JOURNAL OF THE AMERICAN COLLEGE OF TOXICOLOGY
Volume 2, Number 7, 1983
Mary Ann Liebert, Inc., Publishers

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Final Report on the Safety Assessment of Laureths -4 and -23

The Laureths, polyethoxyethers of lauryl alcohol, are used in a wide variety of cosmetic products. Laureth-4 was "practically nontoxic" when administered orally to rats and mice. Acute, subchronic, and chronic dermal tests with diluted formulations on rabbits were negative for systemic toxicity. In eye irritation studies in rabbits, undiluted Laureth-4 was moderately and minimally irritating in the unrinsed and rinsed eye, respectively; 10 and 20% dilutions were both classified as minimally and nonirritating.

The acute oral LD50s for Laureth-23 were 8.6 and 3.5 g/kg for fasted male rats and mice, respectively. Undiluted Laureth-23 caused no primary irritation when applied to the rabbit skin. Undiluted Laureth-23 caused a slight conjunctival reaction in rabbits.

Review of safety test data on closely-related Laureths and other lauryl alcohol ethoxylated compounds indicated no teratological, multiple generation and fertility, and mutagenicity effects for these compounds.

No skin irritation or sensitization was reported in clinical studies with undiluted Laureth-4. A 6% Laureth-4 product produced no evidence of phototoxicity.

No primary cutaneous irritation was observed in clinical studies using 60% Laureth-23. No evidence of sensitization was reported when a 25% solution of Laureth-23 was used in a repeated insult patch test on 168 subjects, nor was there evidence of phototoxicity when tested on a subset of this population.

It is concluded that Laureth-4 and Laureth-23 are safe as cosmetic ingredients in the present practices of use and concentration.

INTRODUCTION

The Laureths are the polyethylene glycol ethers of lauryl alcohol (n-dodecanol) that conform to the following formula:[1]

$$CH_3(CH_2)_{10}CH_2(OCH_2CH_2)_nOH$$

The value of "n" listed in the *Cosmetic Ingredient Dictionary*[1] ranges from 1

to 40. Laureth-4 and Laureth-23, voluntarily reported to the Food and Drug Administration (FDA) as being ingredients used in cosmetics, are reviewed in this report.[2]

The designation of the specific Laureths used in cosmetic products is defined by the average number of moles of ethylene oxide reacted per mole of lauryl alcohol. Therefore, Laureths -4 and -23 are the polyethylene glycol ethers produced by reacting 4 and 23 moles, respectively, of ethylene oxide per mole of lauryl alcohol. Each designated Laureth is the predominant compound in the resultant mixture that will also contain some shorter and longer chain lengths.[3]

PROPERTIES

The Laureths are amphiphiles, with part of the molecule lipophilic (fatty hydrocarbon region) and part hydrophilic (ether region). This dual nature imparts these ingredients with most of their physical properties: increased ethoxylation (increased n value) increases hydrophilicity and esterification increases lipophilicity. Laureths with low n values are water insoluble and oil soluble as a result of the relatively long nonpolar and short polar regions of the molecule. Laureth-4 forms a stable milky dispersion in water. Laureth-23 forms a clear aqueous solution.[4]

Laureths with low n values are colorless liquids.[3] As the n value increases, the viscosity of the ingredient increases until they become white, waxy solids.

The Laureths are nonionic surfactants with a hydrophile–lipophile balance (HLB) range of 5–18 depending on the n value. An HLB rating below 10 places the ingredient on the lipophilic part of the scale; a rating of 10 to 20 places it in the hydrophilic range. The two ingredients in this report, Laureths -4 and -23, have mean HLB ratings of 9.7 and 16.9, respectively.[4] HLB values can be grouped according to their usefulness to the cosmetics industry (Table 1).[4] Laureth-4 is used as an O/W emulsifier; Laureth-23 can serve as either an O/W emulsifier or a solubilizer.

Blends of two surfactants (A,B) can be used to attain an HLB that fits a particular use. This can be determined mathematically according to the formula:

$$HLB_{desired} = \text{percent A} \cdot HLB_A + \text{percent B} \cdot HLB_B.$$

If, for example, one wished to mix Laureths -4 and -23 to obtain a specific physical property, the above equation could be used to generate a chart as shown in Table 2. Whereas neither Laureth-4 nor Laureth-23 alone fits within the HLB-detergent range in Table 1, a blend of 40% Laureth-4 and 60% Laureth-23 meets this requirement. Thus, pure Laureths or blends of them can be used to obtain surfactant-related properties desirable in cosmetic chemistry.

