilize.[45]

Squalene: Two male subjects were given 1 g Squalene per day for 14 days, while a third male subject received similar doses of cholesterol. Each test substance was mixed with 5 g of butter and eaten with bread. Sebum from the three subjects' backs was then collected and its Squalene content was determined. The Squalene content of sebum did not change significantly upon the ingestion of either Squalene or cholesterol. The mean values (with standard deviations) for the percent of Squalene in sebum were 7.8 ± 0.9 and 8.0 ± 1.1, respectively, for the periods before and during administration of cholesterol. The corresponding percentage for the two subjects who ingested Squalene were 7.4 ± 1.5 before and 8.1 ± 6 during Squalene administration for one subject; and 7.4 ± 1.9 before and 7.2 ± 1.4 during Squalene administration for the second subject. Both subjects receiving Squalene showed a marked fall in the Squalene content of sebum just before the first test dose; however, according to the authors, this may have been fortuitous.[46]

After applying Squalene that contained 1.0% 3-methylcholanthracene or 1.0% menthyl anthranilate to the shaved backs of rats, biopsies of the skin were taken at intervals, fixed, frozen, and sectioned. Subsequent fluorescent microscopy gave no evidence that the materials were absorbed.[47]

Oral ingestion of Squalene by rats failed to potentiate adrenocorticotropin because the material was poorly absorbed from the gut.[48,49]

Four drops of 30% Squalene in acetone were applied daily for five or 14 days, or three times weekly for three weeks to the backs of mice less than 50 days old; this caused an increase in the concentration of both Δ^7-cholestenol and cholesterol in the epidermis. The relative increase of Δ^7-cholestenol in the skin was 18.4% for control of mice and 36.9% for treated mice. Application of Squalene to mice aged 50 days or more caused no consistent change in the concentration of Δ^7-cholestenol, although in some instances the concentration of cholesterol appeared to increase.[50] (The hair cycle of mice was not considered. The latter is known to influence appreciably the absorption of chemicals.)

Mice were fed a purified ration containing 1% Squalene for one or two days. In addition, rats were either fasted for one day and then fed the 1% Squalene ration for two days, or fed 1% Squalene for one day without having been fasted. This dietary Squalene caused no increase in the concentration of Δ^7-cholestenol in the livers of the tested rats and mice.[50]

Rats fed Squalene in amounts equivalent to 1% of the diet for 21 days showed a 50% increase in liver sterols and a 33% increase in fecal sterols, though there was no change in the carcass sterols. The sum of liver and fecal sterol increases equalled approximately one-eighth of the Squalene that had been administered.[51]

Vitamin A deficient rats fed β-carotene with either 10 or 50 mg of Squalene for 12–14 days showed a marked reduction in the vitamin A content of the liver and kidneys. When vitamin A instead of β-carotene was fed with Squalene, the vitamin A content of the organs was unaffected; thus Squalene does not interfere with the utilization of vitamin A, but rather with that of β-carotene, the vitamin A percursor.[52]

Matschner et al.[53] reported dietary Squalene inhibits vitamin K absorption in the rat. A vitamin K-deficient diet of the following composition (given in percentages) was fed for two weeks to individually caged adult male rats: casein, 21; corn starch, 43; glucose monohydrate, 27; corn oil, 5; and a supplement of vitamins and minerals. Other rats were fed a diet that was the same as this one, except that added to it was either (a) 0.5% Squalene; (b) Squalene (0.5%) plus

vitamin K (0.25 μg/g of diet); or (c) vitamin K (0.25 μg/g of diet). Feces were collected daily and assayed for vitamin K. As shown in Table 4, rats fed the basal diet alone for two weeks excreted 1415 μg of vitamin K. Rats fed the diet containing 0.5% Squalene had a fecal vitamin K content of 1095 μg. When both vitamin K and Squalane were added to the diet, the rats excreted 560 μg of the 700 μg ingested. When a similar amount (600 μg) was fed in the diet to which vitamin K alone had been added, only 155 μg of the vitamin was recovered. According to the authors, "These data support a mechanism of interrupted absorption and possible diminished bacterial synthesis of vitamin K for the action of dietary Squalene."

It is known that Squalene, a normal constituent of the liver of most higher animals, is synthesized by animal tissues from acetate, and that it can serve as a direct precursor of cholesterol both in vivo and in vitro. In the biogenesis of cholesterol, acetate is converted to mevalonic acid, mevalonic acid is converted to Squalene, Squalene is cyclized to lanosterol, which, in turn, is converted to cholesterol.[9,10,48,54-57]

Hamsters fed a gallstone-producing diet with 1% added Squalene for 42–44 days showed complete protection against the formation of gallstones. The authors suggested this may have been due to the inhibition of biosynthesis of cholesterol in the liver.[58] This does not appear to be consistent with the work of Bloch,[56] according to which it is "virtually certain that Squalene is an obligatory intermediate in sterol biogenesis." McGuire and Lipsky,[55] who confirmed Bloch's earlier findings that both Squalene and cholesterol inhibited the bioconversion of acetate to cholesterol, postulate the following explanation for this paradox. "Squalene, by causing a 'piling up' of hepatic cholesterol may therefore evoke a homeostatic reduction in cholesterol synthesis from all sources" (feedback inhibition).

