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Final Report on the Safety Assessment of Cocamide DEA, Lauramide DEA, Linoleamide DEA, and Oleamide DEA

Cocamide DEA, Lauramide DEA, Linoleamide DEA, and Oleamide DEA are fatty acid diethanolamides that may contain 4–33% diethanolamine. These ingredients are used in cosmetics at concentrations of <0.1–50%, with most products containing 1–25% diethanolamide. Cocamide DEA and Lauramide DEA are inactive ingredients in prescription drugs.

These four fatty acid alkanolamides were slightly toxic to nontoxic to rats in formulations and inert vehicles via acute oral administration. Lauramide DEA was not a significant subchronic oral toxin in rats or dogs. Cocamide DEA, Lauramide DEA, and Linoleamide DEA were not dermal toxins in acute and subchronic animal studies.

Cocamide DEA was a minimal eye irritant and a moderate skin irritant in rabbits. Lauramide DEA and Linoleamide DEA were mild to moderate eye irritants and mild to severe skin irritants. Undiluted Oleamide DEA was not an eye irritant and was a moderate skin irritant in single and cumulative applications.

Lauramide DEA did not demonstrate mutagenic activity in three different Ames-type assays. No data were available on the mutagenic or carcinogenic activity of Cocamide DEA, Linoleamide DEA, and Oleamide DEA.

The clinical information on these ingredients was confined to Cocamide DEA, Lauramide DEA, and Linoleamide DEA. Generally, these products were mild skin irritants but not sensitizers or photosensitizers.

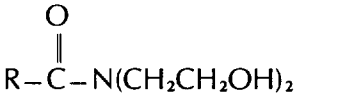
INTRODUCTION

Cocamide DEA (diethanolamine), Lauramide DEA, Linoleamide DEA, and Oleamide DEA are diethanolamides produced by the condensation of fatty acid methyl esters and diethanolamine. These ingredients are manufactured by two processes and may contain varying amounts of free diethanolamine. They are surface active agents and are used primarily as emollients, thickeners, and dispersion aids in cosmetics, such as shampoos, hair dyes, bath products, and lotions.

CHEMISTRY

Structure

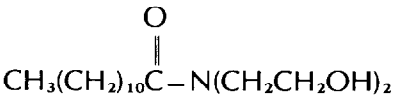
Cocamide DEA (CAS No. 61791-31-9; 68603-42-9) is a mixture of ethanolamides of coconut acid that generally conforms to the formula:



where RCO– represents the coconut acid radical. A review of the safety and chemical description of coconut acid is available.[1]

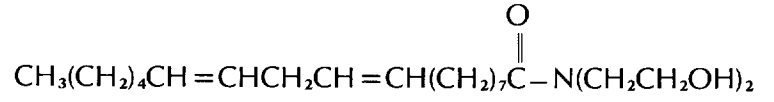
Synonyms for Cocamide DEA include N,N-Bis(2-Hydroxyethyl)Coco Amides, N,N-Bis(2-Hydroxyethyl)Coco Fatty Acid Amide, Coconut Diethanolamide, Coconut Fatty Acid Diethanolamide, and Cocoyl Diethanolamide.[2]

Lauramide DEA (CAS No. 120-40-1) is a mixture of ethanolamides of lauric acid with an empirical formula of $C_{16}H_{33}NO_3$ and generally conforms to:



Synonyms for Lauramide DNA include N,N-Bis(2-Hydroxyethyl)Dodecanamide, N,N-Bis(2-Hydroxyethyl)Lauramide, Diethanolamine Lauric Acid Amide, Lauric Acid Diethanolamide, Lauric Diethanolamide, and Lauroyl Diethanolamide.[2]

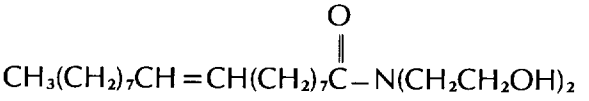
Linoleamide DEA (CAS No. 5686-02-6) is a mixture of ethanolamides of linoleic acid that generally conforms to:



with an empirical formula of $C_{22}H_{41}NO_3$ and an average formula weight of 280.

Synonyms for Linoleamide DEA include N,N-Bis(2-Hydroxyethyl)Linoleamide, N,N-Bis(2-Hydroxyethyl)-9,12-Octodecadienamide, Diethanolamide Linoleic Acid Amine, and Linoleoyl Diethanolamide.[2,3]

Oleamide DEA (CAS No. 93-83-4) is a mixture of ethanolamides of oleic acid. Its empirical formula is $C_{22}H_{43}NO_3$. Oleamide DEA generally conforms to:



Synonyms for Oleamide DEA include N,N-Bis(2-Hydroxyethyl)-9-Octadecenamide, N,N-Bis(2-Hydroxyethyl)Oleamide, Diethanolamine Oleic Acid Amine, Oleic Diethanolamide, and Oleoyl Diethanolamide.[2]

Physical and Chemical Properties

Cocamide DEA is a clear amber liquid with a faint odor. It is water soluble, and the pH of a 10% aqueous solution of Cocamide DEA is 9.5–10.5. Cocamide DEA for cosmetic use is available in various grades depending on molar ratios of starting materials used for the manufacture of the ingredient. A 1:1 molar ratio of coconut fatty acids to diethanolamine yields the highest purity amide. Cocamide DEA for cosmetic use has an acid value of 0.1–85 and an alkali value of 6–200 and can be identified by match to a standard infrared (IR) spectrum. Cocamide DEA contains 4.0–8.5% free diethanolamine and has a melting range of 23–35°C.[4–6]

Lauramide DEA is a light yellow, syruplike liquid or a white to yellow waxlike mass with a melting range of 37–47°C. It has a faint, characteristic odor. Lauramide DEA is dispersible in water, and the pH of a 10% aqueous dispersion is 9.8–10.8. Lauramide DEA for cosmetic use is available in various grades and has a free amine value of 10–35 and a maximum water content of 5.0%. Lauramide DEA's acid value is 0.1–14 and the alkali value is 6–200; it is identified by match to a standard IR spectrum.[4,5,7] The surface tension of Lauramide DEA is 24.6 dynes/cm^2 (0.1% aqueous dispersion at 25.5°C), the density is 0.9790 (30°C), and the refractive index is 1.4708 (n30/L).[8]

Linoleamide DEA is a clear, viscous, amber liquid with a characteristic odor. It is soluble in ethanol, propylene glycol, and glycerin, slightly soluble in water, and insoluble in mineral oil. The specific gravity (25°/25°C) of Linoleamide DEA is 0.972–0.982, and it can be identified by match to a standard IR spectrum. Linoleamide DEA has a maximum acid value of 2.0 and an alkali value (calculated as diethanolamine) of 25–50.[3,4]

Oleamide DEA is an amber liquid that is soluble in alcohols, glycols, ketones, esters, benzenes, chlorinated solvents, and aliphatic hydrocarbons. It is dispersible in water. Oleamide DEA congeals at −8°C and has a specific gravity (25/25°C) of 0.99. Oleamide DEA contains 6.0–7.5% free fatty acid (as oleic) and has a pH of 9–10.[9]

Reactivity

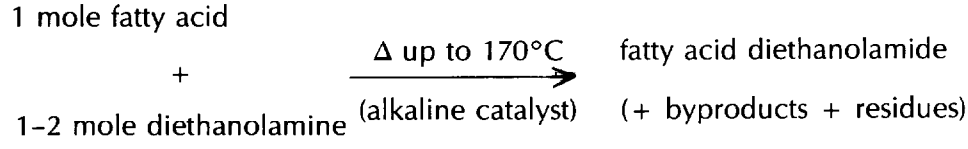
Fatty acid diethanolamides are surface active agents with three functional groups: an alkyl or alkene group, two hydroxy groups, and an imide. They are generally insoluble but dispersible in water and soluble in most organic solvents, with the exception of some aliphatic hydrocarbons. Fatty acid diethanolamides are alkaline (pH 9–11) in aqueous dispersion and are compatible with anionics and cationics over a wide pH range. They are stable in neutral, moderately alkaline, or moderately acid systems but are subject to hydrolysis in the presence of high concentrations of mineral acids or alkali. Individually, fatty acid diethanolamides have poor wetting and detergent properties, but they are synergistic to surfactants (e.g., sodium lauryl sulfate) that possess good wetting and detergent properties. In a study comparing the protein solubility of several surfactants, Lauramide DEA had fewer overall free amino acids in the soluble fraction than water, sodium lauryl sulfate, N,N,N-cetyl trimethyl ammonium bromide, and polyoxyethylene (23 EO) lauryl ether.[3,6,7,9–11]

Analytical Methods

Methods for the normal and reverse phase high-pressure liquid chromatography analyses of Cocamide DEA, Lauramide DEA, and Linoleamide DEA have been published.[12,13]

Methods of Manufacture

These fatty acid diethanolamides are produced by a condensation reaction at a 1:1 or 1:2 molar ratio of the appropriate fatty acids to diethanolamine.[4,5] The 1:2 mixture of fatty acid (or methyl fatty acid) to diethanolamine results in a lower quality diethanolamide with ethylene glycol and free diethanolamine residues. The 1:1 mixture produces a higher quality diethanolamide with much less free amine and is consequently used in lower concentrations than the 1:2 diethanolamide. A review of the cosmetic safety of diethanolamine concluded that diethanolamine is safe for use in cosmetic formulations designed for discontinuous, brief use followed by thorough rinsing from the surface of the skin. In products intended for prolonged contact with the skin, the concentration should not exceed 5%. Diethanolamine should not be used in products containing N-nitrosating agents.[14]



The appropriate fatty acids for the manufacture of Cocamide DEA are methyl cocoate, coconut oil, whole coconut acids, or stripped coconut fatty acids. Lauramide DEA is usually made from a mixture of lauric and myristic acids plus diethanolamine, Linoleamide DEA is manufactured with linoleic acid or its methyl ester, and Oleamide DEA is made from oleic acid.[3,6,7,9]

Impurities

N-nitrosodiethanolamine (<1 ng/g [ppb] to 48,000 μg/g), a potent liver carcinogen in rats via oral administration, has been found in some cosmetics, including products containing diethanolamine and/or triethanolamine plus a nitrosating agent.[15–17] Alkanolamides manufactured by base-catalyzed condensation of diethanolamine and the methyl ester of long chain fatty acids are susceptible to nitrosamine formation. Consequently, methods for the analysis of nitrosamines in alkanolamides, including Cocamide DEA, Lauramide DEA, and Linoleamide DEA, have been developed.[14,18–21] No other information on organic or inorganic impurities for these ingredients was available from published literature.

