JOURNAL OF THE AMERICAN COLLEGE OF TOXICOLOGY
Volume 7, Number 6, 1988
Mary Ann Liebert, Inc., Publishers

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Final Report on the Safety Assessment of Steareth-2, -4, -6, -7, -10, -11, -13, -15, and -20

The steareth group is a series of compounds prepared by reacting stearyl alcohol with ethylene oxide to form polyoxyethylene stearyl ethers. Steareths are waxy solids used primarily as emulsifiers in cosmetics at concentrations of up to 25%.

Steareth-2 and -10 were nontoxic to rats in acute oral toxicity studies. In subchronic testing, steareth-20 was nontoxic to rabbits when administered dermally at concentrations of 4%. Steareth-2 and -10, at concentrations of up to 60% in water, were at most mildly irritating to rabbit eyes and only mild irritants when tested in cosmetic formulations at concentrations of up to 60%.

Structurally similar polyoxyethylene alkyl ethers were neither mutagenic nor tumor promoters.

Steareth-2, -10, and -20 in water were neither primary irritants nor sensitizers to human skin. Steareth-20 was not phototoxic.

On the basis of the available data it is concluded that steareths-2, -4, -6, -7, -10, -11, -13, -15, and -20 are safe as cosmetic ingredients in the present practices of use and concentration.

CHEMISTRY

Definition and Structure

Steareth (CAS No. 9005-00-9) is the Cosmetic, Toiletry and Fragrance Association (CTFA) adopted name for a series of polyethylene glycol ethers of stearyl alcohol. These cosmetic ingredients conform to the formula

$$CH_3(CH_2)_{16}CH_2(OCH_2CH_2)_nOH$$

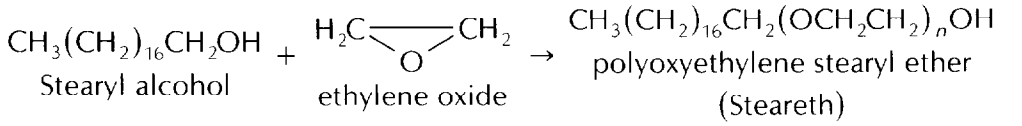
where n has an average value that ranges from 2 (as in the case of steareth-2) to 20 (i.e., steareth-20).[1]

Other names for steareth include polyethylene glycol stearyl ether, polyoxyethylene stearyl ether, polyethylene glycol octadecyl ether, polyethylene

glycol octadecanol ether, polyoxyethylene octadecyl ether, and stearyl alcohol ethoxylate. In addition to the generic CAS No. 9005-00-9 for the entire steareth series, steareth-6 (3,6,9,12,15,18-hexaoxahexatriacontan-1-ol) has the CAS No. 2420-29-3.[1-3] Numerous trade names for the steareth series are presented elsewhere.[1,3]

Method of Manufacture

The steareths are prepared by reacting ethylene oxide with stearyl alcohol[4]:



Chemical and Physical Properties

Steareths-2, -10, and -20 are waxy solids.[5] They are soluble in ethanol and other lower alcohols and insoluble in mineral oil and coal tar hydrocarbons.[5,6] Water solubility varies and increases with increasing ethylene oxide content.[5,7] These compounds have a range in average molecular weight from 358 for steareth-2 to 1150 for steareth-20. In cosmetic-grade steareth (-2, -10, -20), approximately 95% of the alkyl chain is stearyl (C_{18}), with smaller amounts consisting of cetyl (C_{16}) and "other alkyl groups" (not specified) (Table 1).[5]

Analytical Methods

Analytic methods for the separation and/or determination of the steareth compounds include high-performance liquid chromatography,[8] spectro-photometry,[9] and thin-layer chromatography.[10] Davis[11] has described a sensitive chemical test for the analysis of polyoxyethylene compounds as well as for the analysis of products emulsified with polyoxyethylenes. The emulsion stability of steareths and other polyethylene ethers of long-chain, aliphatic alcohols can be determined by gas chromatography[12] and spectral absorption,[13,14] respectively.

Impurities

Information was not available as to the possible presence of trace amounts of 1,4-dioxane or other impurities in the steareth compounds.

COSMETIC USE

The steareths are used in cosmetic products primarily as emulsifiers.[6,16,17,20,21] These ingredients are particularly useful in emulsions of high alkalinity or acidity.[6,17] In addition to their use as lipophilic (steareth-2)

TABLE 1. Chemical and Physical Data for Steareth-2, -10, and -20

Data	*Steareth-2*	*Steareth-10*	*Steareth-20*	*References*
Description	Pale yellow to buff-colored, waxy solid	White to light tan, waxy solid having a slightly fatty odor	White to light tan, waxy solid	5
Hydroxyl value	147–162	70–85	45–60	5
Ethylene oxide contact (mol EO per mol)	1.9–2.5	7–12	14–22	5
Acid value	1.0 maximum	1.0 maximum	1.0 maximum	5
Free polyethylene glycols	1.5% maximum	8.0% maximum	10% maximum	5
Moisture	1.0% maximum	3.0% maximum	3.0% maximum	5
Free ethylene oxide	100 ppm maximum	100 ppm maximum	100 ppm maximum	5
Water solubility	Insoluble	Insoluble	Soluble	5
Viscosity	2000 cP	—	144 cP	15
HLB (hydrophile-lipophile balance)[a]	4.9	12.4	15.3	4, 15–19

[a]The HLB (hydrophile-lipophile balance) of an emulsifier is an expression of the relative simultaneous attraction of an emulsifier for water/oil (or for two phases of a system to be emulsified). An emulsifier that is lipophilic in character is assigned a low HLB number, and an emulsifier that is hydrophilic in character is assigned a high number. The midpoint is approximately 10, and the assigned values have ranged from 1 to 40. The HLB value is useful because it allows a prediction of the control action or behavior that may be expected from a surfactant (i.e., a low value, about 4, will be a water-in-oil emulsifier; a high value, about 16, will be a solubilizer for many standard cosmetic ingredients).[16]

or oil–water (steareth-10 and -20) emulsifiers,[17] steareths may also be used as wetting agents,[6] solubilizers,[17] and nonionic surfactants.[16] At a use concentration of 1 g of a formulation containing 5% of a steareth, which in turn contains 100 ppm free ethylene oxide, the exposure of the consumer is to 5 μg ethylene oxide.

Data submitted to the Food and Drug Administration (FDA) in 1981 by cosmetic firms participating in the voluntary cosmetic registration program indicated that steareth-2 was used in a total of 107 cosmetic products. Steareth-10, -15, and -20 were used in a total of 104 cosmetic formulations (Tables 2 through 6). Products formulated with steareths included personal cleanliness products and deodorants, as well as suntan, fragrance, skin, eye, and hair preparations. Reported concentrations of steareths in these products varied from $\leq 0.1\%$ (lowest reported range) to > 10–25% (highest reported range). The majority of products containing steareth-2 had concentrations within the ranges of > 1–5% or > 0.1–1%. Steareth-10, -15 and -20 were used in products mainly in the > 1–5% and > 0.1–1% concentration ranges (Tables 2 and 3).[22]

The FDA cosmetic product formulation computer printout[22] is compiled through voluntary filing of such data in accordance with Title 21 Part 720.4 of the Code of Federal Regulations.[23] Ingredients are listed in preset 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 cosmetics formulator may not necessarily reflect the actual concentration found in the finished product; the actual concentration is

TABLE 2. Product Formulation Data for Steareth-2

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
Eye and facial preparations	3143	42	—	—	2	40
Hair preparations (coloring and noncoloring)	1178	19	—	—	2	17
Face, body, and hand skin care preparations (including suntan preparations)	4176	46	1	1	32	12
1986 Totals		107	1	1	36	69

Source: From Reference 22.

a fraction of that reported to the FDA. Data submitted within the framework of preset concentration ranges 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.

TABLE 3. Product Formulation Data for Steareth-10, -15, and -20

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
Eye and facial makeup preparations	1571	24	1	23	—
Colognes, toilet waters, hair tonics and other hydro-alcoholic preparations	2044	5	3	2	—
Hair conditioners and shampoos	1377	2	1	—	1
Hair straighteners and permanents	463	9	5	4	—
Hair bleaches	83	2	1	1	—
Deodorants (underarm)	259	2	1	1	—
Other personal cleanliness products	247	19	18	—	1
Skin-cleansing preparations (cold creams, lotions, liquids, and pads)	729	7	2	5	—
Face, body, and hand skin care preparations (excluding shaving preparations)	2813	29	11	18	—
Suntan preparations	229	5	3	2	—
1986 Totals		104	46	56	2

Source: From Reference 22.