Evidence for the in-vivo metabolic conversion of Squalene to glucocorticoids was developed in hypophysectomized male rats given suboptimal injections of ACTH. The resulting increases in adrenal weight and decreases in thymus weight were enhanced when Squalene was injected subcutaneously as little as 24 hours prior to ACTH injection. Squalene alone did not produce statistically significant changes in the organ weights. Orally administered Squalene was not effective. According to the author, these data are consistent with the idea that exogenous Squalene could serve as a ready precursor of glucocorticoids in vivo, and that it may be a potential intermediate in steroid biogenesis.[47,49]

TABLE 4. Fecal Vitamin K in Adult Male Rats.[a]

		Vitamin K				
		Fecal		*Eaten*	*Recovered*	
Diet	*Feces*[b]	*μg/g*	*μg*	*μg*	*μg*	*percent*
Basal diet	101	14.0	1415	–[c]	–	–
Basal diet + Squalene	115	9.5	1095	–	–	–
Basal diet + Squalene + vitamin K	114	14.5	1655	700	560	80
Basal diet + vitamin K	100	15.7	1570	600	155	25

[a]Data from Ref. 53.
[b]Total feces (dry weight, grams) collected from 10 rats for 13 days.
[c]– No data.

Rabbits were injected subcutaneously with Squalene twice a day for up to 12 days. In the body of animals, the test material was oxidized to succinic and laevulinic acids. Urine samples showed succinic acid, along with small amounts of benzoic and hippuric acids. In animals sacrificed either four hours or 90 days after the last injection, there were considerable amounts of stored Squalene in liver, muscle, and skin.[59]

In a study with human subjects, a direct relationship was found between plasma levels of Squalene and triglycerides, but not between the levels of Squalene and cholesterol. Levels of Squalene in plasma rose with increased dietary Squalene and varied directly with the cholesterol synthesis rate. That large amounts of Squalene excreted in skin surface lipids was thought to reflect de novo synthesis in the skin rather than transference from the plasma. Small amounts were excreted in the urine and feces.[7]

Animal Toxicology

General Studies

Acute studies: oral toxicity

Squalane: Squalane was given undiluted in single oral doses to a group of 50 mice to determine its LD50. Doses of 5.0, 12.5, 25.0, and 50 ml/kg were given to 10, 10, 10, and 20 mice, respectively. Since no deaths occurred and no toxic effects were noted, the oral LD50 is greater than 50 ml/kg in mice.[60]

Squalene: The single dose oral LD50 was determined to be greater than 50 ml/kg in mice. Groups of 5, 5, 10, and 10 mice received undiluted doses of 5.0, 12.5, 25.0, and 50.0 ml/kg, respectively. In the seven-day observation period, no toxic effects were observed and no deaths occurred.[61]

Squalene/Hydrogenated Shark Liver Oil: In another study in mice, a mixture of 65% Squalene in hydrogenated shark liver oil had a single oral dose of LD50 >100 ml/kg. Doses of 5, 25, 50, and 100 ml were given undiluted to 4, 4, 4, and 20 mice, respectively. Even the highest dose did not produce visible toxic effects.[62]

Subcutaneous administration

Squalane: Subcutaneous injections of 0.5 ml Squalane per 20 g mouse (25 ml/kg) were made in five mice, and 1.0 ml/20 g mouse was given (50 ml/kg) in 10 mice. After a one-week observation period, all animals were sacrificed and the site of injection was examined. Macroscopic examination showed unabsorbed compound present in 3/5 of the low-dose mice, while 10/10 of the high-dose group had identifiable compound present. No toxic response was noted to either dose.[63]

Intramuscular administration

Squalane: Intramuscular injections of 0.5 ml/20 g mouse (25 ml/kg) were made into each of 10 mice. At the end of a one-week observation period, the animals were sacrificed; microscopic examination revealed residual compound present at the injection site in 9/10 animals. No toxic response was noted.[64]

Skin irritation

Squalane: Undiluted Squalane (0.5 ml) did not produce irritation in three

rabbits when applied to intact and abraded skin for 24 hours according to the method of Draize.[4]

An "official" French method was used to determine the skin irritation potential of undiluted Squalane in six albino rabbits.[65,66] The test material was applied to the clipped skin under occlusive patches for 24 hours. The Primary Irritation Index (PII) was 0.29, indicating that the test material was practically nonirritating.

Squalene: According to the procedure of Draize, undiluted Squalene (0.5 ml) was applied to the abraded and intact skin of three rabbits for 24 hours. No irritation resulted.[67]

Eye irritation

Squalane: When the procedure of Draize was employed, undiluted Squalane did not produce irritation or damage in the eyes of rabbits, regardless of whether the eyes had been washed after instillation.[68]

A modified official French method was used to evaluate the eye irritation potential of undiluted Squalane in six albino rabbits.[65,66] Eye readings were taken at one hour and at one, two, three, four, and seven days. The Ocular Irritation Index (OII) was 4.33 at one hour and 0.0 thereafter. The investigators believed that a compound does not provoke any significant injury if the OII is less than 10.