REACTIVITY

The Laureths are relatively stable compounds resistant to acids and bases. Laureths -4 and -23 may undergo slow autoxidation requiring the addition of antioxidants.[5]

TABLE 1. HLB-Use Relationships.

Group	*HLB range*	*Use*
1	4–6	W/O emulsifier
2	7–9	Wetting agent
3	8–18	O/W emulsifier
4	13–15	Detergent
5	10–18	Solubilizer

Data from Ref. 4.
W/O = water in oil.
O/W = oil in water.

TABLE 2. Surfactant Blending.

L-4: L-23	100:0	80:20	60:40	40:60	20:80	0:100
HLB	9.7	11.2	12.5	13.8	15.3	16.9

Data from Ref. 4.

IMPURITIES

Several suppliers of Laureth-4 use the antioxidants butylated hydroxyanisole (BHA) (0.05%) and citric acid (0.01%) in special grades of their products and one supplier of Laureth-23 indicated the addition of BHA (0.01%) or citric acid (0.005%) to its product.[5]

Lauryl alcohol is a mixture of fatty alcohols containing 55%–64% dodecanol and 21%–28% tetradecanol with up to 13% hexadecanol, 5% decanol, 5% octadecanol, and 0.4% octanol.[5]

The Laureths may contain unreacted ethylene oxide that is not completely purged from the system. A reaction product of ethoxylation, 1,4-dioxane, may also be present in trace amounts; industry is aware of this possible impurity and thus uses additional purification steps to remove it from the ingredient before blending into cosmetic formulations.[6]

USE

Purpose and Extent of Use in Cosmetics

The Laureths are used in cosmetic formulations as solubilizing, emulsifying, and dispersing agents and as emollients and surfactants.

The Laureths are used in a variety of bath (bubble, oils, tablets, salts), eye (liners, shadows, mascara), facial (blushers, makeup bases, masks, wrinkle removers), hair (conditioners, sprays, wave sets, rinses, bleaches, shampoos), nail (creams, lotions), cleansing (creams, lotions, liquids, pads), and suntan (gels, creams, liquids) products. They are also used in cuticle softeners, deodorants, and moisturizing compounds. These products with their corresponding use-concentration ranges are listed in Table 3.[2]

TABLE 3. Product Formulation Data.

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	≤0.1
Laureth 4							
Bath oils, tablets, and salts	237	5	–	2	2	1	–
Bubble baths	475	1	–	–	1	–	–
Other bath preparations	132	2	–	–	–	2	–
Eyeliner	369	1	–	–	1	–	–
Eye shadow	2582	85	–	–	10	75	–
Hair conditioners	478	2	–	–	–	2	–
Hair sprays (aerosol fixatives)	265	2	–	–	–	–	2
Permanent waves	474	10	–	–	–	2	8
Hair rinses (noncoloring)	158	6	–	–	1	2	3
Hair shampoos (noncoloring)	909	4	–	2	1	1	–
Tonics, dressings, and other hair grooming aids	290	2	–	–	2	–	–
Wave sets	180	2	–	–	–	1	1
Hair dyes and colors (all types requiring caution statement and patch test)	811	17	17	–	–	–	–
Hair bleaches	111	3	1	–	–	2	–
Other hair coloring preparations	49	1	–	–	1	–	–
Blushers (all types)	819	4	–	–	–	4	–
Makeup foundations	740	3	–	–	–	3	–
Makeup bases	831	10	–	–	1	9	–
Other makeup preparations (not eye)	530	1	–	–	–	–	1
Nail creams and lotions	25	1	–	–	1	–	–
Other manicuring preparations	50	1	–	–	1	–	–
Bath soaps and detergents	148	1	–	–	1	–	–
Deodorants (underarm)	239	15	–	1	7	7	–
Other personal cleanliness products	227	6	–	–	3	3	–
Aftershave lotions	282	1	–	–	1	–	–
Beard softeners	4	1	–	–	1	–	–
Other shaving preparation products	29	1	–	–	1	–	–
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	680	6	–	2	4	–	–
Face, body, and hand skin care preparations (excluding shaving preparations)	823	2	–	1	–	1	–
Moisturizing skin care	747	1	–	–	–	1	–
Skin fresheners	260	2	–	–	–	2	–
Other skin care preparations	349	3	–	–	1	2	–
1981 TOTALS		202	18	8	41	120	15

TABLE 3. (Continued.)