ABSORPTION AND EXCRETION

No absorption or excretion information is available for the steareth compounds themselves.

The dermal absorption and excretion of an unspecified alcohol ethoxylate was studied in the rat. Rapid absorption of the ^{14}C-labeled ethoxylate occurred after a dose of 12.5 mg/kg was applied to the shaved backs of rats. After 72 h, 29% of the radioactivity administered was excreted in the urine, 11% as $^{14}CO_2$, and 8% in the feces. Most of the remaining radioactivity was contained in the tissues, organs, and carcass.[24]

MICROBIAL AND ENVIRONMENTAL DEGRADATION

Long-chain alcohol polyglycol ethers (alcohol ethoxylates) with the common structural formulation $R(OCH_2CH_2)_nOH$ were studied for microbial degradation by activated sludge. Two degradation mechanisms were identified: intramolecular scission of the surfactant and ω- and β-oxidation of the alkyl chain. Prominent metabolites of stearyl alcohol ethoxylate (seven ethylene oxide units; CAS No. 9005-00-9) included carboxylated polyethylene glycols, polyethylene glycol units, C_2 fragments, oxalic acid, and formic acid.[25,26]

The degradation of steareth (CAS No. 9005-00-9) in coastal water ecosystems and the influence of this degradation on biochemical oxygen demand (BOD) has been evaluated by Bergueiro et al.[27] Steber and Wierich[25,26] reported that stearyl alcohol ethoxylate (seven ethylene oxide units; CAS No. 9005-00-9) undergoes complete biodegradation in the environment.

ANIMAL TOXICOLOGY

Acute Toxicity

Oral

The method of Litchfield and Wilcoxon[28] was used to determine the acute oral toxicities in male rats of three polyoxyethylene stearyl ethers. The following LD_{50} values were reported[4]:

Steareth-2, > 25.1 g/kg
Steareth-10, 2.91 g/kg
Steareth-20, 1.92 g/kg

Treon did not specify whether the reported LD_{50} values pertained to the undiluted polyoxyethylene stearyl ether or to an aqueous solution of the polyoxyethylene stearyl ether (Table 4).

A single oral dose of 25.1 g/kg of steareth-2, 40% in water, was administered to groups of five male (134–144 g) and five female (132–143 g) rats to determine its acute oral toxicity. Sprague-Dawley CD (Charles River) rats were

TABLE 4. Acute Toxicity in Rats

Ingredient (concentration and vehicle)	*No. of animals*	*Method of administration*	*LD_{50}*	*Method and comments*	*Reference*
Steareth-2 (unspecified)	Unspecified	Oral	> 25.1 g/kg	Litchfield and Wilcoxon, 1947	4
Steareth-2 (40% in water)	10	Oral	> 25.1 g/kg	One dose of 25.1 g/kg, 0 of 10 died	29
Steareth-2 (25% in corn oil)	25	Oral	21 g/kg	Five doses from 2.5 to 40.0 g/kg	30
Steareth-2 (unspecified)	Unspecified	Oral	> 16 g/kg	Method unspecified	31
Steareth-2 (2.75% in body lotion with 2.25% steareth-20)	10	Oral	> 5 g/kg	One dose of 5 g/kg, 2 of 10 died	34
Steareth-2 (1.8% in antiperspirant)	10	Oral	> 10 g/kg	One dose of 10 g/kg, 2 of 10 died; one had fibrous tissue encasing heart and lungs	35
Steareth-2 (0.6% in mousse conditioner)	10	Oral	> 5 ml/kg	One dose of 5 ml/kg, 0 of 10 died	36
	6	Oral	> 10 g/kg	One dose of 10 g/kg, 0 of 10 died	37
	10	Oral	> 5 ml/kg	One dose of 5 ml/kg, 0 of 10 died	38
	10	Oral	> 5 ml/kg	One dose of 5 ml/kg, 0 of 10 died	39
Steareth-2 (10% in normal saline)	50	Intraperitoneal	0.76 g/kg	Five doses from 0.50 to 1.26 g/kg	29
Steareth-2 (1% in propylene glycol)	50	Intravenous	0.041 g/kg	Five doses from 0.159 to 0.100 g/kg	29
Steareth-10 (unspecified)	Unspecified	Oral	2.91 g/kg	Litchfield and Wilcoxon, 1974	4
	Unspecified	Oral	> 16 g/kg	Method unspecified	31
Steareth-20 (unspecified)	Unspecified	Oral	1.92 g/kg	Litchfield and Wilcoxon, 1947	4
Steareth-20 (25% in distilled water)	60	Oral	2.07 g/kg	Six doses from 1.26 to 3.98 g/kg	32
Steareth-20 (25% in corn oil)	25	Oral	2.1 g/kg	Five doses from 0.31 to 5.0 g/kg	33
Steareth-20 (1.5% in moisturizer)	10	Oral	> 10 ml/kg	One dose of 10 ml/kg, 0 of 10 died	40
Steareth-20 (10% in isotonic NaCl)	40	Intraperitoneal	0.190 g/kg	Four doses from 0.126 to 0.251 g/kg	32
	50	Intravenous	0.164 g/kg	Five doses from 0.126 to 0.199 g/kg	32

fasted for 16 h prior to the 14 day observation period. None of the rats died during the study (Table 4).[29]

A total of 25 young adult albino rats, Wistar derived, were distributed into groups of 5, each containing 2 females and 3 males. The body weights ranged between 200 and 300 g. The five dosage groups received from 2.5 to 40.0 g/kg of steareth-2 as a 25% corn oil solution and were observed for 14 days. An LD_{50} value of 21 g/kg was reported (Table 4).[30]

An oral LD_{50} value of > 16 g/kg in rats was determined for steareth-2 and steareth-10 in tests "performed according to the French regulations and protocols." Neither the concentration of steareth-10 or steareth-2 nor the vehicle used was stated, and no protocol for the acute oral toxicity test was submitted with the data (Table 4).[31]

Steareth-20, with 0.01% BHA and 0.005% citric acid added as preservatives, was administered in a 25% weight per volume dose in distilled water to determine the LD_{50} value. Doses ranging from 1.26 to 3.98 g/kg were administered to groups of five male and five female Sprague-Dawley CD (Charles River) rats that had been fasted for 16 h. The resulting LD_{50} value of 2.07 g/kg was calculated after a 14 day observation period (Table 4).[32]

In another study, steareth-20 was administered as a 25% corn oil solution to 25 Wistar-derived young adult albino rats (200–300 g). The five dosage groups, consisting of two females and three males, received doses of 0.31, 0.63, 1.25, 2.50, and 5.00 g/kg. After an observation period of 14 days, an LD_{50} value of 2.1 g/kg was determined (Table 4).[33]

A body lotion containing 2.75% steareth-2 and 2.25% steareth-20 was administered to Wistar strain rats (206–244 g), five males and five females, to determine its acute oral toxicity. After 18 h of fasting a single dose of 5 g/kg was given and the rats were observed for 14 days. Of 10 animals, 2 died during the test. The animals were killed after the test and necropsied, and the 2 animals that died during the test had "fibrous tissue encasing heart and lungs," whereas the surviving animals' necropsies were normal (Table 4).[34]

The acute oral toxicity of a roll-on antiperspirant containing 1.8% steareth-2 was determined in another test. Five female and five male Wistar-derived albino rats, weighing between 180 and 216 g, were administered a single 10 g/kg dose of the antiperspirant. The product was "used as received." Of the 10 rats in the study, 2 died. After the 14 day observation period the animals were killed and subjected to necropsy. One of the 2 rats that died during the test was found to have "fibrous tissue encasing the heart and lungs" (Table 4).[35]

A mousse (conditioner) containing 0.6% steareth-2 was given to five female and five male rats in a dose of 5.0 ml/kg. The initial body weight of the rats varied between 184 and 269 g. The animals were observed for 14 days following dosage and killed and necropsied after the test period. All 10 rats survived the test. After necropsy, "organs of the thorax and abdomen appeared normal" (Table 4).[36]

In another study, a mousse formulation containing 0.6% steareth-2 was tested for its acute oral toxicity. Six rats, three males and three females, were fed a single 10 g/kg dose of the mousse. The rats weighed between 200 and

284 at the beginning of the 14 day observation period. All six rats survived and were killed at the conclusion of the test. Upon necropsy no gross changes were found in the organs of the thorax and abdomen (Table 4).[37]