Squalene: The procedure of Draize was used to test undiluted Squalene (0.1 ml) in the eyes of rabbits. The compound did not produce irritation, despite the fact that no attempt was made to wash the eyes after instillation.[68]

Inhalation studies

Squalane: An acute inhalation test was conducted with an antiperspirant spray formulation containing 4% Squalane; investigators used the method of the Federal Hazardous Substances Act (FHSA). Ten (5M, 5F) Wistar-derived albino rats were exposed to a chamber concentration of 181 mg/l for one hour, so that the formulation dose per rat was 45.1 ml/kg. The calculated dose of Squalane was 1.8 mg/kg. Autopsy 14 days after exposure showed "no evidence of compound related tissue abnormality." The test formulation was "not considered toxic" by inhalation to rats under the regulations of the Consumer Product Safety Commission (16 CFR 1500.40).[70]

Ten Sherman-Wistar albino rats were similarly exposed to a deodorant spray containing 4% Squalane. Chamber concentrations were reported to be 345 mg/l, and during the one-hour exposure, the available formulation dose to the rats was 100.9 mg/kg. The calculated dose of Squalane was 9.1 mg/kg. Autopsy 14 days after exposure revealed no abnormalities.[70]

Miscellaneous studies

Squalane: In an anticancer screening program, doses of 350, 400, and 500 mg/kg were administered daily to mice with malignant tumors by intraperitoneal injection for nine to 11 days. The Squalane had no effect on the tumors and no apparent effect on the host animals.[71]

Squalene: As a preliminary investigation to determine whether Squalene had a protective effect against x-irradiation, groups of five mice each were given doses of 500, 1000, 1500, and 2000 mg/kg of the undiluted ingredient by an unspecified route. During the 10-day observation period, no deaths occurred. In the follow-up study, a 10% solution of Squalene at a dose of 2000 mg/kg was given by an unspecified route to 20 mice 15 minutes prior to administration of

575 roentgens of x-radiation. Sixty percent of the animals survived for 30 days. On the other hand, of the mice to which no Squalene was given, only 25% survived the 30-day observation period. When the x-radiation was increased to 800 roentgens, the 10% Squalene solution did not increase survival time. It was concluded that "Squalene is just short of being protective against x-radiation at a mid-lethal dose range . . .".[72]

Subchronic inhalation studies

Squalane: Twice a day, a hair spray containing 2% Squalane was sprayed for 30 seconds into a 200 l chamber containing five immobilized rabbits each weighing 3–4 kg. The rabbits were allowed to remain in the spray atmosphere for 15 minutes after each spraying. Exposure was continued five days a week for 90 days. Throughout the entire experimental period, the test animals ate well and behaved normally. Three of the five rabbits gained weight in the 90 days, while one lost and another remained at its original weight. Hematology findings were within the normal established limits for this strain of rabbit. Organ weights were likewise reported to be "in the range for the size animal employed." (Calculations made of organ weights as a percent of total body weight showed they were essentially normal.) Gross and microscopic examinations of the kidneys, liver, spleen, adrenals, and lungs showed no histopathology. X-rays taken at 30 and 90 days after exposure revealed no pulmonary congestion.[73]

Skin studies

Squalane: To determine the cumulative skin irritation potential of 15% Squalane in aqueous solution and of undiluted Squalane in albino rabbits, investigators employed an official French method.[65,66] Each test material was applied daily for 60 days to the shaved skin of three albino rabbits. Undiluted Squalane gave a mean irritation index of 1.00, indicating that it was "relatively well tolerated." There were vesicles and papules on the skin, but no histological pathology. Squalane in aqueous dispersion was "well tolerated" and produced a mean maximum irritation index of 0.33. There were some vesicles, but no histological pathology.

Squalene: Several studies have shown that Squalene has a reversible depilatory effect on animals.[74-77] In a study by Flesch,[74] a single application of 100% Squalene was made to the skin of rabbits (1 ml), guinea pigs (1 ml), and mice (0.2 ml). The hair in the area of application of all rabbits treated began to fall out in one week; complete baldness in the treated area resulted in 10–12 days. Three of four guinea pigs lost the hair in the area of application after 10 days. The mice showed no depilation. Hair regeneration was visible in all animals at the beginning of the third week, and the fur resumed its normal appearance within a few weeks. No toxic symptoms were observed in any animal. Histological examination of the rabbit skin 12 days after application of Squalene revealed hyperplasia of the cutaneous epithelium. There was no inflammatory reaction of significance. The author's observations apparently did not take into account hair growth cycles at the times he applied Squalene. It is evident that the animals which lost hair had follicles that were in telogen, while those that did not lose hair had anagen follicles. The follicles, apparently in telogen at the time of Squalene application, were stimulated to activity and hair grew back normally.

Flesch[74] found that Squalene inactivated the free sulfhydryl groups of gutathione in human epidermis and mouse liver homogenate. Squalene also inhibited succinic dehydrogenase activity of mouse liver homogenate.

Special Studies

Carcinogenesis

Squalene: Squalene was painted in undiluted form six times weekly for a total of 25 times on the backs of 16 C57B1 mice (the total dose was 1.3 g per mouse). Eight mice survived 100 days, but five of them developed "lymphocytic type of tumors" between days 272 and 849. Tumors were primarily found in the thymus and mesentary of the thymus. Metastases and/or lymphocytic invasions were detected in the peripheral lymph glands, lungs, spleen, liver, and kidneys.[78] This study needs confirmation.