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	≤0.1
Laureth 23							
Baby lotions, oils, powders, and creams	56	1	–	–	–	1	–
Bath oils, tablets, and salts	237	1	–	–	–	1	–
Other bath preparations	132	2	–	–	–	2	–
Eye makeup remover	81	1	–	–	1	–	–
Other eye makeup preparations	230	1	–	–	1	–	–
Colognes and toilet waters	1120	6	–	–	6	–	–
Perfumes	657	3	–	–	3	–	–
Hair conditioners	478	6	–	–	1	3	2
Hair sprays (aerosol fixatives)	265	2	–	–	–	–	2
Hair straighteners	64	1	–	–	1	–	–
Permanent waves	474	94	–	–	22	71	1
Hair rinses (noncoloring)	158	4	–	–	–	1	3
Hair shampoos (noncoloring)	909	11	–	–	5	2	4
Tonics, dressings, and other hair grooming aids	290	5	–	–	–	3	2
Wave sets	180	12	–	–	–	7	5
Other hair preparations (noncoloring)	177	12	–	–	3	8	1
Hair dyes and colors (all types requiring caution statement and patch test)	811	1	–	–	–	1	–
Hair bleaches	111	3	–	–	1	1	1
Other hair coloring preparations	49	2	–	–	1	1	–
Makeup bases	831	1	–	–	–	1	–
Cuticle softeners	32	3	–	–	–	2	1
Other manicuring preparations	50	2	–	–	–	2	–
Bath soaps and detergents	148	3	–	–	3	–	–
Deodorants (underarm)	239	10	–	–	7	3	–
Other personal cleanliness products	227	6	–	–	5	–	1
Aftershave lotions	282	1	–	–	1	–	–
Shaving cream (aerosol, brushless, and lather)	114	3	–	–	3	–	–
Other shaving preparation products	29	1	–	–	1	–	–
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	680	3	–	–	2	1	–
Moisturizing skin care preparations	747	5	–	–	1	4	–
Night skin care preparations	219	4	–	–	1	3	–
Skin fresheners	260	1	–	–	–	1	–
Other skin care preparations	349	7	–	–	2	3	2
1981 TOTALS		218	–	–	71	122	25

Data from Ref. 2.

Laureth-4 is used in 202 cosmetic products. Eighteen uses are reported for hair dyes and bleaches at a concentration between 10% and 25%. The remaining 184 are reported to be used at concentrations below 10%. Laureth-23 is reported to be used in 218 cosmetic formulations at concentrations below 5%.

The cosmetic product formulation computer printout which is made available by the FDA Is compiled through voluntary filing of such data in accordance with Title 21 part 720.4 of the Code of Federal Regulations.[7] 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 concentration in such a case would be a fraction of that reported to the FDA. The fact that data are submitted only within the framework of preset concentration ranges also provides the opportunity for overestimation of the actual concentration of an ingredient in a particular product. An entry at the lowest end of a concentration range is considered the same as one entered at the highest end of that range, thus introducing the possibility of a two- to 10-fold error in the assumed ingredient concentration.

The Laureths are applied to the face (blushers, makeup foundations, wrinkle removers, moisturizers), to the scalp (hair conditioners, sprays, rinses, shampoos, sets, bleaches), around the eyes (liners, shadows, mascara), on the general body surfaces (bath and cleansing products, suntan preparations), to the nails (creams, lotions, cuticle softeners) and to the axillae (deodorants). The duration of application of these formulations may range from a few minutes (bath and hair preparations, cleansing agents) to several hours (eye and facial products, suntan preparations, deodorants).