USE

Purpose in Cosmetics

Fatty acid amides, including Cocamide DEA, Lauramide DEA, Linoleamide DEA, and Oleamide DEA, are used as emollients, thickeners, and foam stabilizers in cosmetics.[11,22-24] They are also used as dispersion aids in hair-drying preparations.[23] Lauramide DEA and Oleamide DEA are used as active ingredients in treating seborrhea and acne. Oleamide DEA is the preferred diethanolamide for this use, and it is used in concentrations of 1–10% by weight.[25]

Scope and Extent of Use in Cosmetics

Cocamide DEA and Lauramide DEA are ingredients in 584 and 604 cosmetic formulations, respectively, in concentrations of <0.1–50%, according to the Food and Drug Administration's (FDA) voluntary listing of cosmetic product ingredients. The major product types containing Cocamide DEA and Lauramide DEA are bath additives, shampoos, and hair dyes. These products usually contain 1–25% diethanolamide. Linoleamide DEA and Oleamide DEA are used in the same types of products in frequencies of 92 and 121, respectively. Linoleamide DEA is used at concentrations ranging from 0.1 to 10%, and Oleamide DEA is used at concentrations ranging from 0.1 to 25%.[26]

Voluntary filing of product formulation data with FDA by cosmetic manufacturers and formulators conforms to the prescribed format of preset concentration ranges and product categories as described in Title 21 part 720.4 of the Code of Federal Regulations (21 CFR 720.4).[27] Since certain cosmetic ingredients are supplied by the manufacturer at less than 100% concentration, the concentration reported by the cosmetic formulator may not necessarily reflect the actual concentration found in the finished product; the actual concentration in such a case would be a fraction of that reported to the FDA. Since data are only submitted within the framework of preset concentration ranges, the opportunity exits for overestimation of the actual concentration of an ingredient in a particular product. An entry at the lowest end of a concentration range is considered the same as one entered at the highest end of that range, thus introducing the possibility of a two- to ten-fold error in the assumed ingredient concentration (Table 1).

Application Sites, Duration, and Frequency

Products containing these fatty acid diethanolamides are applied to or come in contact with all exterior portions of the body including skin, hair, nails, eyes, and mucous membranes. These products remain in contact with the body from minutes up to several days and are applied anywhere from once every few months up to several times daily.

TABLE 1. Product Formulation Data[26]

Product category	Total no. of formulations in category	Total no. containing ingredient	No. of product formulations within each concentration range (%)					
			>25–50	>10–25	>5–10	>1–5	>0.1–1	≤0.1
Cocamide DEA								
Baby shampoos	35	4	–	–	–	4	–	–
Other baby products	15	1	–	–	–	1	–	–
Bath oils, tablets, and salts	237	6	–	–	–	6	–	–
Bubble baths	475	98	–	1	49	47	1	–
Other bath preparations	132	21	–	–	3	18	–	–
Sachets	119	4	–	–	–	4	–	–
Other fragrance preparations	191	1	–	–	–	1	–	–
Hair conditioners	478	3	–	1	–	2	–	–
Permanent waves	474	1	–	–	–	–	1	–
Hair rinses (noncoloring)	158	1	–	–	–	1	–	–
Hair shampoos (noncoloring)	909	255	–	16	48	180	10	1
Tonics, dressings, and other hair grooming aids	290	1	–	–	1	–	–	–
Other hair preparations (noncoloring)	177	2	–	–	–	1	1	–
Hair dyes and colors (all types requiring caution statement and patch test)	811	130	–	66	6	58	–	–
Hair tints	15	1	–	–	–	1	–	–
Hair shampoos (coloring)	16	9	–	–	2	7	–	–
Hair bleaches	111	2	–	–	2	–	–	–
Blushers (all types)	819	1	–	–	–	1	–	–
Lipstick	3319	3	–	–	–	3	–	–
Bath soaps and detergents	148	14	–	3	1	10	–	–
Deodorants (underarm)	239	3	–	–	–	3	–	–
Other personal cleanliness products	227	11	1	–	–	8	2	–
Shaving cream (aerosol, brushless, and lather)	114	2	–	–	–	–	2	–
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	680	8	1	–	1	3	3	–
Face, body, and hand skin care preparations (excluding shaving preparations)	832	1	–	–	–	1	–	–

Other skin care preparations	349	1	–	–	–	1	–	–
1981 TOTALS		584	2	87	113	361	20	1
Lauramide DEA								
Baby shampoos	35	11	–	–	2	4	5	–
Other baby products	15	2	–	–	–	2	–	–
Bath oils, tablets, and salts	237	14	1	–	6	6	1	–
Bubble baths	475	61	1	3	28	26	2	1
Bath capsules	3	2	–	–	–	2	–	–
Other bath preparations	132	31	5	6	3	17	–	–
Eyeliner	396	1	–	–	1	–	–	–
Eye makeup remover	81	1	–	–	–	–	1	–
Other fragrance preparations	191	1	–	1	–	–	–	–
Hair conditioners	478	6	–	–	2	4	–	–
Hair sprays (aerosol fixatives)	265	1	–	–	–	1	–	–
Hair shampoos (noncoloring)	909	269	7	17	57	174	14	–
Tonics, dressings, and other hair grooming aids	290	5	–	–	–	5	–	–
Wave sets	180	3	–	–	–	–	3	–
Hair dyes and colors (all types requiring caution statement and patch test)	811	90	–	–	53	37	–	–
Hair shampoos (coloring)	16	3	–	–	1	–	2	–
Hair bleaches	111	2	–	–	–	–	2	–
Other hair coloring preparations	49	1	–	–	–	–	1	–
Cuticle softeners	32	1	–	–	–	1	–	–
Nail creams and lotions	25	1	–	–	–	1	–	–
Other manicuring preparations	50	2	–	–	–	2	–	–
Bath soaps and detergents	148	54	–	2	7	13	32	–
Other personal cleanliness products	227	2	–	1	–	1	–	–
Shaving cream (aerosol, brushless, and lather)	11	14	–	–	–	5	9	–
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	680	25	–	–	8	16	1	–
Depilatories	32	1	–	–	–	1	–	–
1981 TOTALS		604	14	30	168	318	73	1

TABLE 1. (Continued)

Product category	Total no. of formulations in category	Total no. containing ingredient	No. of product formulations within each concentration range (%)		
			>5–10	>1–5	>0.1–1
Linoleamide DEA					
Bubble baths	475	7	1	6	–
Other bath preparations	132	1	–	1	–
Hair conditioners	478	3	–	3	–
Hair shampoos (noncoloring)	909	26	1	22	3
Hair dyes and colors (all types requiring caution statement and patch test	811	44	2	42	–
Hair bleaches	111	1	–	1	–
Blushers (all types)	819	1	–	1	–
Bath soaps and detergents	148	2	–	2	–
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	680	6	–	6	–
Suntan gels, creams, and liquids	164	1	–	1	–
1981 TOTALS		92	4	85	3

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
Oleamide DEA						
Bubble baths	475	5	–	–	1	4
Hair conditioners	478	2	–	–	–	2
Hair shampoos (noncoloring)	909	10	1	2	4	3
Hair dyes and colors (all types requiring caution statement and patch test)	811	97	–	62	35	–
Hair bleaches	111	1	–	–	1	–
Other hair coloring preparations	49	1	–	–	–	1
Makeup bases	831	1	–	–	1	–
Aftershave lotions	282	1	–	–	–	1
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	680	1	–	1	–	–
Face, body, and hand skin care preparations (excluding shaving preparations)	832	2	–	–	2	–
1981 TOTALS		121	1	65	44	11

Noncosmetic Use

Fatty acid diethanolamides are used as surfactants in bar soaps, light duty detergents, and dishwashing detergents.[23] They are regulated by FDA as "Food additives permitted for direct addition to food for human consumption" and "Indirect food additives" and, as such, are used in pesticide dilutions, adhesive coat-

ings and components, paper and paperboard components, polymers, and adjuvants, production aids, and sanitizers.[27] Cocamide DEA is also regulated by the FDA as a "secondary direct food additive" to be used as a delinting agent for cottonseed.[28]

BIOLOGY

Antimicrobial and Cytotoxic Activity

Lauramide DEA, along with 30 other compounds, was screened for antimicrobial activity against a number of pathogens including gram-positive and gram-negative bacteria, yeasts, and molds. Filter paper discs were saturated with Lauramide DEA and applied to actively growing bacteria, yeast, and mold cultures (on agar) at pH's of 6.8, 4.5, and 7.0, respectively. Growth inhibition by Lauramide DEA was observed after 120 h for 24 species of bacteria, yeasts, and mold.[8]

Several nonionic surfactants were tested for in vitro rabbit kidney cell toxicity and the ability to inactivate herpes simplex virus (HSV) 1 and HSV 2. One percent and 0.1% saline solutions of Lauramide DEA were cytotoxic to primary cortical rabbit kidney cells. Lower concentrations of Lauramide DEA were not cytotoxic. A 1% saline solution of Lauramide DEA inactivated HSV1 and HSV2 by rapidly reducing HSV infectivity. The amide linkage of the surfactant may have inactivated the virus by damaging or destroying the lipid-containing viral membrane.[29]

Absorption

No formal skin absorption studies have been published on these fatty acid diethanolamides.