A 20% solution of Squalene in decahydronaphthalene (Decalin) was applied as a tumor promoter twice weekly to the skin of male C3H mice which had been initiated once with 240 μg of 7,12-dimethylbenz(a)anthracene (DMBA). After 30 weeks of application, two out of 12 mice developed malignant skin tumors. In the control group, where 100 percent decahydronaphthalene was used as a promoter, two out of 15 mice developed benign skin tumors.[79]

In a skin painting study, both freshly purified and "aged" Squalene (compound that had been exposed to open air at 37 °C for four weeks) were painted three times weekly for 14 weeks in undiluted form on the backs of C57B1 and C57BR mice. No skin tumors developed. When a similar procedure was used to paint fresh and "aged" Squalene in combination with 0.3% 3-methylcholanthrene (3-MCA), each form of the compound was determined to be inactive as a cocarcinogen. When 0.3% 3-MCA in Squalene was "aged" by being left to stand for four weeks in the open air at 37 °C, 3-MCA lost its carcinogenic effect on mouse skin. According to the authors, these observations suggest that Squalene in human sebum may play a protective role against hydrocarbon carcinogens.[8,80]

Clinical Assessment of Safety

Contact Sensitization

Squalane

Twenty subjects were patch-tested with repeated 48-hour applications made three weeks apart with 8.0% w/w Squalane in a lip emollient. Nineteen responses to both patches were negative; one response was not reported.[81]

Two-hundred forty patients were patch-tested with repeated 48-hour applications made three weeks apart with a formulation (eye pack) containing 16.6% w/w Squalane. All responses were negative.[82]

Ninety-eight patients patch-tested to 15% Squalane in peach kernel oil showed no skin reactions.[83] The procedure used was similar to that described by Fisher.[84]

One-hundred three females patch-tested by a repeated insult procedure to a blushing cream containing 16.8% w/w Squalane demonstrated no contact allergy or irritant reactions.[85]

Twenty females between the ages of 15 and 54 years were patch-tested according to a modification of the Schwartz–Peck 48-hour patch test system to a "night treatment formulation" containing 20.0% w/w Squalane. Two panelists responded with a 2+ reaction on a scale of 0–4 during a second patch-test reading; these scores indicated a "well defined erythema." No other dermal reactions were noted during the 21-day usage of this formulation.[86]

Six-hundred subjects were patch-tested by the modified Draize procedure to

moisture cream containing 7.2% Squalane. None of the 600 subjects demonstrated contact allergy or irritation.[87]

One-hundred female subjects patch-tested to a cream formulation containing 7.0% Squalane did not demonstrate any contact allergy or irritation.[88]

Another 100 female subjects were subjected to prophetic patch-tests with a lipstick formulation containing 20% Squalane. It was the opinion of the investigators that "the product was not a primary irritant, and the sensitizing potential, if existent at all, is exceedingly low".[89]

Ten subjects showed no visible primary skin irritation when tested by the procedure of Kligman and Wooding with 9.0% Squalane in an aerosol antiperspirant spray.[90]

Twenty-five subjects showed no instances of contact sensitization when tested with 9.0% Squalane in an aerosol antiperspirant spray.[91] The test protocols used were those described by Kligman.[92]

Squalene

"Patch-tests" were conducted on an unspecified number of human subjects with both pure Squalene and the nonsaponifiable matter from shark liver oil containing 76% Squalene. The substances were each left in contact with the intact skin for 72 hours. "There was no detectable effect upon the skin or hairs; no change in the degree of pigmentation occurred, nor was any effect on keratinization observed."[46]

Miscellaneous

Squalene

For six weeks, Squalene was tested in a "small group of volunteers" in which the material was applied daily to "various parts of the body" in "free form" and in vehicles. No depilation of other adverse effects were observed. No other data were presented for this study.[5]

Squalene was injected intradermally at a dose of 50 μg into 29 subjects. There was no erythema, induration, or inflammatory skin lesions in any of the subjects. Upon visual inspection at 24 and 48 hours, the sites of injection were normal. Histological examination of biopsies taken at 24 hours demonstrated the presence of a mild, predominantly lymphocytic, perivascular infiltration which was only slightly more intense than the reaction induced by control injections of physiologic saline containing 0.05 percent Polysorbate 80.[93]

In a study conducted by Boughton et al.,[46] undiluted Squalene (0.2 ml) was injected into the skin of an unspecified number of subjects. No effect other than a "short-lived" inflammatory response was observed. In a second study, undiluted Squalene was applied to the unbroken or blistered skin of an unspecified number of subjects, and the treated areas were exposed to ultraviolet irradiation from a mercury vapor lamp. No effect on pigmentation was noted on either unbroken or blistered skin, and all areas of the blistered skin healed normally. According to the authors, "Squalene apparently had no inhibitory or stimulatory effect on either pigmentation or healing." Shark liver oil containing 76% Squalene and pure Squalene were also applied to affected areas of patients with eczema, psoriasis, vitiligo, ichthyosis, and hirsutism; no therapeutic effect was seen.

SUMMARY

Squalane and Squalene have been identified as natural components of human sebum. Both ingredients are used at concentrations ranging from ≤ 0.1 to $> 50\%$ in a variety of cosmetics. Because cosmetics containing Squalane and Squalene are applied to all body surfaces, these compounds may potentially enter the body through the skin, eyes, lungs, mouth, or other routes.

Squalene can form peroxides on exposure to air, while Squalane is stable to air and oxygen. Animal studies indicate Squalane is slowly absorbed through the skin, while both compounds are poorly absorbed from the gastrointestinal tract. Squalene is a metabolic precursor of cholesterol and other steroids.

The acute toxicity of these ingredients by all routes in animals is low. At 100% concentrations, both compounds are nonirritants to rabbit skin and eyes. According to clinical evidence of formulations containing Squalane, the compound is not a significant skin irritant or sensitizer. Limited contact sensitization tests indicate that Squalene is not a significant contact allergen or irritant.

Reversible depilation is reported from topical application of Squalene to animals, but limited human studies did not show any such effect.

No photosensitivity data for the two ingredients were available.

CONCLUSION

On the basis of the available information presented in this report, the Expert Panel concludes that both Squalane and Squalene are safe as cosmetic ingredients in the present practices of use and concentration.