An acute oral toxicity test was performed on a mousse conditioner containing 0.6% steareth-2. The formulation was administered in a 5 ml/kg dose to five male and five female rats. The rats weighed from 202 to 208 g. All 10 of the rats survived the test, and following the 14 day observation period the animals were killed and necropsied. Following necropsy, "organs of the thorax and abdomen appeared normal" (Table 4).[38]

A mousse (conditioner) formulation containing 0.6% steareth-2 was fed in a dose of 5.0 ml/kg to five male and five female rats. All 10 of the rats (200–209 g) survived the administration of the formulation. After an observation period lasting 14 days, the rats were killed and necropsied and all findings were reported as normal (Table 4).[39]

A rat oral toxicity test was performed for a light yellow, cream moisturizer containing 1.5% steareth-20. Fasted Charles River Fischer 344 rats, five males and five females, which weighed between 120 and 190 g, were used in the study. Each animal received a single dose, by gavage, of 10 ml of the undiluted moisturizer per kg body weight. No signs of toxicity were observed during the 2 week study and none of the animals died. The investigators found "a single 10 ml/kg dose of this formulation represents a nonlethal, nontoxic dose in rats" (Table 4).[40]

Intraperitoneal

Steareth-2, as a 10% weight per volume solution in normal saline, was administered to Wistar SPF rats in an evaluation of acute intraperitoneal toxicity. Five dosage groups of five female and five male rats were fasted for 16 h prior to the test. The doses ranged from 0.50 to 1.26 g/kg, and the animals were observed for 14 days. An intraperitoneal LD_{50} value of 0.76 g/kg was calculated (Table 4).[29]

In another study, steareth-20 was given to four dosage groups of five male and five female Wistar SPF rats. Doses of a 10% weight per volume solution of steareth-20 in isotonic sodium chloride ranged from 0.126 to 0.251 g/kg. After a 14 day observation period an LD_{50} value of 0.190 g/kg was calculated (Table 4).[32]

Intravenous

A 1% weight per volume solution of steareth-2 in propylene glycol was administered to five groups of 10 rats, five females and five males. These Wistar SPF rats were fasted for 16 h prior to being given the doses ranging from 0.0159 to 0.100 g/kg. The resulting LD_{50} value of 0.041 g/kg was calculated after a 7 day observation period (Table 4).[29]

In another study, steareth-20 in a 10% weight per volume solution in isotonic sodium chloride was given to five dosage groups of Wistar SPF rats. The groups, made up of five females and five males, had been fasted for 16 h prior to the test. After a 7 day observation period, an LD_{50} value of 0.164 g/kg was calculated (Table 4).[32]

Irritation

Ocular

Three groups of six rabbits each were used to evaluate the eye irritation potential of steareth-2, -10, and -20. The Draize[41] test methodology was employed. A 60% aqueous solution or dispersion of the polyoxyethylene stearyl ether was instilled in a single 0.1 ml dose in one eye of each rabbit; the untreated eye served as a control. The treated eyes of an unspecified number of rabbits received a water rinse (20 ml) 2 s following instillation of the test material; the treated eyes of the remaining animals received no water rinse. Ocular irritation was assessed at 1, 24, 48, 72, and 96 h and at 7 days. Scores obtained by the Draize system were interpreted according to the terminology of Kay and Calandra.[42] This classification consists of eight descriptive ratings with increasing intensity of irritation as follows: (1) nonirritating, (2) practically nonirritating, (3) minimally irritating, (4) mildly irritating, (5) moderately irritating, (6) severely irritating, (7) extremely irritating, and (8) maximally irritating. In rabbits given no water rinse, steareth-10 was "practically nonirritating" to the conjunctiva, whereas steareth-2 and -20 were "minimally irritating" to the conjunctiva. In rabbits given a water rinse, all three ethers were "nonirritating" to the conjunctiva. No irritation of the cornea or iris was observed in rinsed or nonrinsed eyes (Table 5).[4]

In another rabbit eye irritation study, steareth-2 was tested on six young healthy adult albino rabbits according to the procedure described in 16 CFR 1500.42. The test material, 100 mg, was placed in one eye of each rabbit, and the other eye served as a control. The eyes were examined, and the ocular reactions were recorded 24, 48, and 72 h after the instillation of the test material and again 7 days after the test. No effects were observed in the iris or cornea, although one rabbit had conjunctival redness. The score for this individual rabbit was 2 of a possible 20; the score represented a case in which the "vessels are definitely injected above normal." The conjunctival effects cleared during the 7 day observation period. The investigators reported steareth-2 "is not an irritant to the rabbit eye" (Table 5).[30]

Steareth-2, in solutions of 60, 40, and 10% weight per volume in distilled water, was instilled into rabbit eyes. Nine eyes, three with a water rinse and six without a water rinse, were used for each solution. The eyes were examined and the observations scored at 1, 24, 48, 72, and 96 h after the instillation of the test material and again after 7 days. None of the solutions in rinsed eyes produced scored reactions, whereas the reactions produced by the 60% solution in unrinsed eyes had a total score of 3.3 of a possible 110.0. Reactions produced by both the 40 and 10% solutions had, of 110.0 possible, a score of 0.3. According to the classification scheme of Kay and Calandra, as described earlier, the 60% solution was "minimally irritating" in unrinsed eyes and "nonirritating" in eyes rinsed 2 s after exposure. Both the 40 and 10% solutions were "nonirritating" in rinsed and nonrinsed eyes (Table 5).[29]

Two groups of six rabbits each were used to test the eye irritancy of 10% solutions of steareth-2 and steareth-10 in water. Into one eye of each rabbit 0.10 ml of either solution was instilled; the other untreated eye served as a

TABLE 5. Ocular Irritation

Material tested	*Steareth concentration*	*No. of rabbits*	*Method*	*Degree of irritation and conclusions (MAOI[a])*		*Reference*
				No water rinse	*Water rinse*	
Steareth-2	60% in water	6	References 41 and 42	Minimally irritating	Nonirritating	4
	Unspecified	6	16 CFR: 1500.42; no water rinse	Not an irritant to the rabbit eye (2.0 of 110.0)	—	30
	60% in distilled water	9	Modified Draize[41]; also Reference 42	Minimally irritating (3.3 of 110.0)	Nonirritating (0.0 of 110.0)	29
	40% in distilled water	9	Modified Draize[41]; also Reference 42	Nonirritating (0.3 of 110.0)	Nonirritating (0.0 of 110.0)	29
	10% in distilled water	9	Modified Draize[41]; also Reference 42	Nonirritating (0.3 of 110.0)	Nonirritating (0.0 of 110.0)	29
	10% in water	6	Modified Draize[41]; no water rinse	(6.7 of 110)	—	31
	2.75% in body lotion with 2.25% steareth-20	6	Modified Draize[41]; no water rinse	Not an ocular irritant to rabbits (0.3 of 110.0)		34
	1.8% in antiperspirant	9	Modified Draize[41]; no water rinse	Mild ocular irritant to rabbits (3.3 of 110.0)	(2.0 of 110.0)	35
	0.6% in mousse conditioner	6	Modified Draize[41]; no water rinse	(6.0 of 110.0)	—	36
	0.6% in mousse conditioner	6	Modified Draize[41]; no water rinse	(5.7 of 110.0)	—	38
	0.6% in mousse conditioner	3	Modified Draize[41]; no water rinse	(15.4 of 110.0)	—	37

	0.6% in mousse conditioner	9	Modified Draize[41]	(17.0 of 110.0)	(11.8 of 110.0)	39
Steareth-10	60% in water	6	References 41 and 42	Practically nonirritating	Nonirritating	4
	10% in water	6	Modified Draize[41]; no water rinse	(4.3 of 110.0)	—	31
Steareth-20	60% in water	6	References 41 and 42	Minimally irritating	Nonirritating	4
	Unspecified	6	16 CFR and 1500.42; no water rinse	Moderate irritant to the rabbit eye (23.0 of 110.0)		33
	60% in distilled water	9	Modified Draize[41]	Minimally irritating (0.7 of 110.0)	Nonirritating (0.0 of 110.0)	32
	4% in texturizing conditioner	Unspecified	14 doses of 0.1 ml via unspecified procedure	Slight conjunctivitis throughout study		43
	4% in texturizing conditioner	Unspecified	14 doses of 0.1 ml via unspecified procedure	Slight conjunctivitis throughout study		43
	4% in pink, creamy cosmetic	6	0.1 ml in one eye via unspecified procedure	Slight "conjunctival hyperemia" in 4 of 6 rabbits		44
	4% in pink, creamy cosmetic	6	0.1 ml in one eye via unspecified procedure	Slight "conjunctival hyperemia" in 4 of 6 rabbits		44
	1.5% in moisturizer	6	0.1 ml in one eye via unspecified procedure	Slight conjunctivitis in 6 of 6 rabbits, cleared by 24 h		40