ANIMAL TOXICOLOGY

Acute Oral Toxicity

Cocamide DEA

The acute oral toxicity of undiluted Cocamide DEA was evaluated in male and female Sprague-Dawley rats. Cocamide DEA in varying amounts was administered to five rats in a single dose by gavage following a 16-h fast, then the rats were observed for 14 days. Undiluted Cocamide DEA was slightly toxic, with an LD_{50} of 12.2 g/kg and a 95% confidence limit of 10.7–14.4 ml/kg.[30] Limit tests on formulations containing either 10 or 12% Cocamide DEA were unremarkable[31,32] (Table 2).

Lauramide DEA

Five rats were given a single 5 g/kg dose, by intubation, of 25.0% Lauramide DEA in corn oil, then observed for 7 days. One rat died 48 h after intubation of the test material. The corn oil containing 25% Lauramide DEA was slightly toxic by ingestion.[33]

TABLE 2. Acute Oral Toxicity

Ingredient	*Species*	*Vehicle or product concentration*	*LD_{50}*	*Reference*
Cocamide DEA	Rat	Pure Cocamide DEA	12.4 ml/kg	30
	Rat[a]	"Material"/10% Cocamide DEA	>5 g/kg	31
	Rat	Shampoo/12% Cocamide DEA	>5 ml/kg	32
Lauramide DEA	Rat	Corn oil/25% Lauramide DEA	>5 g/kg	33
	Rat	Water/10% Lauramide DEA	2.7 g/kg	34
	Rat	Shampoo/8% Lauramide DEA	9.63 g/kg	35–37
	Rat	Bubble bath/6% Lauramide DEA	>15 g/kg	38
Linoleamide DEA	Rat	Pure Linoleamide DEA	10.80 ml/kg	39
	Rat	Pure Linoleamide DEA	>5 g/kg	40
	Rat	Water/10% Linoleamide DEA	>5 g/kg	41
	Rat	Product/1.5% Linoleamide DEA	3.16 g/kg	42,43
Oleamide DEA	Rat	Pure Oleamide DEA	12.4 ml/kg	44
	Rat	Unspecified if pure or in solution	>5 g/kg	45
	Mouse	Unspecified if pure or in solution	>10 g/kg	45

[a]Dotted line separates assays performed with pure ingredient (inert vehicle) from assays performed with the ingredient in formulation.

Groups of five female albino rats were given single oral doses, by intubation, of 10% aqueous solutions of Lauramide DEA, then observed for 2 weeks. The doses ranged from 0.252 to 7.95 g/kg body weight. The LD_{50} for Lauramide DEA was 2.7 g/kg by the Weil modification of the method of Thompson. The compound was considered moderately toxic.[34]

The acute oral LD_{50} of a noncoloring shampoo containing 8% Lauramide DEA was determined using 15 rats. Groups of 5 rats were given 2.15, 4.64, or 10.0 g/kg undiluted shampoo in a single dose by gavage. Three of the five rats given 10.0 g/kg died 24 h after intubation. No other rats died during the 7-day observation period, and the LD_{50} of the formulation was 9.63 g/kg.[35–37]

A single dose of 15.0 g/kg of a bubble bath containing 6.0% Lauramide DEA was given to five rats by intubation. One rat died 24 h after intubation, and another rat died 120 h after intubation. The bubble bath was classified as practically nontoxic by ingestion, with an $LD_{50} > 15$ g/kg of the formulation.[38]

Linoleamide DEA

Linoleamide DEA was administered to five male and female Sprague-Dawley rats by gavage at several different doses. Animals were fasted for 16 h before the single dose of Linoleamide DEA, then observed for 14 days. Linoleamide DEA was slightly toxic via acute ingestion, with an LD_{50} of 10.80 ml/kg (95% confidence limits were 9.34–12.50 ml/kg).[39]

Undiluted Linoleamide DEA was given to five rats by gavage. At 5 g/kg, no animals died during the 7-day observation period.[40]

Five grams per kilogram of a 10% aqueous solution of Linoleamide DEA was given to five rats by gavage. One rat died 24 h after intubation of the test material, and the remaining four rats survived the 7-day observation period.[41]

The acute oral toxicity of a product containing 1.5% Linoleamide DEA was evaluated using 10 rats. Half of the rats were given 2.15 g/kg, and the remaining 5 rats were given 5.0 g/kg of the undiluted product. All rats of the low-dose group survived, but 4/5 rats of the high-dose group died 24 h after intubation. The product was moderately toxic, with an LD_{50} of 3.16 g/kg.[42,43]

Oleamide DEA

The acute oral toxicity of undiluted Oleamide DEA was evaluated in five male and female Sprague-Dawley rats. A single dose of varying amounts was given to the animals by gavage following a 16-h fast. The LD_{50} was 12.4 ml/kg, with 95% confidence limits of 11.1–13.9 ml/kg. Undiluted Oleamide DEA was slightly toxic.[44]

Rats and mice were given single oral doses of a diethanolamide of oleic and stearic acid. The LD_{50} was not reached but was greater than 5 g/kg body weight for rats and 10 g/kg for mice[45] (Table 2).

Subchronic Oral Toxicity

The subchronic oral toxicity of Lauramide DEA was studied in SPF rats. Fifteen male and 15 female rats per group were fed for 90 days diets containing 0 (controls), 0.1, 0.5, 1.0, or 2.0% Lauramide DEA. Two male rats in the 1.0% dietary group developed bronchopneumonia and were killed on Days 23 and 58, respectively. No other deaths occurred in any group during the test period. Growth was normal in the 0.1% group, slightly reduced in the 0.5% group, and moderately reduced in those animals consuming 1.0 or 2.0% Lauramide DEA. Growth retardation was associated with reduced food intake, at and above the 0.5% level. Hematological values were normal except for lower hemoglobin, hematocrit, and red blood cell count values in the rats fed 1.0 and 2.0% Lauramide DEA. Serum glutamic oxaloacetate transaminase activities were increased in animals fed diets of 0.5, 1.0, and 2.0% Lauramide DEA. Bone marrow cytological values, renal function tests, and gross and microscopic findings of test animals were comparable to controls. The no-effect dose was 0.1% Lauramide DEA (equivalent to 50 mg/kg per day) in the diet of rats for 90 days.[46]

Groups of 20 male and 20 female Wistar rats were fed diets containing 0, 25, 80, or 250 mg/kg per day Lauramide DEA for 13 weeks. All test animals were comparable to controls in general health, body weight and feed consumption, hematological values at 6 and 12 weeks, mortality (no deaths in any group), organ weights, and gross and microscopic findings. There were no differences between control and test group values of blood urea nitrogen, serum activities of glutamic oxalacetic transaminase and lactic dehydrogenase, or urinalysis (specific gravity, pH, albumin, glucose, and sediment) at either 6 or 12 weeks. A transient increase in blood glucose concentration at 6 weeks was observed when the male animals were consuming 250 mg/kg per day Lauramide DEA. The no-effect dose for rats was 250 mg/kg per day.[47]

The subchronic oral toxicity of Lauramide DEA was studied using dogs. Groups of four male and five female 5- to 7-month-old beagles were fed Lauramide DEA 6 days a week for 12 weeks. The diets contained 0 (control), 500, 1600, or 5000 ppm Lauramide DEA. No deaths occurred in any group, and all groups were comparable to controls in general health, body weight and feed consumption, hematological values, clinical chemistry values, and organ weights. The no-effect concentration of Lauramide DEA for dogs was 5000 ppm.[47]

Acute Dermal Toxicity

Lauramide DEA

The acute dermal toxicity of 50% Lauramide DEA in corn oil was evaluated using six guinea pigs. Six milliliters per kilogram of the test material was applied to the closely clipped backs of the guinea pigs. The test sites were covered with a binding material so that the compound remained in contact with the skin for 24 h. No animals died during the 14-day observation period. Body weights were taken on Days 0, 7, and 14. All six guinea pigs had reduced body weights on Day 7 and reattained or surpassed their initial weight by Day 14. Fifty percent Lauramide DEA in corn oil was classified as nontoxic by percutaneous absorption.[48]

Linoleamide DEA

Linoleamide DEA was evaluated for acute dermal toxicity using six guinea pigs. A single cutaneous exposure of 3 ml/kg was followed by a 14-day observation period. Animals were weighed immediately before test material application and on Days 7 and 14. One guinea pig was found dead on Day 7. The remaining five animals had reduced body weights on Day 7. Animal weights had surpassed initial weights by Day 14. Pure Linoleamide DEA was classified as nontoxic by percutaneous absorption.[49]

A second acute dermal toxicity study using six guinea pigs evaluated 100% Linoleamide DEA. Three grams per kilogram Linoleamide DEA was applied to the clipped back of the test animals, and no animals died during the 14-day observation period. These animals had weight loss by Day 7 and increased weights by the end of the study. The test material was nontoxic by percutaneous absorption.[50]

Ten percent Linoleamide DEA in water was nontoxic to guinea pigs via a single cutaneous administration. Six animals were given 3.0 g/kg to a clipped site on the back. All animals survived the 14-day study, and all animals gained weight during the study.[51]