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Mr. Jonathon Busch, Scientific Analyst and writer, prepared the literature review and technical analysis used by the Expert Panel in developing this chapter.

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~~QUATERNIUM-18, QUATERNIUM-18 HECTORITE, AND QUATERNIUM-18 BENTONITE~~

~~A safety assessment of Quaternium-18, Quaternium-18 Hectorite, and Quaternium-18 Bentonite was published in 1982 with the conclusion that these ingredients are "safe as cosmetic ingredients in the present practices of use and concentration" (Elder 1982). New studies, along with updated information below regarding uses and use concentrations, were considered by the CIR Expert Panel. The Panel determined to not reopen this safety assessment.~~

~~Quaternium-18~~

~~Quaternium-18 is now reportedly used in hair sprays. The effects of inhaled aerosols depend on the specific chemical species, the concentration, the duration of exposure, and site of deposition within the respiratory system. Particle size is the most important factor affecting the location of deposition (Jensen and O'Brien 1993). The mean aerodynamic diameter of pump hair spray particles is ≥80 μ, and the diameter of anhydrous hair spray particles is 60 to 80 μ. Typically less than 1% are below 10 μ, which is the upper limit for respirable particles (Bower 1999). Based on the particle size, Quaternium-18 would not be respirable in formulation.~~

~~Quaternium-18 was used in a total of 20 cosmetic products in 1976, with the largest single use in nail polish and enamel products at concentrations up to 1%. In 2001, Quaternium-18 was reportedly used in 90 cosmetic products (FDA 2001), with the largest single use in hair conditioners at a 2% concentration (CTFA 2001). Table 24 presents the available use information on Quaternium-18.~~

~~Quaternium-18 Bentonite~~

~~Quaternium-18 Bentonite was used in eight products in 1976, with the largest single use in other personal cleanliness preparations at concentrations up to 1%. In 2001, Quaternium-18 Bentonite was reportedly used in 221 products (FDA 2001), with the largest single use in lipsticks at concentrations up to 5% (CTFA 2001). Table 25 presents the available use information on Quaternium-18 Bentonite.~~

~~Quaternium-18 Hectorite~~

~~Quaternium-18 Hectorite was used in 142 products in 1976, with the largest single use in nail polish and enamel products at concentrations up to 5%. In 2001, Quaternium-18 Hectorite was used in 176 products (FDA 2001), with the largest single use in other personal cleanliness products at concentrations up to 19% (CTFA 2001). Table 26 presents the available use information on Quaternium-18 Hectorite.~~

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SQUALENE AND SQUALANE

A safety assessment of Squalene and Squalane was published in 1982 with the conclusion that these ingredients are "safe as cosmetic ingredients in the present practices of use and concentration" (Elder 1982). New studies, along with updated information regarding types and concentrations of use, were considered by the CIR Expert Panel. The Panel determined to not reopen this safety assessment.

Squalene

Squalene was used in 18 cosmetic products in 1976, with the largest use occuring in moisturizing preparations at concentrations of ≤10%. In 2001, Squalene was used in 29 products (FDA 2001), at a maximum use concentration of 10% in face powders (CTFA 2001). Table 27 presents the available use information for Squalene.

Squalane

Squalane was used in 400 products in 1976, with the largest use occuring in moisturizing preparations at concentrations of

[2]Available from Director, Cosmetic Ingredient Review, 1101 17th Street NW, Suite 310, Washington, DC 20036, USA.

TABLE 27
Squalene use

Product category	1976 use (Elder 1982)	2001 use (FDA 2001)	1976 concentrations (Elder 1982)	2001 concentrations (CTFA 2001)
Bath oils, tablets, and salts	—	1	—	—
Other bath preparations	1	—	>0.1%–1%	0.2%
Eyebrow pencil	—	—	—	0.7%
Eyeliner	—	—	—	0.7%
Eye shadow	—	—	—	0.5%
Eye makeup remover	1	—	>1%–5%	—
Shampoos (noncoloring)	—	—	—	0.01%
Blushers (all types)	1	—	>25%–50%	0.5%
Face powders	—	—	—	10%
Foundations	1	2	>0.1%–1%	2%
Lipstick	—	—	—	0.7%
Other makeup preparations	—	—	—	0.02%
Bath soaps and detergents	—	—	—	0.2%
Skin cleansing preparations	—	2	—	0.5%
Face and neck skin care preparations[a]	3	6	≤0.1	0.5%
Body and hand skin care preparations[a]		6		0.08%–0.5%
Foot powders and sprays	—	1	—	—
Moisturizing preparations[b]	6	7	≤10%	0.06%–0.5%
Wrinkle smoothing (removers)[b]	1	—	≤1%	—
Night preparations	1	2	>1%–5%	0.5%
Paste mask (mud packs)	—	—	—	0.5%
Skin fresheners	1	—	≤1%	—
Other skin care preparations	1	2	≤5%	0.5%
Suntan gels, creams, and liquids	1	—	>0.1%–1%	0.02%–0.3%
Other suntan preparations	—	—	—	0.2%
Totals/ranges	18	29	≤1% to 50%	0.02%–10%

[a]Originally, Face and Neck and Body and Hand were combined as one category, but now they are separated.
[b]Wrinkle smoothing (removers) was added to the Moisturizing category.