[a]Maximum average ocular irritation.

control. The treated eyes that did not receive a water rinse were observed 1, 2, 3, 4, and 7 days after the instillation of the test solution. The average ocular index (AOI) score, measured after 24 h, was 6.7 for steareth-2 and 4.3 for steareth-10 of a 110 possible maximum (Table 5).[31]

A roll-on antiperspirant formulation containing 1.8% steareth-2 was tested for ocular irritancy using nine New Zealand albino rabbits weighing between 1.8 and 2.4 kg. The antiperspirant was used "as received," and 0.1 ml of the formulation was instilled into the rabbit eyes. Three of the rabbits received a 30 ml water rinse 15 s after the instillation of the product. In the group that received no water rinse the maximum score was 3.3 of 110 possible, and for the rinsed eyes the maximum score was 2.0. The investigators found that the formulation was a "mild ocular irritant to rabbits under the conditions of this test" (Table 5).[35]

Each of two formulations of mousse conditioner containing 0.6% steareth-2 was instilled into the eyes of six rabbits. Scores were recorded 1, 24, 48, and 72 h and 7 and 14 days after the test. In both tests, 0.1 ml of the product was instilled into the eyes and the eyes were not rinsed with water. The maximum mean score for one test was 6.0 of 110.0, and the scores ranged from 2 to 12 of 110.[36] In the other test the maximum mean score was 5.7 of 110.0 and the range was from 4 to 6 of 110.[38] All the observed effects involved the conjunctiva alone, and all had cleared by the 72 h observation period (Table 5).

In another study, 0.1 ml of a mousse conditioner containing 0.6% steareth-2 was instilled into the eyes of three rabbits. The eyes were not rinsed with water. The reactions were observed and scored at 1, 24, 48, and 72 h and 7 and 14 days after the instillation. The maximum mean irritation score was 15.4 of 110.0, and individual scores ranged from 2 to 22 of 110. Corneal effects were observed in one rabbit, and all three rabbits had conjunctival effects. All reactions had cleared by the 72 h observation period (Table 5).[37]

Steareth-2, 0.6% in a mousse conditioner formulation, was instilled as a 0.1 ml dose to the eyes of nine rabbits. The resulting reactions were scored at 1, 24, 48, and 72 h as well as 7 and 14 days after the test. The eyes of three of the nine rabbits were rinsed with water 15 s after the instillation of the product. In the unrinsed eyes four of the rabbits had corneal lesions, and all six of the animals had conjunctival lesions. The maximum mean irritation score for the unrinsed eyes was 11.8 of 110.0, and all the lesions had cleared by the 7 day observation period. In the rinsed eyes, the maximum mean score was 17.0 of 110.0. All three of the rabbits had scores for conjunctival lesions, and two of the animals had corneal lesions. All the reactions had cleared by the 7 day observation period (Table 5).[39]

A body lotion formulation containing 2.75% steareth-2 and 2.25% steareth-20 was tested for its eye irritation potential. Six New Zealand white rabbits each received an application of 0.1 ml of the formulation in one eye; the other eye remained untreated and served as a control. The eyes did not receive a water rinse. The reactions were scored 24, 48, and 72 h after the instillation of the body lotion. A score of 0.3 of a maximum of 110 was reported, and all the effects had cleared by the 48 h observation period. The investigators reported

that "this test article is not an ocular irritant to rabbits under conditions of this test" (Table 5).[34]

Steareth-20 was instilled into one eye of six young adult albino rabbits in another test of eye irritation potential. The administration of the sample was not followed by a water rinse, and the untreated eye served as a control. The procedure, as described in 16 CFR 1500.42, calls for observation and recording of the toxic eye effects at 24, 48, and 72 h and at 7 days after the instillation. Corneal effects were observed in one animal with a rating of 0 of 80 at 24 h and 5 of 80 on day 7. Two animals had irideal effects with scores of 5 of 10 at 24 h; one of these animals had a score of 5 of 10 after 7 days, whereas the effect in the other animal had cleared by this time. Conjunctival effects were observed in all six of the animals with a range of scores at 24 h of 8–14 of 20, and after 7 days, of 2–8 of 20. In total the animals had a range of scores, maximum value of 110, from 8 to 19 at 24 h, 8 to 21 at 4 h, 4 to 23 at 72 h, and 0 to 13 after 7 days. Steareth-20, as tested earlier, was reported as a moderate irritant to the rabbit eye when the instillation of the test material was not followed by a water rinse (Table 5).[33]

The eyes of nine rabbits were exposed to a 60% w/w solution of steareth-20 in distilled water. Into one eye of each rabbit 0.1 ml of the solution was instilled; the other untreated eye served as a control. Six of the rabbits received no water rinse; three of the rabbits had their eyes rinsed with 20 ml of water 2 s after the instillation of the test material. The eyes were observed and the reactions scored 1, 24, 48, 72, 96, and 168 h after the test. No corneal or iridial effects were observed in the nine rabbits. The maximum score for the conjunctiva was 0.7 of a maximum of 110 for the unrinsed eyes; the rinsed eyes had no conjunctival effects. Steareth-20 (60%), according to the classification of Kay and Calandra as described earlier, was "minimally irritating" in unrinsed eyes and "nonirritating" in rinsed eyes (Table 5).[32]

A comparative ocular irritation study was completed for a texturizing conditioner versus a texturizing conditioner base, both formulations contained 4% steareth-20. Rabbits received 14 doses of 0.1 ml of the product via an unspecified procedure. The results reported by the investigators stated that "both formulations elicited slight conjunctivitis which persisted intermittently throughout the study." No corneal or iridial effects were observed (Table 5).[43]

Two formulations of a pink creamy cosmetic containing 4% steareth-20 were submitted for acute ocular irritation testing. New Zealand albino rabbits, three of each sex, were used to test each formulation. Each rabbit was treated once in one eye with 0.1 ml of the full-strength formulation. It was not stated how many, if any, of the animals received a water rinse. Ocular reactions were observed and scored 1, 24, 48, and 72 h and also 7 days after the instillation of the product. One formulation caused slight conjunctival hyperemia to develop within 1 h in 4 of 6 rabbits. The rabbits treated with the other formulation had slight conjunctivitis 1 h after the treatment. All the effects from both formulations cleared within 24 h (Table 5).[44]

Six New Zealand albino rabbits were used to evaluate the acute ocular irritation potential for a moisturizer formulation containing 1.5% steareth-20.

TABLE 6. Rabbit Skin Irritation

Material tested	*Steareth concentration*	*No. of rabbits*	*Method*	*PII*[a]	*Degree of irritation*	*Reference*
Steareth-2	60% in aqueous solution	6	Draize[41]; 24 h patch	1.0	Mild irritant	4
	60% in aqueous solution	6	Draize[41]; 24 h patch	1.0	Mild irritant	29
	40% in aqueous solution	6	Draize[41]; 24 h patch	0.17	Mild irritant	29
	10% in aqueous solution	6	Draize[41]; 24 h patch	0.0	Nonirritant	29
	Unspecified	6	Draize[41], 24 h patch	0.13	Nonirritant	30
	10% in aqueous solution	Unspecified	Modified Draize[41]; 24 h patch	0.1	—	31
	2.75% steareth-2 and 2.25% steareth-20 in body lotion	6	Draize[41]; 24 h occlusive patch	0.50	Not a primary irritant	34
	1.8% in roll-on antiperspirant	6	Draize[41]; 24 h occlusive patch	0.0	Not a primary irritant	35
	0.6% in mousse conditioner	6	Draize[41]; 24 h patch	0.92	Not a primary irritant	39
	0.6% in mousse conditioner	6	Draize[41]; 24 h patch	0.59	Slight irritant	37
	0.6% in mousse conditioner	6	Modified Draize[41]; 4 h occlusive patch	0.13	Not a primary irritant	36
	0.6% in mousse conditioner	6	Modified Draize[41]; 4 h occlusive patch	0.33	Not a primary irritant	38
Steareth-10	60% in aqueous solution	6	Draize[41]; 24 h patch	0.17	Mild irritant	4
	10% in aqueous solution	Unspecified	Modified Draize[41]; 24 h patch	0.3	—	31
Steareth-20	60% in aqueous solution	6	Draize[41]; 24 h patch	0.0	Nonirritant	4
	60% in aqueous solution	6	Draize[41]; 24 h patch	0.0	Nonirritant	32

Unspecified	6	Draize[41]; 24 h patch	0.83	Mild irritant	33
5.0% in solid antiperspirant	4	Draize[41]; 24 h occlusive patch; same rabbits used to test another formulation at the same time	2.8	Mild irritant	45
5.0% in solid antiperspirant	4	Draize[41]; 24 h occlusive patch; same rabbits used to test another formulation at the same time	1.8	Mild irritant	46
4% in pink, creamy cosmetic	3	Four daily 0.5 ml doses for 7 days; same rabbits as used with formulation below	3.0	—	44
4% in pink, creamy cosmetic	3	Four daily 0.5 ml doses for 7 days; same rabbits as used with formulation above	2.8	—	44
1.5% in moisturizer	3	Four daily 0.5 ml doses for 7 days	3.1	—	40

[a]Primary irritation index (maximum = 8.0).