Subchronic Dermal Toxicity

Cocamide DEA

Five products, including a shaving cream containing 1.92% Cocamide DEA, were evaluated for dermal toxicity in a 4-week study. Forty-eight New Zealand rabbits were allotted into six groups of eight animals (four male and four female) and were given daily applications of the test material 5 days a week for a total of

20 applications. The eight rabbits given the shaving cream received 500 mg/kg per application undiluted product to a shaved area of the back. The test site was abraded in four animals and left intact on the remaining four rabbits. Four male and four female rabbits served as untreated controls. Test animals were compared to controls with respect to survival, signs of toxicity and skin irritation, hematological and blood chemistry values, absolute and relative organ weights, and gross changes. No skin irritation was observed in control animals. Moderate erythema, wrinkling, cracking, and dry skin were noted during the first week and continued throughout the study in animals receiving the shaving cream. Skin irritation was observed at both intact and abraded sites. All other observed parameters were comparable to controls except that blood glucose values and serum alkaline phosphatase activities were significantly higher and blood urea nitrogen values were significantly lower than control values ($P < 0.05$). No systemic effects were attributed to treatment with the Cocamide DEA-containing shaving cream.[52]

Lauramide DEA

The dermal toxicity of three products, including a medicated liquid cleanser containing 5.0% Lauramide DEA, was evaluated in a 13-week study. Test and control groups consisted of 10 male and 10 female Sprague-Dawley rats. The medicated cleanser was applied as a 4.8% aqueous solution to a shaved skin site on the back of the animals. Two milliliters per kilogram of the solution (96.0 mg/kg product) were applied to the test site once a day, 5 days a week, for a total of 67 applications. Control animals were untreated. Body weight, survival, and appearance and behavior were monitored throughout the experiment, and blood and urine were analyzed at 7 and 13 weeks. All animals surviving the study had weight gains comparable to controls. Minimal skin irritation was noted during the first week only in females treated with the Lauramide DEA-containing cleanser. Hematological and urinalysis values were within normal limits. Histological findings were comparable to controls. The medicated liquid cleanser containing 5.0% Lauramide DEA did not have any cumulative, systemic toxicity.[53]

A cream cleanser containing 4.0% Lauramide DEA was evaluated for dermal toxicity following the procedure outlined above with two modifications: test groups consisted of 15 female Sprague-Dawley rats, and the product was administered as a 0.45% aqueous solution in a daily 2.0 ml/kg dose (9 mg product/kg per day). All animals survived the 13-week study. Blood and urine values were within the normal range, and gross and histopathological findings were comparable to those observed in untreated control rats. The cream cleanser was not considered a dermal or systemic toxin when applied repeatedly over 13 weeks.[54]

Linoleamide DEA

The dermal toxicity of a shampoo containing 3.0% Linoleamide DEA was evaluated using groups of 10 male and 10 female Sprague-Dawley rats. The shampoo was applied to an anterior dorsal shaved site once a day, 5 days a week, for 66 or 67 applications. The product was administered to three groups as a 2.5% solution, a 25% solution, or a 25% solution that was rinsed off with tap

water 15 minutes after application. There were two control groups: one untreated and the other rinsed with tap water only. All animals survived the full 13-week term of the study. All parameters examined in the 2.5% group were within normal limits. Body weight gains were depressed in all rats receiving 25% shampoo with or without rinsing. Skin irritation at the test site was observed throughout the study in male and female rats. The irritation ranged from minimal to severe, and the rats of the rinsed group generally had less irritation. Urinalysis parameters, organ weight values, and gross and histological findings were comparable to controls. The investigators concluded that aside from skin irritation, the shampoo containing 3.0% Linoleamide DEA was not a cumulative systemic toxicant.[55]

A summary of dermal toxicity studies is presented in Table 3.

Ocular Irritation

Cocamide DEA

Thirty percent Cocamide DEA in propylene glycol was tested for ocular irritation in three female rabbits. A single 0.1 ml aliquot of the solution was instilled into the conjunctival sac of the rabbits' left eyes, and the untreated right eyes served as controls. Eyes were examined for irritation and inflammation of the iris, cornea, and conjunctiva 1 h after instillation and daily thereafter up to a maximum of 7 days. The Draize scoring system for eye irritation was used.[56] Only maximum scores for the one hour and day three readings were reported. The irritation scores for the iris and cornea were 0, and the maximum conjunctival score was 6 at 1 h and 4 at Day 3. All eyes were normal by Day 4. The cumulative ocular irritation rating was not reported, but 30% Cocamide DEA was at least a mild eye irritant.[57]

Lauramide DEA

Aqueous emulsions of 1, 5, or 25% Lauramide DEA were administered into rabbit eyes to evaluate irritancy. Three rabbits were tested per concentration of Lauramide DEA. Two drops of the surfactant were applied to each eye of the rabbit. Within 30 seconds, one eye was rinsed for 2 minutes with flowing tap water. The other eye was left unrinsed. Both eyes were evaluated for immediate effects and again after 1 h, 24 h, 48 h, and 1 week. The 1% aqueous emulsion of Lauramide DEA caused no effect to a "very slight effect, disappearing within 24 hours. [The reaction] may consist of appreciable pain initially and some conjunctival irritation. No corneal injury." The 5% Lauramide DEA caused "slight to moderate injury which disappeared within a week. These injuries may consist of appreciable conjunctival irritation and superficial corneal injury, with no loss of vision expected." The 25% aqueous Lauramide DEA caused moderate to severe corneal and conjunctival injury with some impairment of vision. Washing the eye reduced the irritation of the 5 and 25% emulsions. Thirteen surfactants were tested for eye irritation according to the above protocol, and Lauramide DEA had the greatest potential for producing ocular injury.[34]

The eye irritation of 10 and 20% aqueous solutions of Lauramide DEA and five products containing 6–8% Lauramide DEA was evaluated in groups of six al-

bino rabbits (unless otherwise noted). A single application of 0.1 ml test material was instilled into one eye of each animal, and the contralateral eye served as control. Eyes were not rinsed unless specified. The cornea, iris, and conjunctiva were scored for injury and irritation according to the Draize[58] criteria on Days 1, 2, 3, 4, and 7. The results of the eight studies were as follows: Lauramide DEA (20% aqueous) was a moderate eye irritant with group average scores of 17 on Day 1, 12 on Day 2, 9 on Day 3, 4 on Day 4, and 2 on Day 7.[59] Lauramide DEA (10% aqueous) was a moderate eye irritant in two separate assays. The group average scores were 22 and 23 on Day 1, 22 and 21 on Day 2, 19 and 18 on Day 3, 12 and 6 on Day 4, and 6 on Day 7. There were no scores recorded for Day 7 in one assay.[60,61] A noncoloring hair shampoo was moderately irritating with group average scores of 36 on Day 1, 28 on Day 2, 28 on Day 3, 26 on Day 4, and 14 on Day 7. The shampoo contained 8% Lauramide DEA and was applied full strength.[62] A noncoloring shampoo containing 8% Lauramide DEA applied full strength was practically nonirritating when the rabbits' eyes were washed. The group average score was 1 on Day 1, and 0 on Day 2. Only three rabbits were used in this study.[63] No irritation was observed in three rabbits following instillation of a noncoloring shampoo containing 8% Lauramide DEA. The rabbits eyes were washed. All scores were 0.[64] A bubble bath containing 6% Lauramide DEA was practically nonirritating (average group score of 1 on Day 1 and 0 on Day 2) in three rabbits. The undiluted product was applied and eyes were rinsed.[65] A bubble bath containing 6% Lauramide DEA was moderately irritating when eyes were not rinsed. The scores for the undiluted product were 41 on Day 1, 37 on Day 2, 35 on Day 3, 30 on Day 4, and 16 on Day 7.[66]

Linoleamide DEA

Undiluted Linoleamide DEA (0.1 ml) was instilled into the left eye of three albino rabbits, then the eyes were immediately rinsed with distilled water for 60 seconds. The untreated right eye served as control. Eyes were scored for irritation according to the Draize[58] scoring system. Linoleamide DEA was minimally irritating, with a maximum irritation score of 4. All traces of irritation were gone by Day 2.[67]

Undiluted Linoleamide DEA when applied and not rinsed from the eye was a moderate eye irritant. Six albino rabbits received 0.1 ml Linoleamide DEA in one eye, and the untreated contralateral eye was used as the control. Draize scores[58] for irritation were 34 on Day 1, 27 on Day 2, 26 on Day 3, 18 on Day 4, and 13 on Day 7. These scores were the average of the six individual animals' scores.[68]

Ten percent aqueous Linoleamide DEA was evaluated for eye irritation in two groups of six albino rabbits. In neither group were the eyes rinsed after instillation of 0.1 ml test solution following the usual test procedures. In one group, 10% Linoleamide DEA was practically nonirritating, with a group Draize score of 1 on Day 1 and 0 on Day 2. The test solution was mildly irritating in the other group, with group scores of 4 on Day 1, 2 on Day 2, 1 on Days 3 and 4, and 0 on Day 7.[69]

Products containing 1.5% Linoleamide DEA were mild to moderate eye irritants. In one assay, the product was applied undiluted to the eyes of three rabbits, and the eyes were not washed. The Draize scores on Days 1, 2, 3, 4, and 7