TABLE 28
Squalane use

Product category	1976 use (Elder 1982)	2001 use (FDA 2001)	1976 concentrations (Elder 1982)	2001 concentrations (CTFA 2001)
Baby lotions, oils, powders, etc.	2	2	>0.1%–1%	—
Bath oils, tablets, and salts	9	—	>0.1%–10%	—
Other bath preparations	1	—	≤0.1	—
Eyebrow pencil	—	—	—	2%
Eyeliner	7	—	>0.1%–5%	2%
Eye shadow	8	30	>0.1%–25%	10%
Eye lotion	—	5	—	3%
Eye makeup remover	2	1	>0.1%–5%	5%
Mascara	3	—	>1%–10%	0.01%
Other eye makeup preparations	—	6	—	10%–15%
Perfumes	2	2	>1%–5%	—
Powders	1	2	>0.1%–1%	3%
Other fragrance preparations	1	8	>5%–10%	—
Hair conditioners	4	9	>0.1%–5%	5%

(Continued on next page)

TABLE 28
Squalane use *(Continued)*

Product category	1976 use (Elder 1982)	2001 use (FDA 2001)	1976 concentrations (Elder 1982)	2001 concentrations (CTFA 2001)
Hair sprays (aerosol fixatives)	4	2	≤1%	—
Hair straighteners	—	4	—	—
Permanent waves	15	—	>0.1%–1%	—
Rinses (noncoloring)	1	—	>0.1%–1%	0.8%
Shampoos (noncoloring)	2	—	≤1%	—
Tonics, dressings, and other hair grooming aids	—	1	—	—
Other hair preparations	1	1	>1%–5%	—
Blushers (all types)	13	13	≤25	10%
Face powders	12	26	>0.1%–1%	9%
Foundations	7	50	≤10%	3%–31%
Lipstick	2	62	>10%–50%	3%–17%
Makeup bases	19	12	>0.1%	5%
Rouges	5	—	>1%–10%	—
Makeup fixatives	—	1	—	—
Other makeup preparations	11	12	>1%–25%	6%–30%
Cuticle softeners	1	2	>5%–10%	—
Nail creams and lotions	1	1	>10%–25%	—
Nail polish and enamel removers	1	1	>1%–5%	—
Other manicuring preparations	1	2	>0.1%–1%	—
Bath soaps and detergents	—	—	—	0.1%–1%
Deodorants (underarm)	—	—	—	3%
Other personal cleanliness products	4	1	>0.1%–10%	—
Aftershave lotions	—	3	—	2%
Shaving cream	—	2	—	0.1%–1%
Skin cleansing preparations	—	21	—	2%–5%
Face and neck skin care preparations[a]	13	15	>0.1%–50%	3%–97%
Body and hand skin care preparations [a]		51		0.1%–4%
Foot powders and sprays	1	2	>0.1%–1%	—
Moisturizing preparations	71	128	≤25%	2%–36%
Night preparations	29	28	>0.1%–50%	5%–6%
Paste mask (mud packs)	3	15	≤10%	1%–4%
Skin lighteners	3	—	>0.1%–5%	—
Skin fresheners	2	—	≤0.1%	—
Wrinkle smoothing (removers)	2	—	≤5%	—
Other skin care preparations	16	61	>0.1%–25%	3%–10%
Suntan gels, creams, and liquids	5	8	>0.1%–25%	0.3%
Indoor tanning preparations	1	2	>1%–5%	—
Other suntan preparations	—	3	—	—
Totals/ranges	400	595	≤0.1%–50%	0.01%–97%

[a]Originally, Face and Neck and Body and Hand were combined as one category, but now they are separated.

≤25%. In 2001, Squalane was used in 595 products (FDA 2001), at use concentration up to 97% reported for face and neck skin care preparations (CTFA 2001). Table 28 presents the available use information for Squalane.

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[2]Available from Director, Cosmetic Ingredient Review, 1101 17th Street NW, Suite 310, Washington, DC 20036, USA.

~~TABLE 29~~
~~Stearalkonium Chloride use~~

~~Product category~~	~~1976 use (Elder 1982)~~	~~2001 use (FDA 2001)~~	~~1976 concentrations (Elder 1982)~~	~~2001 concentrations (CTFA 2001)~~
~~Bubble baths~~	—	~~5~~	—	—
~~Hair conditioners~~	~~78~~	~~107~~	~~≤0.1%–5%~~	~~0.7%–7%~~
~~Hair sprays (aerosol fixatives)~~	~~9~~	~~3~~	~~≤0.1%–1%~~	—
~~Hair Straighteners~~	~~1~~	—	~~>0.1%–1%~~	—
~~Permanent waves~~	~~6~~	~~2~~	~~≤0.1%–5%~~	—
~~Rinses (noncoloring)~~	~~60~~	~~5~~	~~>0.1%–5%~~	~~3%~~
~~Shampoos (noncoloring)~~	—	~~4~~	—	~~2%~~
~~Hair tonics, dressings, etc.~~	~~4~~	~~14~~	~~≤0.1%–5%~~	~~2%–3%~~
~~Wave sets~~	~~8~~	~~2~~	~~≤0.1%~~	—
~~Other hair preparations~~	~~5~~	~~3~~	~~≤0.1%–1%~~	~~2%~~
~~Hair dyes and colors~~	~~21~~	—	~~≤0.1%–5%~~	~~0.5%–2%~~
~~Hair rinses (coloring)~~	~~47~~	—	~~>0.1%–5%~~	—
~~Hair bleaches~~	—	—	—	~~0.4%~~
~~Nail creams and lotions~~	1	—	~~>0.1%–1%~~	—
~~Nail polish and enamel~~	—	~~1~~	—	—
~~Other personal cleanliness products~~	—	~~1~~	—	—
~~Aftershave lotions~~	1	—	~~≤0.1%~~	—
~~Skin cleansing preparations~~	~~2~~	—	~~>0.1%–5%~~	—
~~Body and hand skin care preparations~~	—	~~2~~	—	—
~~Moisturizing skin care preparations~~	~~5~~	1	~~>0.1%–5%~~	~~0.3%~~
~~Other skin care preparations~~	~~1~~	1	~~>1%–5%~~	—
~~Totals/ranges~~	~~249~~	~~151~~	~~≤0.1%–5%~~	~~0.3%–7%~~