Each animal was treated once in one eye with a dose of 0.1 ml of the undiluted formulation. It was not stated whether the eyes received a water rinse. The ocular reactions were observed and scored 1 h after treatment and on days 1, 2, 3, and 7. Slight conjunctivitis developed in all the treated eyes 1 h after the treatment. No other signs of irritation were reported (Table 5).[40]

Dermal

The Draize procedure was used to assess the skin-irritating effects of steareth-2, -10, and -20.[41] The three polyoxyethylene stearyl ethers were each evaluated at a concentration of 60% in aqueous solution or dispersion. A 1 inch patch containing 0.5 ml of one of the test solutions or dispersions was applied to intact and abraded sites of the clipped skin of six albino rabbits. After 24 h, the patch was removed and the treated site graded for skin irritation. The treated site was scored a second time 48 h following patch removal. A primary irritation index* value was calculated for each material from scores of irritation based on a scale of 0 (no erythema or edema) to 8 (severe erythema and edema). The primary irritation index scores for steareth-2 and -10 were 1.00 and 0.17, respectively, indicating mild skin irritation. The primary irritation index score for steareth-20 was 0.0 indicating no skin irritation (Table 6).[4] The report did not indicate whether these scores were for the first or second evaluation (grading) and whether the scores related to intact or abraded sites.

In order to test their dermal irritancy, three solutions of steareth-2; 60, 40, and 10% weight per volume in water, were applied to the skin of New Zealand albino rabbits. Using the Draize 1959 procedure, 0.5 ml of each solution was placed on a 1 inch square of gauze and applied to the skin of six rabbits. Three of the rabbits for each solution had intact skin; the other three had abraded skin. The bandages were removed after 24 h and the reactions to the test solution were scored then and again after 72 h. The scores, based on the scale described earlier, were averaged for both time periods and for both intact and abraded skin. The primary irritation index values reported were 1.0 for the 60% solution, 0.17 for the 40% solution, and 0.0 for the 10% solution. The 60 and 40% solutions were classified as "mild irritants," and the 10% solution was classified as a "nonirritant" (Table 6).[29]

Steareth-2 at an unspecified concentration was tested for its dermal irritation potential. The method was patterned after the 16 CFR 1500.41 description of the Draize 1959 procedure. This acute skin irritation test was performed on six adult albino rabbits. Steareth-2, 0.5 ml or 0.5 g, was introduced under a 1 inch square of gauze to the shaved backs of the animals. The skin on half of the animal was left intact and the skin on the other side was abraded. The patches were removed and the reactions scored 24 h and again 72 h after the administration of the steareth-2. The primary irritation index

*The primary irritation index (PII) is a value depicting the average skin response of the test group as a whole; it is calculated by adding the irritation scores of all animals and then dividing the total by the number of animals tested.

value was reported as 0.13 and was averaged over both time periods and intact and abraded sites. Steareth-2 was not an irritant to rabbit skin (Table 6).[30]

A modified Draize[41] procedure was used to determine the dermal irritancy of steareth-2 and steareth-10 in 10% aqueous solutions. Each solution, 0.5 ml, was applied under gauze measuring 6.2 cm^2 in area to the shaved backs of an unspecified number of rabbits. Half the shaved skin of each animal was abraded and the other half remained intact. The patches were removed after 24 h, and the reactions were scored then and again after 72 h using the scale described earlier. Averaged for both time periods and both intact and abraded sites, the primary irritation index value was 0.1 for the steareth-2 solution and 0.3 for the steareth-10 solutions (Table 6).[31]

A body lotion formulation containing 2.75% steareth-2 and 2.25% steareth-20 was tested for primary dermal irritation in rabbits. The lotion was used as received in a modification of the procedure described by Draize in 1959. Six albino New Zealand rabbits were prepared by shaving their backs and slightly abrading half the shaved skin. The lotion, 0.5 ml, was applied to the backs under an occlusive patch. The dermal reactions were scored on a scale as described earlier, after the patches were removed at 24 h and again after 72 h. The reported primary irritation index score was 0.50 and was averaged over both time periods and both intact and abraded sites. The investigators reported the lotion "is not a primary dermal irritant to rabbits under conditions of this test" (Table 6).[34]

A modified Draize procedure was used to test the dermal irritancy of a roll-on antiperspirant formulation containing 1.8% steareth-2. Three male and three female New Zealand albino rabbits were used for the test; the skin on the backs was shaved and half of it slightly abraded; the other half remained intact. A single application of 0.5 ml of the antiperspirant was applied under an occlusive patch to both intact and abraded sites. The patches were removed after 24 h and the reactions scored both at 24 and 72 h after the application of the patches. The primary irritation index was 0.0, indicating that the antiperspirant formulation "is not a primary irritant to rabbits under conditions of this test" (Table 6).[35]

Two mousse formulations, each containing 0.6% steareth-2, were tested for their dermal irritancy. Each sample was applied to intact and abraded sites on the skin of six rabbits. The dermal reactions were scored at 24 and 72 h after the application of the sample. One formulation had a primary irritation index of 0.92 reported,[39] and the primary irritation index was reported as 0.59 for the other formulation.[37] The PII scores were averages calculated from the scores for both the 24 and 72 h time periods and the intact and abraded sites. The former was considered "not a primary skin irritant," whereas the latter was classified as "being slightly irritating to the skin" (Table 6).

In two other studies, two formulations of mousse conditioner each containing 0.6% steareth-2 were also tested for their dermal irritation potential. One formulation was applied in an occlusive patch for 4 h to the intact and abraded skin of six rabbits; the reactions were scored 24 and 72 h after the application of the sample. The primary irritation index score was 0.13, indicating that the formulation "is not a primary skin irritant".[36] The other mousse conditioner preparation was placed into contact with the intact and abraded

skin of six rabbits for 4 h. After the 24 and 72 h observation periods, the primary irritation index was calculated as 0.33, again indicating that the sample "is not a primary skin irritant".[38] Both PII scores were averaged over the intact and abraded sites as well as both time periods (Table 6).

A 60% aqueous dispersion of steareth-20, with 0.01% BHA and 0.005% citric acid added as preservatives, was applied to the skin of New Zealand albino rabbits to determine its dermal irritancy. The dispersion, 0.5 ml, was placed on a 1 inch piece of gauze and applied to the bare skin of the rabbit. Six rabbits, three with intact skin and three with abraded skin, received such patches. The patches were removed after 24 h and the reactions scored then and again after 72 h. All scores reported for both intact and abraded skin at both time periods were zero. On the scale described earlier, the investigators found the dispersion of steareth-20 is "nonirritating" (Table 6).[32]

A primary skin irritation study with rabbits was undertaken with an unspecified concentration of steareth-20. The method employed in this study was patterned after the Draize procedure described in 16 CRF 1500.41. The material, 0.5 ml or 0.5 g, was placed on the shaved skin of six adult albino rabbits. The skin on half of the back of each rabbit was abraded; the other half remained intact. The patches, made of 1 inch square gauze, were removed after 24 h and scored then and again after 72 h. The scale used was described in an earlier portion of this section, and a primary irritation index value of 0.83 was reported; the PII was averaged over both sites and time periods. The test material, steareth-20, was a mild irritant to the rabbit skin (Table 6).[33]

A solid antiperspirant formulation containing 5.0% steareth-20 was tested for dermal irritancy. Occlusive patches containing 0.5 ml of the undiluted antiperspirant were applied to the clipped skin of four New Zealand white rabbits. The adult rabbits weighed between 1.4 and 2.1 kg. Two patches were applied to each rabbit; one was on intact skin, and the other was placed on abraded skin. These same four rabbits were being used to test another solid antiperspirant at the same time as this test. It was not stated whether the other solid antiperspirant formulation contained steareth-20. The dermal reactions were observed after 24 h, when the patches were removed, and again after 72 h. A primary irritation index score was 2.8, averaged for both intact and abraded sites as well as both time periods, and the investigators reported the formulation was "mildly irritating" (Table 6).[45]