TABLE 3. Dermal Toxicity

Ingredient	*Test type and duration*	*No. of animals*	*Concentration and vehicle*	*Dose*	*Comments*	*Reference*
Cocamide DEA	Subchronic—4 weeks	4M + 4F rabbits	1.92% in shaving cream	500 mg/kg per day (5 days/week)	Applied to abraded and intact skin; moderate skin irritation at test sites throughout study; 1 animal died—not treatment related; no systemic effects attributable to treatment; not a systemic toxin when administered via the skin	52
Lauramide DEA	Acute—14 days	6 guinea pigs	50% in corn oil	6 ml/kg (single, 24-h application)	No animals died; all animals lost weight by Day 7 and regained it by Day 14; not an acute dermal toxin	48
	Subchronic—13 weeks[a]	10M + 10F rats	5% in medicated liquid cleanser applied as a 4.8% aqueous solution	2 ml/kg, 5 days/week (96 mg/kg product)	No animals died; minimal skin irritation at application site; not a cumulative systemic toxin	53
	Subchronic—13 weeks	15 rats	4% in cream cleanser applied as a 0.45% aqueous solution	2 ml/kg, 5 days/week (9 mg/kg product)	No animals died; not a cumulative systemic toxin	54

Linoleamide DEA	Acute–14 days	6 guinea pigs	100%	3 ml/kg	An animal found dead on Day 7; remaining animals had reduced body weights on Day 7, regained weight by Day 14; classified as "nontoxic by percutaneous absorption"	49
	Acute–14 days	6 guinea pigs	100%	3 g/kg	No animals died; all animals lost weight by Day 7 and regained it by Day 14; "nontoxic via percutaneous absorption"	50
	Acute–14 days	6 guinea pigs	10% in water	3 g/kg	No animals died; all animals had consistent weight gains throughout study; not an acute dermal toxin	51
	Subchronic–13 weeks[a]	3 groups of 10M + 10F rats	3% in a shampoo applied as either a. 2.5% aqueous solution b. 25% aqueous solution c. 25% aqueous solution, then site washed 15 minutes after application	9.6 ml/kg (240 and 2400 mg product/kg)	All animals survived the 13-week study; no treatment-related abnormalities in 2.5% group; body weight gain was depressed and skin irritation at application site in both 25% groups; a few statistically significant variations in hematological and clinical chemistry values, but not considered clinically significant; shampoo was a skin irritant but not a cumulative systemic toxin	55

[a]Dotted line separates assays performed with pure ingredient (inert vehicle) and assays performed with the ingredient in formulation.

were 36, 30, 14, 5, and 0, respectively.[70] In the other two assays, the products were applied as 25% aqueous solutions and six rabbits were used. The eyes were not rinsed and the contralateral eyes served as controls. The scores for one assay were 24 on Day 1, 20 on Day 2, 7 on Day 3, and 0 on Day 4.[71] The results from the other assay were 32, 27, 11, 4, and 3 for Days 1, 2, 3, 4, and 7, respectively.[72] The product types were not specified in the three assays.

Oleamide DEA

Undiluted Oleamide DEA was applied in a 0.1 ml dose to the left eye of three albino rabbits, and the right eye served as an untreated control. Eyes were not rinsed, and the maximum Draize score recorded was 2 for conjunctival irritation. No irritation was observed by Day 2. Undiluted Oleamide DEA was practically nonirritating under these test conditions.[73]

Table 4 is a summary of the ocular irritation assays.

Skin Irritation

Lauramide DEA

Four groups of six guinea pigs were used to evaluate the skin irritation and percutaneous toxicity of 0.5% (w/v) aqueous Lauramide DEA. The same immersion test procedure was used for all four groups of animals: the guinea pigs were clipped free of abdominal hair, then immersed up to the axillae in the test solution 4 h/day for 3 consecutive days. The test solutions were kept at 40°C, and animals were weighed before the first immersion and 48 h after the final immersion. All but one animal gained weight (3–23 g) during the tests. Forty-eight hours after the third immersion, the skin of the abdomen was graded on a 1 (moribund due to skin injuries) to 10 (normal) scale. Six animals had scores of 7 (slight "scurfing" over the entire skin, slight loss of elasticity), 12/24 animals had scores of 8 (moderate scaling, no loss of elasticity), and 6/24 animals had scores of 9 (first hint of scaling). Lauramide DEA in 0.5% aqueous solution was a mild skin irritant. No controls were included in these tests.[74–77]

Lauramide DEA was evaluated for skin irritation in another four groups of six guinea pigs in immersion tests using the 1–10 scoring scale. Two groups were immersed in 0.25% aqueous Lauramide DEA 4 h/day for 3 consecutive days; this concentration of Lauramide DEA was minimally irritating. The animals had skin irritation scores of 8 (4/12 animals), 9 (5/10), and 10 (3/12).[78,79] The other two groups of guinea pigs were immersed in 0.1% aqueous Lauramide DEA following the same schedule of immersion. The immersion scores (nine grade 9 and three grade 10) indicated that 0.1% Lauramide DEA was a minimal skin irritant.[80,81]

A noncoloring shampoo containing 8% Lauramide DEA and a bubble bath containing 6% Lauramide DEA were minimal skin irritants under the test conditions of the guinea pig immersion test. Both products were tested at 0.5% (w/v) in water. Animal scores for the shampoo assay were 8 (2/6 animals), 9 (2/6), and 10 (2/6).[82] The bubble bath was even less irritating than the shampoo, with four guinea pigs having a skin grade of 9 and two having a grade of 10.[83]

Linoleamide DEA

Linoleamide DEA was evaluated for dermal irritation and toxicity in six guinea pig immersion tests all following the same protocol. Six animals were immersed in the test solution 4 h/day for 3 consecutive days. Animals were weighed before the first immersion and 48 h after the third immersion. The shaved area of the abdomen was scored for irritation at the same time the final weights were taken. Irritation was graded on a 1–10 scale as described above,[74] with 10 denoting no irritation. The results of the six assays were: 0.5% aqueous Linoleamide DEA was a slight irritant in one assay with animal scores of 8 and 9[84]; 0.5% aqueous Linoleamide DEA was a minimal irritant in a second assay, with one animal having a score of 8 and the remaining animals having no irritation[85]; 0.5% aqueous Linoleamide DEA was nonirritating in a third assay and all animals had skin irritation scores of 10[86]; 0.25% aqueous Linoleamide DEA was a slight skin irritant—three animals had skin grades of 7 and the other three guinea pigs had skin grades of 9[87]; 0.1% aqueous Linoleamide DEA was a minimal irritant with animal scores of 9 and 10[88]; a product containing 1.5% Linoleamide DEA was a slight skin irritant when tested as a 0.5% aqueous solution. A skin grade of 7 was observed for two animals, grade 8 for three animals, and the last animal had a skin grade of 9.[89]

Primary Irritation

Cocamide DEA

Six rabbits were used to evaluate the irritation of a 30% solution of Cocamide DEA in propylene glycol. The dorsal area of each rabbit was shaved, and 0.3 ml of the test material was applied via a patch to either an intact or abraded site. The entire trunk of each animal was wrapped in cellophane, and the patches remained in skin contact for 23 h. Test sites were scored for irritation 1 and 49 h after patch removal. Thirty percent Cocamide DEA was a moderate skin irritant; the primary irritation index (PII) was 3.1 (max 8). No control data were available.[90]

Lauramide DEA

The skin irritation of Lauramide DEA was tested on the shaved abdominal area of rabbits. Lauramide DEA was tested at concentrations of 1, 5, and 25% in water. Each animal had one intact and one abraded test site. Ten applications of 5 ml each were made over a period of 14 days to intact sites, and three applications were made to abraded test sites. One percent Lauramide DEA caused little or no irritation. On a 1–6 scale, 5% Lauramide DEA had scores ranging from 2 (very slight hyperemia on intact skin, likely more irritating to abraded skin) to 5.5 (burn from two to four 24-h applications to intact skin). The 25% solution was severely irritating, with scores of 5.5–6 (burn from one 24-h application to intact skin). Small amounts of these three concentrations of Lauramide DEA were also applied daily to the intact rabbit ear and scored by the same scale. A score of 1 (essentially no irritation to intact skin) was recorded for 1% Lauramide DEA. Five percent Lauramide DEA was more irritating, with scores of 1.1–3 (slight hyper-

TABLE 4. Ocular Irritation

Ingredient	*No. of rabbits*	*Concentration and vehicle/product*	*Dose*	*Eyes washed*	*Comments*	*Reference*
Cocamide DEA	3	30% in propylene glycol	0.1 ml	No	Conjunctival irritation through Day 3—max score of 6[a]; minimal eye irritant	57
Lauramide DEA	3 groups of 3 rabbits	1, 5, and 25% in water	"Two drops"	1 eye washed and other eye unwashed for each animal (both eyes received test material)	1% was mildly irritating; 5% was slightly to moderately irritating; 25% was moderately to severely irritating; washing lessened severity of irritation in 5 and 25% groups	34
	6	20% in water	0.1 ml	No	Group average scores were 17 on Day 1 and 2 on Day 7; moderate eye irritant	59
	6	10% in water	0.1 ml	No	Group average scores were 22 on Day 1 and 6 on Day 7; moderate eye irritant	60
	6	10% in water	0.1 ml	No	Group average scores were 23 on Day 1 and 6 on Day 4; moderate eye irritant	61
	6[b]	8% in noncoloring shampoo	0.1 ml	No	Group average scores were 36 on Day 1 and 14 on Day 7; moderate eye irritant	62
	6	8% in noncoloring shampoo	0.1 ml	Yes	Group average scores were 1 on Day 1 and 0 on Day 2; practically nonirritating	63
	3	8% in noncoloring shampoo	0.1 ml	Yes	No irritation; not an eye irritant	64
	3	6% in a bubble bath	0.1 ml	Yes	Group average scores were 1 on Day 1 and 0 on Day 2; practically nonirritating	65
	6	6% in a bubble bath	0.1 ml	No	Group average scores were 41 on Day 1 and 16 on Day 7; moderate eye irritant	66