Noncosmetic Use

Laureths -4 and -23 are used in the pharmaceutical industry as amphoteric solubilizing, dispersing and emulsifying agents for drugs. They are used to alter absorption rates, release rates, stability and percent binding. For example, Laureth-4 significantly increases percutaneous absorption of salicyclic acid,[8] whereas Laureth-23 decreases the rate of absorption through the skin of naproxen, D-2-(6'-methoxy naphthyl) propionic acid.[9] Laureth-23 has been found to enhance greatly the dissolution and release rate of Tripelenamine HCl from wax matrices in the presence of a synthetic gastric juice solution. The surfactant properties of Laureth-23 may make more channels in the wax available to the gastric fluid to leach out the drug.[10] Laureth-23 also increases the release of chloramphenicol from suppository bases[11] and is a superior binding agent for various drugs.[12] In studies of the solubilization of benzocaine by Laureth-23 at 30°, 50°, and 70°C, it was found that solubilization increased in the presence of 3%–15% surfactant.[13]

Laureth-4 is approved as an indirect food additive in modified industrial starches.[14]

BIOLOGICAL PROPERTIES

General Effects

The acute aquatic toxicity of Laureths -4 and -23 versus Laureth-14 mono- and di-laurates has been studied. Young *Salmo salar* L. and adult *Gammarus oceanicus* Sergestrale were kept 10 and 7 days, respectively, in aquaria to which surfactant was added. The ethers were more toxic than the esters: Laureth-4 was nine times more toxic than Laureth-14 mono-laurate.[15] There was a negative linear relationship between the degree of ethoxylation and toxicity; the shorter the polyether chain, the greater the toxic effect. The polyethers are more toxic than ether-esters. Similar conclusions have been reached by other investigators.[16,17]

Pelejero et al.[18] investigated the solubilizing potential of anionic, cationic, and nonionic (Laureth-23) surfactants on wool and zein (corn gluten) in an attempt to elucidate the origin(s) of skin irritation and found that Laureth-23 (0.3% in water) is a weak protein solubilizing agent.

The ability of ionic and nonionic (Laureth-23) surfactants to swell the stratum corneum of excised guinea pig skin has been studied. Laureth-23 (0.05 *M*, pH 4.8) caused little or no swelling; anionic surfactants caused the most swelling.[19] Protein denaturation or solubilization by surface-active agents, as suggested by Pelejero et al.,[18] does not appear to be involved in swelling.

Absorption, Metabolism, and Excretion

In general, alcohol ethoxylates are readily absorbed through the skin of guinea pig and rat and through the gastrointestinal mucosa of rats. They are quickly eliminated from the body through the urine, feces, and expired air.[17,20,21]

Nonionic surfactants have been shown to enhance the transmucosal transfer of other compounds in the gastrointestinal tract of rabbits.[22]

Ingredient Safety Testing

Laureth-4

Animal toxicity

Acute Oral: When five dose levels (unspecified) of Laureth-4 were administered orally to four groups (5F, 5M) of 16-hour fasted rats and mice and to one group of fed female rats, 14-day LD50s were reported as 8.6, 9.1, 4.9, 7.6, and 8.5 g/kg (for fasted male rats, fasted female rats, fasted male mice, fasted female mice, and fed female rats, respectively).[23] From these data, Laureth-4 was classified as "practically nontoxic." Treon[24] suggested fed-fasted, species, and sex differences in the oral toxicity of Laureth-4.

Swiss mice (25–30 g) given undiluted Laureth-4 (5, 10, or 15 g/kg) by stomach tube and monitored for 14 days had a mortality rate of 0/10, 10/15, and 5/5, respectively. The acute oral LD50 was reported to be between 5 and 10 g/kg.[3]

A bath oil containing 1.8% Laureth-4 was tested for oral toxicity in rats (5M,

5F) given 25 ml/kg of undiluted product by stomach tube. There were no mortalities and all animals appeared normal after 24 h.[3]

Acute Dermal: A greaseless gel containing 6% Laureth-4 was evaluated for acute percutaneous toxicity in rabbits with intact (two females) or abraded (two females) skin. A single 10 g dose of the test material was applied and maintained in contact with the skin with a rubber sheet for 24 h. None of the animals died in 14 days.[3]

A body shampoo containing 17% Laureth-4 was screened for acute dermal toxicity in two groups of four rabbits (2M, 2F) each exposed to 6.8 or 10.2 g/kg of undiluted product. The application sites on intact skin were covered for 24 h. None of the animals died within 14 days. There were no indications that the product was absorbed through the skin. However, at the test sites, the skin showed moderate to severe edema and erythema in all animals at 24 h. Severe eschar formation developed by Day 7 and persisted until Day 14.[3]

A bath oil containing 1.8% Laureth-4 was tested on rabbits (4F, 4M). Ten ml/kg of a 5% aqueous dispersion of the product were applied to the abraded and intact skin for 24 h under occlusive conditions. There was slight skin irritation and no signs of systemic toxicity.[3]