Four New Zealand white rabbits were used to test the dermal irritation potential of a solid antiperspirant formulation containing 5.0% steareth-20. A dose of 0.5 g of the undiluted antiperspirant was applied under occlusive patches to two sites per rabbit, one abraded and one intact. Another solid antiperspirant was being tested on the same rabbits at the same time. It was not stated whether the other antiperspirant formulation contained steareth-20. The primary irritation index score was reported as 1.8 after observing and scoring the sites at 24 and 72 h. The PII value was averaged to include both time periods and skin conditions (intact or abraded). Using the scale described earlier, this formulation would be considered "mildly irritating" (Table 6).[46]

Two formulations of a pink, creamy cosmetic containing 4% steareth-20 were tested for their acute dermal irritation potentials. Three New Zealand

albino rabbits were used to compare the irritancy of the two different formulations of the cosmetic. Four daily 0.5 ml doses of each formulation were placed on opposite sides of the three rabbits, and the dermal irritation was evaluated daily for 7 days. Slight erythema was noted on all treatment sites 1 day after the initial application, which developed into well-defined erythema and slight edema after 3 days. The irritation persisted, and slight desquamation was observed after 7 days on the test. Both formulations caused a pink stain to develop on the treated skin. The primary irritation index score reported was 3.0 for one formulation and 2.8 for the other (Table 6).[44]

Three New Zealand albino rabbits were used to evaluate the dermal irritancy of a moisturizer formulation containing 1.5% steareth-20. The back of the animals were shaved, and four daily doses of the undiluted cosmetic were applied to the shaved area. It was not stated whether the sites treated were abraded or intact skin. Dermal reactions were evaluated daily for 7 days. Slight to well-defined erythema and slight edema developed 24 h after the first application, moderate to severe erythema developed after 3–4 days, and mild desquamation was observed by day 7. An irritation index of 3.1 was calculated for the moisturizer formulation (Table 6).[40]

Subchronic

Dermal

A 3 month dermal toxicity study was conducted on a cosmetic formulation containing 4% steareth-20. A total of 30 New Zealand white rabbits were divided into three dosage groups each containing five males and five females. One group was the untreated control, whereas the other two groups received doses of 4.4 mg/cm^2 per 5.6% body surface area and 6.6 mg/cm^2 per 11.2% body surface area. These doses were chosen to represent factors of 4 and 12, respectively, over the maximum anticipated human exposure of 2.2 mg/cm^2 per 2.8% body surface area. The determination of human exposure was made on the assumption that a 55 kg person would use 1.0 g of the formulation each day to cover an approximate area on the face of 450 cm^2 or 2.8% of the body surface area. The animals were treated daily with the test material and observed daily for changes in behavior or appearance. Observations of the skin were also made each day, and the reactions were scored for dermal irritation using the standard Draize scale as described in the dermal irritation sectio of this report. Body weights, feed consumption, clinical chemistry, hematologic studies, urinalyses, organ weights, and gross and microscopic evaluation of organs and tissues were the other monitored parameters. The cosmetic formulation caused persistent well-defined to moderate erythema, slight edema, and slight desquamation. A single male animal receiving a dose of 4.4 mg/cm^2 per day died of purulent pneumonia after 43 days of the test. The results of clinical chemistry and hematologic studies conducted on all animals involved in the study were negative for any toxicologically significant findings. The male rabbits in the two groups receiving doses of the formulation had a slight increase in liver weight relative to the controls. No

treatment-related changes other than mild inflammation at the application site were found by histopathologic examination. The investigators reported that "under the conditions of this test, there was no evidence of systemic toxicity that would contraindicate the use of [the cosmetic product]." The irritation to the skin observed in the rabbits was thought not to indicate a potential hazard in humans.[47]

Forty New Zealand white rabbits were used in a 3 month, subchronic toxicity study of a cosmetic formulation containing 4% steareth-20, administered dermally. The four dosage groups each contained five males and five females and consisted of an untreated control group, a vehicle control group, and two treatment groups receiving 7.5 mg/cm^2 per 10% body surface area and 15 mg/cm^2 per 10% body surface area. The doses selected represent multiples of 132 and 268 over the anticipated maximum human exposure of 2.25 mg/cm^2 per 0.25% body surface area. The vehicle control was applied at the highest dose; it was not stated whether the vehicle control contained steareth-20. The animals were observed daily for changes in appearance or behavior. They were also observed and scored for dermal irritation each day. The other monitored parameters included body weight, feed consumption, hematology, clinical chemistry, organ weight, enzyme induction, and gross and microscopic evaluation of tissues and organs. A single female rabbit died of pneumonia after 83 days on the test in the vehicle control group. The investigators reported that "the death was not treatment related." Both doses of the cosmetic caused less dermal irritation than the vehicle control. Dermal irritation of rabbits in the vehicle control group ranged from slight to severe erythema, slight to moderate edema, and slight to moderate desquamation. Rabbits in both dosage groups of the cosmetic formulation had reactions ranging from slight to moderate erythema and slight to moderate edema. These dermal irritation reactions were the only treatment-related efects observed. The investigators reported that under the conditions of this test the cosmetic formulation caused no systemic toxicity and only slight to moderate dermal irritation.[48]

MUTAGENICITY

No mutagenicity information on the steareth compounds themselves is available.

An alcohol ethoxylate with an unspecified alcohol chain length and an average value of six ethylene oxide units was tested for its mutagenic potential. In an acute dominant lethal assay, male mice were given oral doses of either 100, 500, or 1000 mg/kg of the ethoxylate. In a subacute dominant lethal assay, male mice were given oral doses of either 20, 100, or 200 mg/kg of the ethoxylate. The mutagenic indices did not significantly vary from control values.[24]

Hamsters were given oral doses of 80, 400, or 800 mg/kg of the alcohol ethoxylate described earlier. The animals were killed at 6, 24, or 48 h after the dose was given. No significant differences in chromosomal anomalies were noted in the bone marrow cells of the hamsters.[24]

Human leukocytes were incubated for 18, 24, and 48 h with concentrations of 2, 20, or 100 μl/kg of the alcohol ethoxylate. No significant chromosomal anomalies were observed.[24]

CARCINOGENICITY

A polyoxyethylene alkyl ether (PAE) was tested to determine its carcinogenic and cocarcinogenic properties. The length of the alkyl chain and number of ethylene oxide units were not stated and the formula was listed as $R\text{-}O(CH_2CH_2O)_nH$. The PAE was tested in a solution of 50% in benzene. A drop of the solution was painted on the skin of mice twice each week for 1 year. PAE alone did not produce skin tumors in mice.[49]

CLINICAL ASSESSMENT OF SAFETY

Dermal Irritation and Sensitization

A Schwartz patch test was conducted to determine the skin irritation potential of steareth-2, -10, and -20. A cotton dressing saturated with one of the test materials (60% in aqueous solution) was applied to the skin of 200 human subjects by means of an elastic adhesive patch. The dressing was allowed to remain in contact with the skin for 72 h. A second 72 h occlusive dressing was applied to the original exposure site 10 days after the initial application. Steareth-2, steareth-10, and steareth-20 produced no skin irritation (Table 7).[4]

Steareth-2 in a concentration of 60% in water was used in a prophetic patch test to determine its potential for dermal irritation and sensitization in humans. A 1 inch piece of cotton twill was covered with the solution and applied to the skin of the human subjects with an elastic adhesive patch 2 inch square. The patch was left in contact with the skin for a 72 h period. After this time period the patch was removed and the treated skin observed. The solution was reapplied in exactly the same manner to the same area of skin 10–14 days after the removal of the first patch. After the second 72 h time period that the solution was left in contact with the skin the dermal reactions were once again observed. None of the 200 subjects tested reacted to either patch test. The 60% solution of steareth-2 in water was neither a primary dermal irritant nor a sensitizer to humans (Table 7).[29]

A white foam mousse conditioner containing 0.6% steareth-2 was tested to assess its irritancy potential to human skin caused by repetitive topical application. The sample, in a 1:2 dilution in water, was applied to the forearms of 17 volunteer men and women between 18 and 65 years of age. These same volunteers were also being tested at the same time with five other cosmetic formulations not containing steareth-2. The procedure used was a modification of that described by Kligman and Frosch.[58] A plastic cup 16 mm in diameter was filled with cotton cloth onto which 0.2 ml of the sample had

been placed. The cup was then applied to the forearm using a nonocclusive tape. The cup was left in place for 24 h the first day of the test and then for 6 h for the remaining 6 days of the test; the reactions were scored after the removal of the cup on all 7 days of the study. The scale used measured erythema from values of 1, slight spotty or diffuse redness, to 4, very red with edema; scaling from values of 1, fine scaling, to 3, severe scaling with large flakes; and fissures from values of 1, fine cracks, to 3 wide cracks with hemorrhage or exudation. For the formulation tested, the values ranged from 0 to 2 for erythema and 0 to 1 for scaling and fissures over all 17 subjects tested.