Linoleamide DEA	3	100%	0.1 ml	Yes	Max individual score reported was 4; minimal eye irritant	67
	6	100%	0.1 ml	No	Group average scores were 34 on Day 1 and 13 on Day 7; moderate eye irritant	68
	6	10% in water	0.1 ml	No	Group average scores were 1 on Day 1 and 0 on Day 2; practically nonirritating	69
	3[b]	15% in product	0.1 ml	No	Group average scores were 36 on Day 1 and 0 on Day 7; moderate eye irritant	70
	6	15% in product; product applied as a 25% aqueous solution	0.1 ml	No	Group average scores were 24 on Day 1 and 0 on Day 4; mild eye irritant	71
	6	1.5% in product; product applied as a 25% aqueous solution	0.1 ml	No	Group average scores were 32 on Day 1 and 3 on Day 7; moderate eye irritant	72
Oleamide DEA	3	100%	0.1 ml	No	Max score reported was 2 for conjunctival irritation; practically nonirritating	73

[a]Draize scoring system used in all assays: 80 (cornea) + 10 (iris) + 20 (conjunctiva) = 110 max score.
[b]Dotted line separates assays performed with pure ingredient (inert vehicle) from assays performed with the ingredient in formulation.

emia on intact skin, may or may not burn abraded skin). The highest concentration of Lauramide DEA was very irritating and had irritancy scores ranging from 3 to 6. No control data were available.[34]

The skin irritation of 20% aqueous Lauramide DEA was evaluated in nine healthy female albino rabbits. A single, 24-h occlusive patch containing 0.5 ml of the test solution was applied to a clipped area of the back of each rabbit. The sites were scored for irritation on a 0 (no effect) to 4 (severe—deep red erythema with vesiculation or weeping with or without edema) scale 2 and 24 h after patch removal. Skin irritation was severe at 2 h; seven grade 4 reactions and two grade 3 reactions were noted. At 24 h, the irritation was moderate to severe: two grade 4s, four grade 3s, and three grade 2 reactions. The group mean primary skin irritation (PSI) score was 3.78 (max 4). Twenty percent aqueous Lauramide DEA was a marked skin irritant.[91]

Ten percent aqueous Lauramide DEA was tested for skin irritation using two groups of nine female rabbits. Single, 24-h occlusive patches were applied, then the test sites were scored for irritation 2 and 24 h after patch removal using a 0 (no effect) to 4 scale. The group mean PSI was 0.05 for one group and 0.72 for the other group. The test material was slightly irritating to practically nonirritating.[92,93]

One and one quarter percent (1.25%) aqueous Lauramide DEA tested as described above was practically nonirritating in nine rabbits. The mean group PSI was 0.06 on a scale of 0–4.[91,94]

A liquid soap containing 10% Lauramide DEA was evaluated for skin irritation in three male and three female New Zealand rabbits. One-half milliliter of undiluted product was applied to one abraded and one intact site on the clipped back of each rabbit. Sites were covered with occlusive patches for 24 h, then patches were removed and sites were scored for erythema and edema immediately and 48 h following patch removal. Sites were scored according to the scale set forth in the Code of Federal Regulations, Title 16.[95] The product PII was 5.6 (max 8), severely irritating.[96]

Two liquid soap products containing 10% Lauramide DEA were evaluated for skin irritation using two male and two female albino rabbits. The dorsal area of each animal was shaved 24 h before a single 0.5 ml application of undiluted product. The site was not covered, and the test material was removed after 2 h. Sites were scored according to Draize et al.[56] 1, 24, and 72 h after removal of the test material. One product was a mild skin irritant with a PII of 2.4 (max 8), and the other product was a moderate irritant with a PII of 3.2.[97,98]

Linoleamide DEA

Twenty percent aqueous Linoleamide DEA was tested for primary skin irritation in nine female albino rabbits. A single occlusive 24-h patch containing 0.5 ml test material was applied to the shaved back of each animal. Test sites were scored for irritation on a 0 (no effect) to 4 scale 2 and 24 h after patch removal. The test sites were moderately irritated 2 h after patch removal; one grade 1 score, four grade 2 scores, three grade 3 scores, and one grade 4 score were recorded. The test sites were severely irritated 24 h after patch removal. Individual primary irritation scores at 24 h were five grade 3 scores and four grade 4 scores. Twenty percent Linoleamide DEA was a severe skin irritant.[99]

Ten percent aqueous Linoleamide DEA was a mild skin irritant in a study using nine rabbits. The test procedure and scoring system were identical to that described above.[99] The group mean primary skin irritation index was 1.17.[100]

Six female New Zealand rabbits were used to evaluate the skin irritation of 5% Linoleamide DEA in corn oil. A single occlusive patch containing 0.3 ml test solution was applied to the clipped dorsal area of each rabbit for 24 h, then scored for irritation 1 and 48 h after patch removal. The group PII was 0 (max 8). Linoleamide DEA was not irritating at this concentration in corn oil.[101]

A product containing 1.5% Linoleamide DEA was tested for skin irritation at a concentration of 2.5% in water. Nine female albino rabbits received single occlusive 24-h patches, and test sites were scored for irritation 2 and 24 h after patch removal. The group mean irritation index was 0.11 (max 4). The diluted product was a minimal skin irritant.[102]

Oleamide DEA

Two groups of six New Zealand rabbits were used to evaluate the skin irritancy of Oleamide DEA. Each animal received a single 24-h occlusive patch containing 0.3 ml test material. Test sites were scored for erythema, eschar formation, and edema 1 and 48 h after patch removal. One group was given 70% Oleamide DEA in propylene glycol, and the other group received 5% Oleamide DEA in propylene glycol. The group irritation index was 3.3 (max 8) for the 70% group and 1.9 for the 5% group. Five percent Oleamide DEA was a mild skin irritant, and 70% Oleamide DEA was a moderate skin irritant. No control data were available.[103,104]

Mucous Membrane Irritation

The irritancy of a liquid soap containing 10% Lauramide DEA was compared to the irritancy of a marketed, competitor's liquid soap. A mucous membrane irritation test was performed according to the procedure of Eckstein et al.[105] Low, medium, or high dose concentrations of the products were repeatedly inserted into rabbit vaginas, then the mucosal tissue was evaluated histologically for irritancy. No significant difference in irritation was observed between the two products, and both soaps were significantly more irritating than a water control.[106]

See Table 5 for a summary of animal skin irritation studies.

Mutagenicity

Lauramide DEA, at 0.5–200 μg/plate, did not have mutagenic activity in *Salmonella typhimurium* strains TA98 and TA100 after activation with S9 liver fractions from rats, hamsters, and guinea pigs induced with polychlorinated biphenyls, phenobarbital, or 3-methylcholanthrene.[107]

Inoue et al.[108] tested 10 surfactants, including Lauramide DEA, in three mutagenicity assays; *S. typhimurium* (strains TA98 and TA100) mutagenicity, DNA damage in *Bacillus subtilis* strains H17 and M45, and in vitro transformation of hamster embryo cells. Lauramide DEA did not have mutagenic activity in any of these assays. In further testing of surfactants, Lauramide DEA was not active in in vitro transformation of Syrian golden hamster embryo cells or the *S. typhimurium* (strains TA98 and TA100) mutagenicity assay.[109]

TABLE 5. Animal Skin Irritation Studies

Ingredient	*Test type*[a]	*No. of animals and species*	*Vehicle or product*	*Ingredient concentration in vehicle/product*	*Dose*	*Comments*	*Reference*
Cocamide DEA	Primary irritation; single patch	6 rabbits	Propylene glycol	30%	0.3 ml	Group PII = 3.1 (max 8); moderate skin irritant	90
Lauramide DEA	Immersion	24 guinea pigs, tested in groups of 6	Water	0.5%	N/A[b]	Animal irritation scores were 6 grade 7, 12 grade 8, and 6 grade 9 (1–10 scale, 10 = normal); mild skin irritant	74–77
	Immersion	12 guinea pigs, tested in groups of 6	Water	0.25%	N/A	Animal irritation scores were 4 grade 8, 5 grade 9, and 3 grade 10 (1–10 scale, 10 = normal); minimal skin irritant	78–79
	Immersion	12 guinea pigs, tested in groups of 6	Water	0.10%	N/A	Animal irritation scores were 9 grade 9 and 3 grade 10 (1–10 scale, 10 = normal); minimal skin irritant	80,81
	Cumulative irritation	Rabbits, number not specified	Water	1, 5, and 25%	5 ml/application	1% not an irritant; 5% moderate irritant; 25% severe irritant	34
	Primary irritation; single patch	9 rabbits	Water	20%	0.5 ml	Group PSI = 3.78 (max 4); severe skin irritant	91
	Primary irritation; single patch	9 rabbits	Water	10%	0.5 ml	Group PSI = 0.05 (max 4); practically nonirritating	92
	Primary irritation; single patch	9 rabbits	Water	10%	0.5 ml	Group PSI = 0.72 (max 4); slight skin irritant	93
	Primary irritation; single patch	9 rabbits	Water	1.25%	0.5 ml	Group PSI = 0.06 (max 4); practically nonirritating	64
	Immersion[c]	6 guinea pigs	Shampoo (noncoloring)	8%; product tested as 0.5% aqueous solution	N/A	Animal irritation scores were 2 grade 10 (1–10 scale, 10 = normal); slight skin irritant	82

