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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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