TABLE 7. Clinical Assessment of Safety: Human Dermal Irritation, Sensitization, and Photosensitization

Ingredient	*Type of test*	*No. of subjects*	*Results and Comments*	*Reference*
Steareth-2 (60% in water)	SIPT[a]	200	No skin irritation	4
	SIPT	200	No skin reactions, not a primary irritant or a skin sensitizer	29
Steareth-2 (0.6% in mousse conditioner)	A 24 h patch, followed by six 6 h patches over 7 days	17	Total mean irritation 1.353 of 10.0	50
Steareth-2 (2.75% in a tan product with 2.25% steareth-20)	Phototoxicity, one exposure of UV-B light	25	No reaction to moderate erythema attributed to the erythema dosage of UV-B; not phototoxic or a primary irritant	56
Steareth-10 (60% in water)	SIPT	200	No skin irritation	4
Steareth-20 (60% in water)	SIPT	200	No skin irritation	4
	SIPT	200	No skin irritation; not a primary irritant or a skin sensitizer	32
Steareth-20 (4% in a cosmetic)	RIPT[b]	205	Four reactions during induction phase, 13 reactions at challenge, not a primary irritant or an allergic contact sensitizer	51
	RIPT	200	Seven reactions during induction phase, one reaction at challenge, not a primary irritant or an allergic contact sensitizer	52
	Cumulative irritation test, 21 days	11	Irritation score 24 of 630; mild material with no evidence of cumulative irritation	54
	RIPT	25	Two reactions during induction phase, no reactions at challenge, not a dermal irritant or sensitizer	55
Steareth-20 (1.5% in a moisture lotion)	RIPT	189	During induction phase 21 reactions; 9 reactions at challenge; not an allergic contact sensitizer	53
Steareth-20 (4% in a cosmetic)	Photoallergy, RIPT with UV-A and UV-B during induction, UV-A only at challenge	31	Slight reactions on all irradiated sites during induction phase; no reactions at challenge; not an inducer of contact photoallergy, contact dermatitis, or sensitization	55
	Phototoxicity, SIPT with UV-A exposure	10	No reactions, not a contact dermal photoirritant	57

[a]Single-insult patch test.
[b]Repeat insult patch test.

The total mean irritation score reported was 1.353 of a maximum of 10 (Table 7).[50]

A prophetic patch test was conducted using a 60% solution of steareth-20 in water. The solution was placed on a 1 inch square of cotton twill that was then applied to the skin of the human subjects with an elastic adhesive patch. The patch remained in contact with the skin for 72 h, after which it was removed and the dermal reactions observed. A second patch was applied in exactly the same manner 8 days after the removal of the first patch, and skin was evaluated again after a contact period of 72 h. Of the 200 subjects tested, none reacted to either the first or second application. The 60% solution of steareth-20 was neither a skin sensitizer nor a primary irritant to human skin (Table 7).[32]

A cosmetic formulation containing 4% steareth-20 was used in a repeated insult patch testing study based on a modified Draize-Shelanski method. The study was conducted on healthy men and women ranging in age from 18 to 65; 205 subjects completed the 6 week testing period. The undiluted cosmetic, 0.1 g, was placed in occlusive patches on the upper back or inner upper arm of the subjects. During the first 3 week induction period the patches were applied on Monday, Wednesday, and Friday to be left on for 24 h, and the reactions were scored from these patches prior to the application of the next patch. In the fourth week patches were applied on Monday and the reactions read 48 h after the application on Wednesday of week 4. On Monday of week 6 the final challenge patch tests were applied, 1 to the original testing site and 1 to a previously untreated site. These challenge patches were left in contact with the skin for 48 h and were scored then and again 72 h after they were applied. The patch sites were scored on a scale with values of 0 (negative), 1+ (erythema only), 2+ (erythema and edema or induration), 3+ (erythema, edema or induration, and vehiculation), and 4+ (erythema, edema or induration, bulla (blisters), with or without ulceration). After the second and the fifth induction patches, 1 of 205 subjects had a 1+ reaction. Following the sixth and seventh induction patches, 1 of 205 subjects had a 2+ reaction. Following the challenge patch testing, 9 of 204 subjects and 3 of 205 subjects had a 1+ reaction 48 h after the patch was applied to the original and unteated site, respectively. At the challenge untreated site after 72 h, 1 of 205 subjects had a 1+ reaction and none of the subjects reacted to the challenge patch at the original site after this time. The investigators found the test product did not appear to be an allergic contact sensitizer or a primary irritant (Table 7).[51]

A repeated insult patch test using a modified Draize-Shelanski method was conducted on a cosmetic formulation containing 4% steareth-20. The procedure used was the same as described in the previous paragraph, with the exception that semiocclusive patches were used and the challenge patches were applied to previously untreated sites only. After induction patches numbered 2, 7, 8, 9, and 10, one of the 200 subjects completing the study had a 1+ reaction. A single subject had a 2+ reaction following the fourth induction patch. Another 2 subjects had a 1+ reaction after the fifth induction patches. No reactions were observed from the challenge patch after 48 h, and 1 of 200 subjects had 1+ reactions to the challenge patch at the 72 h observation period. The investigators reported the rare 1+ and 2+ reactions

in the testing of the formulation were irritant in nature and were not considered clinically significant. Therefore, the test product was neither a primary irritant nor an allergic contact sensitizer (Table 7).[52]

A moisturizing lotion formulation containing 1.5% steareth-20 was tested using a modified Draize-Shelanski method as described in the previous paragraphs. The challenge patches were applied only to previously untreated sites. After the third induction patch, 1 of 189 had a 1+ reaction and 2 of 189 had 2+ reactions. Following the fourth patch, 1 of 189 subjects had a 2+ reaction. After the fifth induction patch, 2 of 188 subjects had 1+ reactions. Following the sixth induction patch, 3 of 188 subjects had a 1+ reaction and 2 of 188 had 2+ reactions. After the seventh induction patch, 3 of 188 subjects had 1+ reactions and 1 of 188 had a 2+ reaction. After the eighth induction patch 5 subjects had skin reactions; 3 of 187 had 1+ reactions and 2 of 187 had 2+ reactions. A single subject had a 1+ reaction after the tenth induction patch. After the challenge patch on the untreated site, 1 of 189 had a 1+ reaction and 1 of 189 had a 2+ reaction following the 48 h contact and observation period. After the 72 h observation period, 6 of 189 had 1+ reactions and 1 of 189 had a 2+ reaction. The reactions of 3 subjects were explained as caused by a cumulative irritation reaction, multiple cutaneous allergic reactions in the past, and moderately severe hand dermatitis. The remaining 1+ and rare 2+ reactions "were judged to be irritant in nature, and are not considered to be clinically significant." The cosmetic formulation was not an allergic contact sensitizer (Table 7).[53]

A human skin test of cumulative irritation was performed for a cosmetic formulation containing 4% steareth-20. A panel of 11 subjects, 1 male and 10 females with an age range of 18–59 years, was used to test the irritancy of 10 test materials simultaneously. The scores for 1 panelist were not included in the calculations because that panelist was believed to be presensitized to a common ingredient in all the cosmetic formulations tested. The sample, 0.2 ml, was applied under a closed patch for 23 h for 21 consecutive days. The skin reactions were observed 1 h after the removal of each patch for a total of 22 days. The sample containing the steareth-20 had a score of 24 of a maximum possible of 630. This formulation was a mild material with "essentially no evidence of cumulative irritation under conditions of the test" (Table 7).[54]