Subchronic Dermal: Four male and four female rabbits were treated topically with 0.4 ml/kg/day of Laureth-4 (6% in 52% ethanol in water solution) for 21 days. This corresponds to a total dose of 0.5 ml/kg of Laureth-4 in 21 days. The epidermal acanthosis that developed was ascribed to the high concentration of alcohol in the preparation. There were no clinical, hematological, serum, or urine changes and no gross or histopathologic lesions suggestive of systemic toxicity.[3]

Chronic Dermal: The same compound at the same concentration as above was used in a study on rabbits (5F, 5M). A dose of 1.5 ml/kg was applied topically on 100 cm^2 of skin surface twice daily for three months. There was no demonstrable systemic toxicity with respect to serum chemical, clinical, ophthalmologic, or gross and histopathologic parameters. The application sites developed edema, erythema, and eschar formation along with hyper- and parakeratosis, acanthosis, and dermatitis. These alterations were ascribed to the high alcoholic content of the diluent and not to the ingredient. However, no control experiments with alcohol alone were reported.[3]

Primary Skin Irritation: One square inch gauze patches containing undiluted Laureth-4 (0.5 ml) were placed on abraded and intact skin sites on two groups of three rabbits each. The patches were secured for 24 h and the exposure sites examined at 24 and 72 h. No erythema or edema was reported at 24 h; however, edema was noted in both the intact and abraded skin groups at 72 h. The Primary Irritation Index (PII) was calculated to be 0.58 (maximum of 8).[23]

A bath oil product containing 1.8% Laureth-4, undiluted or 2% aqueous dispersion, was applied topically to six rabbits per group. The sites were exposed under occlusion to the product for 4 h. The product was reported to be nonirritating to the skin.[3]

Eye Irritation: Three concentrations of Laureth-4 (100%, 20%, and 10% w/v in water at pH 4.5) were screened in three rabbits each for primary eye irritancy according to the Draize procedure. The undiluted ingredient was classified as

moderately irritating in unwashed eyes and minimally irritating in irrigated eyes. The 10% and 20% dilutions were classified as minimally irritating and nonirritating to unwashed and washed eyes, respectively (Table 4).

A body shampoo containing 17% Laureth-4 was instilled undiluted into the conjunctival sac in each of five rabbits. The treated eye was held shut for 4 sec after which it was irrigated with 40 ml of water. Corneal, iridial, and conjunctival irritation scores were 33/110 at 1 h, 5/110 at 24 h, and zero thereafter.[3] Laureth-4 has not been reported to be used in shampoos at a concentration above 10%.[2]

An undiluted bath oil containing 1.8% Laureth-4 was instilled (0.1 ml) into one eye (unwashed) in each of six rabbits and into one eye (irrigated with water for 30 sec) in each of three rabbits. Mild conjunctivitis (washed and unwashed eyes) was observed, accompanied by transient iritis (two of three washed eyes). All eyes were normal within 72 h. There was a transitory inhibition of corneal reflex for 1 h. When a 2% aqueous dispersion of this product was tested, no corneal reflex inhibition was observed; only minimal, transient conjunctivitis was noted.[3]

Special studies

Teratology: A teratologic study was reported in which rats were treated topically with 6% Laureth-4 in 52% ethanol and water solution at the rate of 0.4 ml/kg/day on Days 6 through 15 of gestation. A similar study using the same materials and dose on rabbits on Days 6 through 18 of gestation was also reported. The total dose of Laureth-4 in the rat test was 0.24 ml/kg, whereas the rabbit dose was 0.31 ml/kg. The results of both studies were described as demonstrating no teratogenic or embryotoxic effects.[3]

Multiple Generation and Fertility: Twelve male rats were treated topically with 0.4 ml/kg/day of Laureth-4 solution (6% in 52% ethanol in water solution) for 60 days before mating. Another 24 rats were similarly treated beginning 14 days before mating and continuing through weaning at 21 days. Half of the females were sacrificed at Day 13 of gestation and the remainder at weaning. Reproductive performance was judged to be normal; none of the animals died and none showed systemic toxicity.[3]

Peri- and Post-Natal Development: Twenty-six pregnant rats treated topically

TABLE 4. Eye Irritation of Laureth-4.