	Immersion	6 guinea pigs	Bubble bath	6%; product tested as 0.5% aqueous solution	N/A	Animal irritation scores were 4 grade 9 and 2 grade 10 (1–10 scale, 10 = normal); practically nonirritating	83
	Primary irritation; single patch	3M and 3F rabbits	Liquid soap	10%	0.5 ml	Group PII = 5.6 (max 8); severe skin irritant	96
	Primary irritation; single patch	2M and 2F rabbits	Liquid soap	10%	0.5 ml	Group PII = 2.4 (max 8); mild skin irritant	97
	Primary irritation; single patch	2M and 2F rabbits	Liquid soap	10%	0.5 ml	Group PII = 3.2 (max 8); moderate skin irritant	98
	Mucous membrane irritation	8 groups of 4F rabbits	Liquid soap	10%; product tested at 3.3, 18.5, and 33% in water	1 ml daily for 10 days	Controls consisted of water only and a low, medium, and high dose group of another liquid soap; no difference in irritation between products; both products significantly more irritating than water control	106
Linoleamide DEA	Immersion	18 guinea pigs; tested in groups of 6	Water	0.5%	N/A	Animal irritation scores were 8 and 9 in one assay (1–10 scale, 10 = normal), 8 and 10 in another assay, and all 10 in the third assay; not an irritant to slightly irritating	84–86
	Immersion	6 guinea pigs	Water	0.25%	N/A	Animal irritation scores were 3 grade 7 and 3 grade 9 (1–10 scale, 10 = normal); slight skin irritant	87
	Immersion	6 guinea pigs	Water	0.1%	N/A	All animals had scores of 9 and 10 (1–10 scale, 10 = normal); minimal skin irritant	88
	Primary irritation; single patch	9F rabbits	Water	20%	0.5 ml	Animal scores were 1, 2, 3, and 4 (max 4) at 2 h and all 3 and 4 at 24 h following patch removal; severe skin irritant	99

TABLE 5. (Continued)

Ingredient	*Test type*[a]	*No. of animals and species*	*Vehicle or product*	*Ingredient concentration in vehicle/product*	*Dose*	*Comments*	*Reference*
	Primary irritation; single patch	9 rabbits	Water	10%	0.5 ml	Group PSI = 1.17 (max 4); mild skin irritant	100
	Primary irritation; single patch	6 rabbits	Corn oil	5%	0.3 ml	Group PII = 0 (max 8); not a skin irritant	101
	Immersion[c]	6 guinea pigs	Product	1.5%; product was tested as a 0.5% aqueous solution	N/A	Animal scores were 2 grade 7, 3 grade 8, and 1 grade 9 (1–10 scale, 10 = normal); slight skin irritant	89
	Primary irritation; single patch	9F rabbits	Product	1.5%; product was tested as a 2.5% aqueous solution	0.5 ml	Group PSI = 0.11 (max 4); minimal skin irritant	102
Oleamide DEA	Primary irritation; single patch	6 rabbits	Propylene glycol	70%	0.3 ml	Group PII = 3.3 (max 8); moderate skin irritant	103
	Primary irritation; single patch	6 rabbits	Propylene glycol	5%	0.3 ml	Group PII = 1.9 (max 8); mild skin irritant	104

[a]See text for detailed procedures and results.
[b]Not applicable.
[c]Dotted line separates assays performed with pure ingredient (inert vehicle) from assays performed with the ingredient in formulation.

Lauramide DEA was assayed in the *Salmonella*/microsome system using the same five strains of *S. typhimurium*. Lauramide DEA was not mutagenic when 0.001 μl to 0.1 μl per plate were tested. One microliter Lauramide DEA per plate was cytotoxic to all *S. typhimurium* strains. A spot test was performed with and without metabolic activation (S9 liver fractions from Aroclor 1254-induced Sprague-Dawley rats) using five strains of *S. typhimurium*: TA98, TA100, TA1535, TA1537, and TA1538; 50 μg of Lauramide DEA was judged to be mutagenic in the spot test in TA1535 and TA100 without metabolic activation, but quantitative results were not provided.[110]

Carcinogenicity

Cocamide DEA and Lauramide DEA are currently being tested in a National Toxicology Program (NTP) long-term carcinogenicity bioassay using rats and mice. The route of administration is topical (skin painting). Evaluation of histopathological data is currently in progress in both studies.[111] No other carcinogenicity data on these ingredients were available in the published literature.

CLINICAL ASSESSMENT OF SAFETY

Skin Irritation

Lauramide DEA

Three Lauramide DEA-containing products were tested for skin irritation according to the following procedure: 20 subjects were patch tested with a diluted sample of the product. The occlusive patches remained in skin contact for 24 or 48 h, then test sites were scored for irritation (0–4 scale, 4 defined as severely irritating) 2 and 24 h after patch removal. A noncoloring shampoo containing 8% Lauramide DEA (tested as a 1.25% aqueous solution) was a mild skin irritant in a 19-member panel. The group PII was 0.95 (max 4).[112] A bubble bath containing 6.0% Lauramide DEA was tested as a 1.25% aqueous solution and was a mild irritant. The 18-member test panel had a PII of 0.92.[113] The third product contained 5% Lauramide DEA and was tested at 1% using 17 panelists. The product was a minimal irritant with a PII of 0.59.[114]

Three liquid soap products containing 10% Lauramide DEA were assessed for irritancy in the soap chamber test. The products were tested as 8% aqueous solutions. Five applications of 100 μl of the diluted product were administered to each of 12 or 15 panelists on 5 consecutive days. The soaps were applied using a Duhring chamber consisting of cotton cloth snugly fitted into chambers that were attached to the volar forearm with nonocclusive tape. The first application remained in contact with the skin 24 h, and the remaining four patches remained in skin contact for 6 h. Sites were scored for erythema (1+–4+), scaling (1+–3+), and fissue formation (1+–3+) 36 h after removal of the final patch. One soap was nonirritating, and the other two soaps were mild skin irritants, with group mean irritation scores of 0.58, 1.2, and 1.28 (max 10), respectively.[115–117]

Seven panelists participated in a 21-day cumulative irritation assay[118] to evaluate the irritancy of eight cleansing products. One of the products tested was a medicated liquid soap containing 5% Lauramide DEA. Twenty-one occlusive patches containing a 25% soap solution were applied for 21 consecutive days. Patches remained in skin contact for 24 h, then were removed. The test site was scored for irritation (0–4 scale) 30 minutes later, and a fresh patch was immediately applied to the same test site. Individual cumulative irritation scores ranged from 13 to 57 (max 84), with a mean score of 32.3. The group total irritation score was 226.5 (max 588). The Lauramide DEA-containing soap was a moderate cumulative skin irritant.[119]

Linoleamide DEA

The irritancy of a product containing 1.5% Linoleamide DEA was evaluated with an occlusive patch test using 20 panelists. The product was tested as a 1.25% aqueous solution. A 24- or 48-h occlusive patch was applied to the volar surface of the forearm and/or the inner and outer aspect of the arm of each subject. Test sites were scored 2 and 24 h after patch removal. The product PII was 1.15 (max 4), a mild skin irritant.[120]

Sensitization

Lauramide DEA

Two liquid soaps containing 10% Lauramide DEA were evaluated in a repeat insult patch test (RIPT) for sensitization. The soaps were tested as a 1% aqueous solution using two panels of 159 and 41 subjects. Ten occlusive 48–72-h patches were applied to the back of each subject over a 6-week period. Each patch contained 0.2 ml of the test solution. Following a 10-day nontreatment period, a 48-h occlusive challenge patch was applied. In the first study, 20/159 subjects had reactions to one or more induction patches, and 2/20 reactions were severe. Five subjects had mild reactions to the challenge patch; four subjects scored 0.5 and one scored 1 of the maximum possible 3.[121] In the second study, 13/41 subjects had mild irritant reactions (scores of 0.5 or 1) during induction, and one subject reacted mildly (score of 0.5) to the challenge patch.[122] Neither product was considered to be a sensitizer under these test conditions.

A modified Draize-Shelanski repeat insult procedure was used to test a noncoloring shampoo containing 8% Lauramide DEA. A panel of 99 subjects completed the study. Ten 48-h induction patches were applied in a quadrant system to the back of each subject. Applications one, four, seven, and ten were applied to the second quadrant, and three, six and nine were applied to the third quadrant. An eleventh patch, the challenge patch, was applied to the fourth quadrant after a 2-week nontreatment period. Patches one, two, and three contained a 0.1% aqueous solution of shampoo, and patches four through challenge contained 0.5% shampoo. Applications one, four, six, seven, and eleven were evaluated for reactions (0–3+ scale) immediately upon patch removal and 48 h later. Applications two and eight were scored immediately upon patch removal and 72 h later. The third application was scored 72 and 96 h after patch removal, and the fifth application was evaluated 96 and 120 h after patch removal. The tenth application was scored only once, immediately after patch removal. All 99 subjects reacted to at least one induction patch. There were 151 scores of a 1+

(1881 scores recorded) and four scores of 2+. Six subjects reacted with a 1+ score to the challenge patch, five immediately after patch removal and three 48 h later (two subjects' reactions had not cleared by the second reading). The three subjects who reacted 48 h after the first challenge patch were given a second challenge with 0.5% and 0.25% 48-h occlusive patches. They were also instructed to apply the product (0.5%) to their arm three times/day. All results were negative for the second challenge patches and the open patch. The product was an irritant but not a sensitizer.[123]

The sensitization of a bubble bath containing 6% Lauramide DEA was evaluated using 99 subjects. Occlusive induction patches containing 1.25% aqueous solution of shampoo were applied on Mondays, Wednesdays (48-h patches), and Fridays (72-h patches) for a total of 10 patches. Test sites were scored for reactions on a 0+–3+ scale at the time of patch removal. After a 14-day nontreatment period, a 48-h challenge patch was applied and scored immediately after patch removal and 48 h later. Patches were applied in a quadrant system. The first quadrant received applications one, four, seven, and ten, the second quadrant received applications two, five, and eight, and the third quadrant received applications three, six, and nine. The fourth quadrant received the challenge patch only. There were 43 1+ reactions to induction patches five through ten. Four subjects had 1+ reactions to the 0.5% aqueous shampoo challenge patch. These four subjects were rechallenged at a later date, and all scores were negative for open and closed patches. The bubble bath was not a significant irritant or sensitizer under these test conditions.[124]