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TABLE 30
Wheat Germ Glycerides use

Product category	1976 use (Elder 1980a)	2001 use (FDA 2001)	1976 concentrations (Elder 1980a)	2001 concentrations (CTFA 2001)
Eyeliner	—	—	—	0.05%–2%
Eye shadow	3	—	>0.1%–1%	2%
Other eye makeup preparations	4	—	≤0.1%–1%	—
Hair conditioners	—	—	—	0.001%
Hair tonics, dressings, etc.	—	—	—	0.1%
Face powders	2	—	>0.1%–1%	—
Foundations	9	—	≤0.1%–1%	2%
Lipstick	114	126	≤0.1%–5%	0.3%–25%
Makeup bases	6	—	≤0.1%–1%	—
Other makeup preparations	—	1	—	0.3%
Cuticle softeners	—	1	—	2%
Deodorants (underarm)	1	—	>0.1%–1%	—
Aftershave lotions	—	—	—	0.4%
Cleansing preparations (cold creams, cleansing lotions, liquids, and pads)	8	—	≤0.1%–1%	—
Face and neck skin care preparations[a]	12	—	>0.1%–5%	—
Body and hand skin care preparations[a]		—		—
Hormone (creams, lotions)[b]	1	—	>0.1%–1%	—
Moisturizing preparations[c]	24	—	≤0.1%–1%	—
Wrinkle smoothing (removers)[c]	1	—	≤0.1%	—
Night (creams, lotions)	11	—	≤0.1%–5%	—
Skin fresheners	1	—	≤0.1%	—
Other skin care preparations	15	—	>0.1%–1%	—
Totals/ranges	212	128	≤0.1%–5%	0.001%–25%

[a]Originally, Face and Neck and Body and Hand were combined as one category, but now they are separated.
[b]No longer a product category.
[c]Wrinkle smoothing (removers) are now part of the Moisturizing category.

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STEARALKONIUM CHLORIDE

A safety assessment of Stearalkonium Chloride was published in 1982 with the conclusion that this ingredient is "safe when incorporated in cosmetic products in concentrations similar to those presently marketed" (Elder 1982). New studies, along with the updated information regarding uses and use concentrations, were considered by the CIR Expert Panel. The Panel determined to not reopen this safety assessment.

In 1976, Stearalkonium Chloride was used in 249 cosmetic products, with the largest single use in rinses (noncoloring) in the concentration range of >0.1% to 5%. In 2001, Stearalkonium Chloride was used in 151 products (FDA 2001), with the largest single use reported for hair conditioners. The highest concentration of use was also in hair conditioners (0.7% to 7%) in 2001 (CTFA 2001). Table 29 presents the available use information.

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[2]Available from Director, Cosmetic Ingredient Review, 1101 17th Street NW, Suite 310, Washington, DC 20036, USA.

SQUALANE	01B - Baby Lotions, Oils, Powders, and Creams	11
SQUALANE	02A - Bath Oils, Tablets, and Salts	5
SQUALANE	02D - Other Bath Preparations	1
SQUALANE	03A - Eyebrow Pencil	6
SQUALANE	03B - Eyeliner	28
SQUALANE	03C - Eye Shadow	153
SQUALANE	03D - Eye Lotion	105
SQUALANE	03E - Eye Makeup Remover	5
SQUALANE	03F - Mascara	12
SQUALANE	03G - Other Eye Makeup Preparations	57
SQUALANE	04B - Perfumes	4
SQUALANE	04C - Powders (dusting and talcum, excluding aftersha\	1
SQUALANE	04E - Other Fragrance Preparation	7
SQUALANE	05A - Hair Conditioner	15
SQUALANE	05B - Hair Spray (aerosol fixatives)	1
SQUALANE	05C - Hair Straighteners	1
SQUALANE	05F - Shampoos (non-coloring)	8
SQUALANE	05G - Tonics, Dressings, and Other Hair Grooming Aids	29
SQUALANE	05I - Other Hair Preparations	15
SQUALANE	07A - Blushers (all types)	58
SQUALANE	07B - Face Powders	106
SQUALANE	07C - Foundations	87
SQUALANE	07E - Lipstick	253
SQUALANE	07F - Makeup Bases	30
SQUALANE	07G - Rouges	9
SQUALANE	07H - Makeup Fixatives	6
SQUALANE	07I - Other Makeup Preparations	70
SQUALANE	08B - Cuticle Softeners	1
SQUALANE	08C - Nail Creams and Lotions	2
SQUALANE	08G - Other Manicuring Preparations	1
SQUALANE	10A - Bath Soaps and Detergents	8
SQUALANE	10B - Deodorants (underarm)	3
SQUALANE	10E - Other Personal Cleanliness Products	10
SQUALANE	11A - Aftershave Lotion	19
SQUALANE	11B - Beard Softeners	1
SQUALANE	11E - Shaving Cream	5
SQUALANE	11F - Shaving Soap	3
SQUALANE	11G - Other Shaving Preparation Products	4
SQUALANE	12A - Cleansing	69
SQUALANE	12C - Face and Neck (exc shave)	435
SQUALANE	12D - Body and Hand (exc shave)	221
SQUALANE	12F - Moisturizing	575
SQUALANE	12G - Night	117
SQUALANE	12H - Paste Masks (mud packs)	43
SQUALANE	12I - Skin Fresheners	7
SQUALANE	12J - Other Skin Care Preps	134
SQUALANE	13A - Suntan Gels, Creams, and Liquids	5
SQUALANE	13B - Indoor Tanning Preparations	31