Concentration (%)	No. of rabbits	Eye treatment	Average total scores (110 maximum)					
			1 h	24 h	48 h	72 h	96 h	7 days
100	3	Unwashed	7.0	31.9	31.3	16.6	12.6	10.6
	3	Washed, 2 sec	2.6	4.0	0	0	0	0
20	3	Unwashed	0.66	0	0	0	0	0
	3	Washed, 2 sec	0	0	0	0	0	0
10	3	Unwashed	0	1.0	0	0	0	0
	3	Washed, 2 sec	0	0	0	0	0	0

Data from Ref. 23.

with 0.4 ml/kg/day of Laureth-4 (6% in 52% ethanol in water solution) from Day 15 of pregnancy through weaning showed neither mortalities nor toxic effects. Peri- and post-natal performances of mothers and pups were normal.[3]

Clinical assessment of safety

Primary Skin Irritation and Sensitization: Laureth-4 (100%) was tested on 50 human subjects. Sample (0.1 ml) was applied to one-inch square patches which were taped to the skin for 72 h. Seven days after patch removal, sample was applied a second time at the same site and held in place under occlusive patch conditions for 72 h. There were no reactions to the induction or the challenge application. The experiment was repeated by a separate testing laboratory on 10 different subjects with the period of contact reduced to 48 h. No irritation or sensitizing reactions occurred.[23]

A bath oil containing 1.8% Laureth-4 was tested for primary dermal irritation on 10 subjects. Undiluted sample (1.3 ml) applied to the same site (occlusive patch) daily for 10 consecutive days gave no evidence of irritation.[3]

A body shampoo containing 17% Laureth-4 was screened by 12 panelists for sensitizing potential in a 26-day test consisting of fifteen 30-minute exposures (Days 1–5, 15–19, and 22–26) on the medial aspect of the arm and three overnight (Days 1, 15, and 25) challenge applications. Gauze patches (3 × 3 in) were dipped in sample, applied to the arm for 30 min and then removed. The sites were washed, dried, and scored. The overnight patches were maintained in place for 17–18 h, and then removed. No sensitization reactions were produced.[3]

A bath oil with 4% Laureth-4 was tested on 25 subjects using Kligman's maximization procedure. There was no evidence of delayed hypersensitivity.[3,25]

Phototoxicity: A solution of 6% Laureth-4 in 52% ethanol w/w was tested for phototoxicity on human subjects (8F, 2M), ages 19–22 years. Sample was applied for 6 h under occlusion to a site (5 × 5 cm) on the lower back. When the patches were removed, the center of the exposure site was irradiated for 12–14 min with UVA light from a 150-watt xenon arc solar simulator. The peripheral, exposed, unirradiated area of each site served as a control. Reactions were scored at 0, 24, and 48 h postirradiation. The minimal erythema dose (MED) was determined using full spectrum UV light before the experiment for each subject and then at each reading. There was no evidence of phototoxic reaction.[3]

A bath oil containing 1.8% Laureth-4 was evaluated for phototoxicity and photocontact allergenicity. Ten adult subjects were exposed to undiluted sample (5 μl/cm^2 of occlusive patch) and then irradiated with a solar simulator (irradiance not specified) after 6 and 24 h. In another study, 25 subjects were similarly exposed to the sample and irradiated after 24 h. The procedure was repeated twice per week for three weeks. A challenge dose was applied 10 days after the last induction dose. Neither study showed evidence of phototoxic or photoallergenic reaction.[3]

Laureth-23

Animal toxicity

Acute Oral: Five dosage levels of Laureth-23 (20% w/v aqueous solution) were administered orally to fed or 16-hour fasted rats and mice. The LD50 values

were estimated as 8.6, 9.4, 3.5, 4.0, and 7.8 g/kg, respectively, for the following groups of five animals each: fasted male rats, fasted female rats, fasted male mice, fasted female mice, and fed female rats. Animals that died during the study had irritation of the gastrointestinal tract and changes in the liver, spleen, and kidneys.[26] Laureth-23 is apparently more toxic to mice than rats.[24]

Acute Dermal: A foam skin cleanser containing 4.0% Laureth-23 was applied undiluted to the intact skin of four rabbits for 24 h. After 14 days, there were no gross or histopathologic abnormalities. Urinalysis and hematology findings were normal. All animals had slight to moderate erythema at the exposure sites at 24 h. None of the animals died.[3]