A formulation containing 4% steareth-20 was used in a repeat insult patch test to determine its skin irritation and sensitization potential. Occlusive patches containing 0.2 g of the undiluted cosmetic were applied to the upper back of the subjects, ranging in age from 18 to 65, and were left on for 24 h followed by a 24 h nontreatment period. The patches were applied for a total of nine times every Monday, Wednesday, and Friday for 3 weeks. The skin reactions were scored before the next induction patch was applied. After a 2 week nontreatment period a challenge patch was applied to a previously untreated site for 24 h and the reactions were scored then and again 48 and 72 h after the patch was applied. After the second induction patch, 1 of 27 subjects had a faint, minimal reaction. Following the seventh induction patch, 1 of 26 subjects had a faint, minimal reaction. None of the 25 subjects completing the study had any reaction to the challenge patch. The formula-

tion did not induce either dermal irritation or sensitization in human subjects (Table 7).[55]

Photosensitization

The phototoxicity of two different cosmetic formulations was tested using human panelists and a xenon-mercury arc lamp. This type of lamp emits ultraviolet-A (UV-A), UV-B, and some UV-C light with a wavelength range of 260–620 nm. With a Mylar sheet as a filter, only UV-A light reaches the subject; both the UV-B and UV-C light is filtered out. One formulation was a white cream tanning product containing 2.75% steareth-2 and 2.25% steareth-20; the other formulation was a yellow cream sunblock containing 3.30% steareth-2 and 2.70% steareth-20. A group of 25 adult female panelists completed the study. On the first day of the test, three sets of two patches each containing 0.3 ml of either of the test products were applied to the thigh of each panelist. The other thigh was exposed to the UV light for a range of time intervals from 10 to 60 s in order to calculate the minimal erythemic dose (MED) for each individual. On the second day of the study the patches were removed and the irritation scored from ±, barely perceptible, through 3, severe, for both erythema and edema. Following the scorings the patches of the test materials were reapplied and left in contact with the skin for 30 minutes. The patches were then removed and the skin cleansed with acetone. One of the three test areas for each formulation was exposed to 1 MED of unfiltered UV light; the second was exposed to 6 MED of UV light filtered through a Mylar film. The third patch for each product was not exposed to the UV light and was covered with a light-occlusive patch for the next 24 h. To serve as a control, one untreated site was exposed and scored the same way as the treated sites. All the test sites were scored again for dermal reactions on the third and fourth day of the test. Scores ranging from 0, no reaction, to 2, moderate erythema, were observed 24 and 48 h after the UV light exposure, and similar responses were observed in the controls. The investigators found no indication that either of the samples was phototoxic or a primary irritant when compared to untreated sites. Any irritation observed at the treatment sites was reported to be caused by the erythema dosage used to challenge each site (Table 7).[56]

A white cream cosmetic formulation containing 4% steareth-20 was tested for its potential to induce contact photoallergy in humans. A total of 31 subjects, 6 men and 25 women ranging in age from 18 to 64 years, completed the test. A series of nine occlusive induction patches containing 0.2 g of the undiluted cosmetic was applied to both forearms of the subjects on Mondays, Wednesdays, and Fridays for 3 weeks. Each patch remained in place for 24 h, at which time the subject returned to the laboratory, the patches were removed, and the dermal reactions scored. A scale ranging from 0 (no reaction) to 4 (fiery colored erythema, marked edema, and substantial vehiculation far beyond the patch margins) was used for the scoring. The designated forearm was then irradiated and scored again immediately after the irradiation, and the other arm served as an unirradiated control. The irradiation was 15 minutes of UV-A light from four F40 BL fluorescent tubes and the lesser of

two MEDs or 120 s of UV-B irradiation from the Solarium 300 lamp. The test sites were marked with gentian violet, and the same sites were repatched until the nine induction patches and irradiations were complete. After a nontreatment period of approximately 2 weeks, challenge patches were applied to a previously untreated site and the original patch sites were observed again. Each subject reported to the laboratory again 24 h later, at which time the patches were removed and the reactions scored. The designated forearm was then irradiated with UV-A light only. The reactions were scored immediately after the irradiation and then again 24 and 48 h later. A single subject had a two-level reaction 24 h after the second irradiation, and he was judged a presensitized reactor and was removed from the test. All but the aforementioned subject had slight reactions on the irradiated sites during the induction phase. Several subjects also had slight transient reactions on the control irradiated site with no test material applied. All irradiated sites had a slight tanning response. Slight reactions were observed in several subjects on the sites to which the formulation was applied but that did not receive irradiation. No reactions were observed at the challenge testing. This formulation "did not induce contact dermal photoallergy or contact dermatitis or sensitization in human subjects" (Table 7).[55]

In another study a white creamy cosmetic formulation containing 4% steareth-20 was tested to determine its phototoxicity potential in humans. A total of two men and eight women, with ages ranging from 26 to 58 years, completed the study. Occlusive patches each containing approximately 0.2 g of the undiluted cosmetic were applied to both forearms of the subjects. The patch was left in contact with the skin for 24 h, at which time it was removed and the dermal reactions were scored. The designated forearm was then irradiated with UV-A light from four F40 BL fluorescent tubes for an unspecified amount of time. The dermal reactions were scored immediately after the irradiation and again after 24 to 48 h. No reactions were observed on either forearm during any part of the study. The cosmetic test material did not induce a contact dermal phototoxic response in humans (Table 7).[57]

SUMMARY

The steareth group is a series of compounds prepared by reacting stearyl alcohol with ethylene oxide to form polyoxyethylene stearyl ethers. The number of oxyethylene units corresponds to the number of the steareth (i.e., steareth-2). These compounds are generally waxy solids soluble in lower alcohols and insoluble in hydrocarbons.

Steareths are primarily used as emulsifiers in cosmetics. In 1986, steareth-2 was used in 107 cosmetic products, and steareth-10, -15, and/or -20 were used in a total of 104 cosmetic products. The products formulated with steareths included personal cleanliness products and deodorants as well as suntan, fragrance, skin, eye, and hair preparations. The maximum reported concentration in use was 25%.

Microbial and environmental degradation breaks down the steareths into metabolites including carboxylated polyethylene glycols, polyethylene glycol units, C_2 fragments, and oxalic and formic acids.

Steareth-2 and -10 were nontoxic to rats in acute oral toxicity studies both at concentrations of 40% in water and in formulations. Steareth-20 was nontoxic in formulations and had an oral LD_{50} value in rats of approximately 2.0 g/kg at concentrations of 25% in corn oil or water. Steareth-2 had an IP (10% in saline) LD_{50} value of 0.76 g/kg and an IV (1% in propylene glycol) LD_{50} value of 0.041 g/kg in rats. Steareth-20 (10% in saline) had an IP LD_{50} value of 0.190 g/kg and an IV LD_{50} value of 0.164 g/kg in rats.

In subchronic testing, steareth-20 was nontoxic to rabbits when administered dermally at concentrations of 4% in a cosmetic formulation.

Steareth-2 and -10, at concentrations of up to 60% in water, were at most mildly and minimally irritating, respectively, to rabbit eyes. Steareth-20 was a moderate ocular iritant to rabbits at an unspecified concentration.

Steareth-2 and -10 were at most mild irritants to rabbit skin when tested in cosmetic formulations and at concentrations of up to 60% in water. Steareth-20 was a mild dermal irritant to rabbits in a 60% aqueous solution and a moderate irritant in cosmetic formulations.

A structurally undefined polyoxyethylene alkyl ether was neither carcinogenic nor was it a tumor promoter. An unspecified alcohol ethoxylate was nonmutagenic in three separate assays.

Steareth-2, 60% in water, was not a primary irritant or a sensitizer to human skin. In clinical studies of cosmetic formulations, steareth-2, 0.6% in a mousse, was a mild irritant and was not phototoxic at a concentration of 2.75% with 2.25% steareth-20 in a body lotion. Steareth-10 was not an irritant to human skin at a concentration of 60% in water. Steareth-20, at concentrations of up to 60% in water and in cosmetic formulations, was neither an irritant nor a sensitizer and was not phototoxic to human skin.

DISCUSSION

The Cosmetic Ingredient Review Expert Panel decided that the data on steareth-2, -10, and -20 are sufficient for a decision to be made on the entire steareth group, including steareth-4, -6, -11, -13, and -15 because of the chemical similarity of all the steareths.

An alcohol ethoxylate of unspecified chain length was not mutagenic in three separate studies. Because of structural similarities, the expert panel considers the data on the alcohol ethoxylate sufficient so that mutagenicity testing of the steareth group is not required.

CONCLUSION

One the basis of the data included in this report, the CIR Expert Panel concludes that steareth-2, -4, -6, -7, -10, -11, -13, -15, and -20 are safe as cosmetic ingredients in the present practices of use and concentration.

ACKNOWLEDGEMENT

Nancy J. Toy, Scientific Analyst and Writer, prepared the technical analysis used by the expert panel in developing this report.

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