SQUALANE	13C - Other Suntan Preparations	8

SQUALENE	01B - Baby Lotions, Oils, Powders, and Creams	2
SQUALENE	02A - Bath Oils, Tablets, and Salts	1
SQUALENE	02B - Bubble Baths	6
SQUALENE	02D - Other Bath Preparations	5
SQUALENE	03A - Eyebrow Pencil	1
SQUALENE	03C - Eye Shadow	7
SQUALENE	03D - Eye Lotion	7
SQUALENE	03G - Other Eye Makeup Preparations	4
SQUALENE	04E - Other Fragrance Preparation	1
SQUALENE	05A - Hair Conditioner	1
SQUALENE	05F - Shampoos (non-coloring)	2
SQUALENE	07B - Face Powders	2
SQUALENE	07E - Lipstick	71
SQUALENE	07I - Other Makeup Preparations	17
SQUALENE	10A - Bath Soaps and Detergents	6
SQUALENE	10E - Other Personal Cleanliness Products	199
SQUALENE	11A - Aftershave Lotion	1
SQUALENE	12A - Cleansing	5
SQUALENE	12C - Face and Neck (exc shave)	37
SQUALENE	12D - Body and Hand (exc shave)	30
SQUALENE	12F - Moisturizing	93
SQUALENE	12G - Night	6
SQUALENE	12H - Paste Masks (mud packs)	2
SQUALENE	12J - Other Skin Care Preps	18
SQUALENE	13A - Suntan Gels, Creams, and Liquids	2
SQUALENE	13B - Indoor Tanning Preparations	1

Concentration of Use by FDA Product Category – Squalane and Squalene

Ingredient	Product Category	Maximum Concentration of Use
Squalane	Baby lotions, oils and creams Not powder	2%
Squalane	Other baby products Rinse-off	0.03%
Squalane	Other bath preparations	0.14%
Squalane	Eyebrow pencils	0.1-13.9%
Squalane	Eyeliners	3-4%
Squalane	Eye shadows	3.2-21.6%
Squalane	Eye lotions	0.0001-17%
Squalane	Mascaras	0.001-0.3%
Squalane	Other eye makeup preparations	38%
Squalane	Hair conditioners	0.005-2.3%
Squalane	Hair sprays Aerosol	0.048%
Squalane	Shampoos (noncoloring)	0.001-0.0075%
Squalane	Tonics, dressings and other hair grooming aids	0.005-2%
Squalane	Other hair preparations (noncoloring)	0.44%
Squalane	Blushers	0.1-14.7%
Squalane	Face powders	1-3.4%
Squalane	Foundations	0.5-85.4%
Squalane	Lipstick	0.001-22.8%
Squalane	Makeup bases	1.9%
Squalane	Rouges	13%
Squalane	Makeup fixatives	10%
Squalane	Other makeup preparations	1.2-5.8%
Squalane	Basecoats and undercoats (manicuring preparations)	0.0001%
Squalane	Cuticle softeners	1%
Squalane	Nail creams and lotions	96.8%
Squalane	Nail polish and enamel	0.0001%
Squalane	Nail polish and enamel removers	0.0001%
Squalane	Bath soaps and detergents	0.005-10%
Squalane	Deodorants Not spray	0.18-4%
Squalane	Other personal cleanliness products	1-2%
Squalane	Aftershave lotions	0.25-4.8%
Squalane	Shaving cream	3.5%
Squalane	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.01-34.9%
Squalane	Face and neck products Not spray	0.13-17%
Squalane	Body and hand products	

	Not spray Spray	0.77-40.1% 0.15%
Squalane	Foot powders and sprays	0.15%
Squalane	Moisturizing products Not spray	 0.53-38.7%
Squalane	Night products Not spray	 0.78-4%
Squalane	Paste masks and mud packs	0.5-18.5%
Squalane	Skin fresheners	12%
Squalane	Other skin care preparations	0.26-85%
Squalane	Suntan products Not spray	 0.77-8.6%
Squalane	Indoor tanning preparations	0.7%
Squalane	Other suntan preparations	0.23%
Squalene	Eye shadows	0.0046%
Squalene	Eye lotions	0.07%
Squalene	Hair conditioners	1.2%
Squalene	Tonics, dressings and other hair grooming aids	0.07%
Squalene	Other hair coloring preparations	0.2%
Squalene	Foundations	0.01%
Squalene	Lipstick	0.0045-0.09%
Squalene	Bath soaps and detergents	0.004%
Squalene	Deodorants Not spray	 0.06%
Squalene	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.004%
Squalene	Face and neck products Not spray	 0.6-0.7%
Squalene	Body and hand products Not spray	 0.05%
Squalene	Moisturizing products Not spray	 0.055%

Information collected in 2018

Table prepared June 26, 2018