Primary Skin Irritation: Undiluted Laureth-23 was tested on six rabbits as previously described for Laureth-4; all erythema and edema scores were 0. The ingredient was classified as a nonirritant.[23]

A skin cleanser containing 4.0% Laureth-23 was applied undiluted under occlusion for 24 h to abraded and intact skin sites on four rabbits. The PII was 0.4/8.0.[3]

Eye Irritation: Undiluted Laureth-23 was tested for rabbit eye irritation as described for Laureth-4. No corneal or iridial effects were recorded. There was a slight conjunctival reaction (2.0/110) in both washed and unwashed eyes for up to 72 h.[23]

An undiluted skin cleanser containing 4.0% Laureth-23 was instilled into the eyes of three rabbits. In eyes irrigated after 4 sec, the score was 2.6/110 at 1 h, and zero thereafter. In nonirrigated eyes, the total score was 5.6/110 at 1 h and 1.2/110 at 24 h.[3]

Clinical assessment of safety

Primary Skin Irritation and Sensitization: A 60% w/v aqueous preparation of Laureth-23 was applied under occlusion for 72 h to the skin of 50 subjects. The sites were untreated for a week, then sample was reapplied for another 72 h. There were no reactions after either application. In a similar test, undiluted Laureth-23 was tested on 10 subjects for a 48-hour contact followed by a seven-day nontreatment period, and an additional 48-hour contact period. One panelist experienced slight skin dryness at the exposure site after the initial application. A second panelist had dryness and erythema following both applications.[23]

A repeated insult patch test was performed on 168 subjects (115F, 53M) using 0.1 ml of a 25% water solution of Laureth-23. The test material was applied at 48-hour intervals, three times per week for three weeks on the back of the subjects. The test area was occluded for 24 h and washed with distilled water. The test sites were read at 48 h, after which fresh test material and the occlusive patch were reapplied. After a three-week nontreatment period, the test area as well as an untreated site were challenged using the same procedure. The sites were scored for sensitization at 24, 48, and 72 h. The investigator reported that Laureth-23 was neither an irritant nor a sensitizer.[27]

A 3% aqueous solution of Laureth-23 was used to assess irritation and sensitization on healthy, female, Caucasian subjects. Mineral oil and propylene glycol were included in the study as nonirritating and mildly irritating controls, respectively. Of the 108 subjects enrolled, 103 completed the study and were in-

cluded in the evaluation. Each subject received a patch applied to the intact skin of the upper back under semiocclusion. The patches remained in place for 48 h (72 h on weekends) at which time they were removed, the sites examined for irritation, and new patches applied. This was repeated 10 times for each subject followed by a two-week nontreatment period and rechallenge. A mean cumulative irritation score of 0.126 ± 0.055 was reported. The nonirritating control was 0.388 ± 0.071. There were no skin reactions consistent with sensitization associated with the test ingredient.[28]

In a repeated insult patch test using the procedures of Marzulli and Maibach,[29] no evidence of skin sensitization was observed in a panel of 150 subjects exposed to 0.2 ml of a 5% aqueous solution of Laureth-23 under occlusion.[30]

A 21-day repeated insult patch test of an underarm deodorant containing 2.5% Laureth-23 was conducted on 24 adult males. A 0.3 ml volume was applied to a Webril patch under an occlusive tape once daily to the same site for 21 days, excepting weekends. There were three cases of slight erythema. No response was observed on 21 subjects. It was concluded that the formulation was neither a primary irritant nor a sensitizer.[31]

A skin cleanser containing 4.0% Laureth-23 was applied undiluted to the medial surface of the arm of 14 subjects. Patches (1.25 in^2) moistened with sample were applied under occlusion for 5 h per day for four consecutive days. Skin irritation was monitored once daily. The cleanser was found to be "relatively nonirritating."[3]

Phototoxicity/Sensitization: Twenty-nine of the 168 subjects tested for irritation and sensitization as previously discussed were randomly selected to test the ability of a 25% Laureth-23 solution to induce a phototoxic or photosensitization reaction following ultraviolet exposure. The test protocols were the same except that the forearm was used as a test site. The 29 subjects were divided into two groups; 20 received only UVA light and nine received both UVA and UVB. The UVA (320–400 nm) light was applied for 15 min to the 20 subjects (4.4 $\mu W/cm^2$ at the skin surface measured at a 360 nm wave length peak). The UVB was applied at two times Mean Erythema Dose (MED) to nine subjects from a 150-watt Xenon Arc Solar Simulator emitting at 280–320 nm. The subjects receiving the UVB exposure were also exposed for 5 min to UVA under conditions described above. The investigator concluded that there was no evidence to indicate that Laureth-23 was a photosensitizer.[27]

An eye makeup preparation containing 0.899% Laureth-23 was tested for phototoxicity and photoallergy on a panel of 27 normal subjects. Two $\mu l/cm^2$ of the formulation was applied to two different skin sites and covered. After 24 h, the patches were removed and one treated and one nontreated site were exposed for 30 sec of window-glass-filtered light from a Krohmeyer hot quartz spot lamp. This procedure was repeated four additional times, followed by a 12-day nontreatment period before a 24-hour challenge application and reexposure to the light source. The results indicated no instances of phototoxicity or photoallergenicity.[32]

History of Product Use: Four hundred forty-two product safety-related com-

plaints were received for a deodorant over a 9.75 year period for over 200 million units sold. It was estimated that this product was applied more than a billion times.[31]

SUMMARY

The Laureths, polyethoxyethers of lauryl alcohol, are used in a wide variety of cosmetic products and may be applied to all areas of the skin daily over an extended period of time. Laureths -4 and -23 are reported to be used in concentrations ≤0.1%–25% and ≤0.1%–5%, respectively.

Laureth-4 is "practically nontoxic" when administered orally to rats and mice. Acute, subchronic, and chronic dermal tests with diluted formulations on rabbits were negative for systemic toxicity. The PII of undiluted Laureth-4 was found to be 0.58/8.0 for the rabbit. In eye irritation studies in rabbits, undiluted Laureth-4 was moderately and minimally irritating in the unrinsed and rinsed eye, respectively; 10% and 20% dilutions were both classified as minimally and nonirritating to unrinsed and rinsed eyes, respectively. No abnormalities were found in teratogenicity, multiple generation and fertility, and peri- and postnatal development studies in the rat; each study used 0.4 ml/kg/day of a 6% Laureth-4 solution applied topically. The interpretation of these latter results is limited to the concentration tested as well as to the route of exposure.

No irritation or sensitization was found in 60 subjects treated with 100% Laureth-4 in a Schwartz prophetic patch test or in 10, 12, and 25 subjects treated with formulations containing 1.8%, 17%, and 4.0% Laureth-4, respectively. A 6% Laureth-4 product produced no evidence of phototoxicity; a 1.8% Laureth-4 product was nonphototoxic and nonphotoallergenic.

The acute oral LD50s for Laureth-23 were 8.6 and 3.5 g/kg for fasted male rats and mice, respectively. No systemic toxicity was found in rabbits treated topically with a 4.0% Laureth-23 formulation. Undiluted Laureth-23 caused no primary irritation when applied to the rabbit skin; a 4.0% Laureth-23 product produced a 0.4/8.0 PII value. Undiluted Laureth-23 caused a slight conjunctival reaction in rabbits; a 4.0% Laureth-23 formulation produced mild, transient conjunctivitis and iritis.

No primary cutaneous irritation was observed in 50 people treated with 60% Laureth-23. Undiluted Laureth-23 caused erythema in one of 10 subjects. A 4% Laureth-23 formulation was found to be "relatively nonirritating" to 14 subjects treated 5 h per day for four days.

A 3% and 5% aqueous solution of Laureth-23 was used in two repeated insult patch tests on 96 and 150 subjects, respectively. No evidence of sensitization was reported. Similar results were obtained when a 25% aqueous solution of Laureth-23 was used in a repeated insult patch test on 168 subjects. No evidence of human phototoxicity or photoallergenicity was produced, either by a formulation containing 0.9% Laureth-23, or by a 25% solution of the raw ingredient.

DISCUSSION

In preparing this report the Panel also reviewed safety test data on closely related Laureths and other lauryl alcohol ethoxylated compounds that are in consumer products, but not in cosmetic formulations. Teratological, multiple generation and fertility, and mutagenicity data were all negative for these compounds.[17] These data supported the Panel's conclusion.

CONCLUSION

On the basis of the available information presented in this report, the Panel concludes that Laureth-4 and Laureth-23 are safe as cosmetic ingredients in the present practices of use and concentration.

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