Eighty-six subjects participated in an RIPT on a medicated liquid cleanser containing 5% Lauramide DEA. Approximately 0.1 ml of a 0.5% aqueous solution of the product was applied to each panelist's back under an occlusive patch for 24 h. Patches were applied Monday, Wednesday, and Friday for 3 consecutive weeks. Sites were scored on a 0–4 scale just before application of the next patch, usually 24 h after patch removal. A single 24-h challenge patch was applied to a previously unpatched site followng a 2 1/2-week nontreatment period. Challenge sites were scored for reactions 24 and 48 h after patch removal. Two subjects had barely perceptible reactions after the first induction patch, and another panelist had a mild reaction (score of 1) 24 h after challenge patch removal, which had become barely perceptible (score of ±) by 48 h. A subsequent rechallenge to the one reactor was negative. The product was not a sensitizer.[125]

Fifty-two subjects took part in a RIPT following the procedure described above.[125] A skin cleanser containing 4% Lauramide DEA was tested as a 0.25% aqueous solution. Thirteen barely perceptible reactions (scores of ±) were observed in nine panelists during the induction phase. Two panelists had barely perceptible reactions to the challenge patch. One of the two reactors was rechallenged with negative results. The diluted skin cleanser was not a sensitizer.[126]

Linoleamide DEA

Undiluted Linoleamide DEA was evaluated for sensitization using 102 individuals in an RIPT. Ten 48-h occlusive induction patches were followed, after a 2-week nontreatment period, by a single 48-h occlusive challenge patch. No reactions were observed to any induction or challenge patch. Linoleamide DEA was not an irritant or sensitizer.[127]

One hundred one panelists completed a repeated insult patch test of 10 products, including a dandruff shampoo containing 1.5% Linoleamide DEA. Nine 24-h occlusive patches containing 0.4 ml 1% aqueous shampoo solution were applied on the upper arm of each panelist on Monday, Wednesday, and Friday for 3 consecutive weeks. Sites were scored for erythema and edema (4 max for each) according to the Draize[58] procedure immediately before application of the next patch. Two weeks after the last induction patch, two challenge patches per panelist were applied and scored for reactions 48 and 96 h after application. One challenge patch contained the 1% aqueous shampoo solution, and the other patch contained 0.5% shampoo. Challenge patches were applied to adjacent, previously unpatched sites. The shampoo was a slight to moderate irritant during induction; 14 panelists had slight irritant reactions and 16 panelists had moderate reactions. Seven panelists had mild reactions (scores of 1) to the 1% solution at challenge, and one panelist reacted mildly to the 0.5% challenge patch. These reactions were considered to be irritant in nature. The dandruff shampoo was an irritant but not a sensitizer under these test conditions.[128]

Photosensitization

A liquid soap containing 10% Lauramide DEA was evaluated for phototoxicity using 25 subjects. The soap was diluted to 1% with water, then 2 μl was applied to two sites on the lower back of each subject. After drying, one site was covered and the other site was exposed to 1 MED (minimal erythemal dose) of UV light. Sites were scored for irritation immediately, covered with cotton patches, then scored again at 24 and 48 h. No irritation was observed immediately after irradiation. Mild erythema (+ score, 0–4+ scale) was observed at irradiated and nonirradiated sites 24 and 48 h after application and irradiation in all panelists. The product was not considered to be phototoxic.[129]

The photosensitivity of a liquid soap containing 10% Lauramide DEA was evaluated in 25 panelists. Two microliters of a 1% aqueous solution of the soap was applied to two sites on each subject's back and covered with patches. Twenty-four hours later, one treated site and an untreated site were irradiated with a Krohmeyer hot quartz spot lamp (discontinuous bands with peaks at 265, 303, 313, and 366 nm) for 30 seconds. This process was repeated five times during a 3-week induction period. Sites were scored for irritation immediately after irradiation and prior to the subsequent UV exposure. A challenge patch/irradiation was administered after a 10-day nontreatment period. Challenge patches were scored for reactions 24 and 48 h after irradiation. Nine panelists had mild erythema (+ score on 0–4+ scale) at one or more irradiated induction patch sites, and four panelists had mild erythema at irradiated sites 24 h after challenge. The product was not considered to be a photosensitizer.[129]

In-Use Studies

Cocamide DEA

One hundred four women participated in an in-use study to determine the safety and efficacy of a shampoo containing 2% Cocamide DEA. Each panelist was patch tested on the upper arm with 2% aqueous shampoo, 15 ppm (in

water) of the shampoo's preservative system, and 5% shampoo fragrance in mineral oil. The three occlusive patches were applied and scored for irritation 48 h later at the time of patch removal. The subjects were then instructed to shampoo daily with the test product for 87 days. Ten days after the final use of the shampoo, challenge patches were administered following the same procedure as the initial patches except the preservative concentration was increased to 50 ppm and an additional scoring for reactions was made 24 h after patch removal. No reactions were observed to the preservative or fragrance patches. Eleven subjects reacted to the 2% shampoo initial patch; eight had mild erythema (1+ scores on a 0–4 scale), one had intense erythema (2+), and two subjects had erythema and edema (3+). Twenty-four subjects had irritation scores of 1+ (18/24), 2+ (3/24), and 3+ (3/24) 48 h after challenge patch application of the shampoo. Thirty subjects had 1+ (25/30) or 2+ (5/30) irritation scores at the second challenge reading. All reactions were considered to be irritant in nature. The shampoo was an irritant but not a sensitizer.[130]

Lauramide DEA

A liquid soap containing 10% Lauramide DEA was evaluated for irritation in a 4-week study. One hundred fourteen female panelists were instructed to bathe as normal with the material for 4 weeks. Whole body clinical evaluations for irritation were made on Days 0, 14, and 28. There was minimal clinical and subjective irritation. The product did not cause unusual irritation with normal use.[131]

Six acne products, including a liquid cleanser containing 5% Lauramide DEA, were evaluated for efficacy. Groups of approximately 50 subjects used the products twice daily for 6 weeks. The Lauramide DEA-containing soap was a mild irritant, but in consideration of the acne products' mechanism of action, the product was considered safe for marketing.[132]

See Table 6 for tabulation of clinical studies.

SUMMARY

Cocamide DEA, Lauramide DEA, Linoleamide DEA, and Oleamide DEA, fatty acid diethanolamides, are viscous liquids or waxy solids that are insoluble but dispersible in water and soluble in organic solvents and may contain 4–33% diethanolamine. They are surfactants used primarily as emollients, thickeners, foam stabilizers, and dispersion aids in shampoos, hair dyes, and bath additives. These ingredients are used in approximately 1500 cosmetics in concentrations of <0.1–50%, with most products containing 1–25% diethanolamide. Fatty acid diethanolamides are also used in packing materials. Cocamide DEA and Lauramide DEA are inactive ingredients in prescription drugs.

Nitrosamine contamination of these ingredients is possible in one of two ways: either by preexisting contamination in the diethanolamine used to manufacture the diethanolamide or by nitrosamine formation via the presence of nitrosating agents in formulations containing a diethanolamide.

These four fatty acid alkanolamides were slightly toxic to nontoxic to rats in formulation and inert vehicles via acute oral administration. Lauramide DEA was the most toxic with an LD_{50} of 2.7 g/kg. Lauramide DEA was not a significant oral toxin in rats or dogs when administered orally in concentrations of up to 2% of

TABLE 6. Clinical Assessment of Safety

Ingredient	*Test type*[a]	*No. of subjects*	*Vehicle/product type*	*Ingredient concentration/ test solution concentration*	*Comments*	*Reference*
Cocamide DEA	In-use study	104	Shampoo	2% patched as 2% aqueous solution, used full strength for 87 days	Subjects were patched before and after normal use of product; 11 subjects reacted to initial patch, 30 subjects reacted to challenge patch; all irritant reactions; an irritant, not a sensitizer	130
Lauramide DEA	Primary irritation; single patch	19	Shampoo	8% tested as 1.25% aqueous solution	PII = 0.95 (max 4); mild skin irritant	112
	Primary irritation; single patch	18	Bubble bath	6% tested as 1.25% aqueous solution	PII = 0.95 (max 4); mild skin irritant	113
	Primary irritation; single patch	17	Unspecified product	5% tested as 1% aqueous solution	PII = 0.59 (max 4); minimal skin irritant	114
	Cumulative irritation; soap chamber test	12	Liquid soap	10% tested as 8% aqueous solution	PII = 0.58 (max 10); essentially nonirritating	115
	Cumulative irritation; soap chamber test	12	Liquid soap	10% tested as 8% aqueous solution	PII = 1.2 (max 10); mild skin irritant	116
	Cumulative irritation; soap chamber test	15	Liquid soap	10% tested as 8% aqueous solution	PII = 1.28 (max 10); mild skin irritant	117
	21-day cumulative irritation	7	Medicated liquid soap	5% tested as 25% solution	Group total irritation score was 226.5 (max 588); moderate skin irritant	119

RIPT	159	Liquid soap	10% tested as a 1% aqueous solution	20 subjects reacted to induction patches, 2 severely; 5 subjects had mild reactions to challenge patch; all reactions considered irritant; an irritant, not a sensitizer	121
RIPT	41	Liquid soap	10% tested as a 1% aqueous solution	13/41 mild irritant reactions during induction; 1/41 mild reaction to challenge; not a sensitizer	129
RIPT	99	Shampoo	8% tested as 1% and 0.5% aqueous solution	All subjects had at least one mild reaction during induction; 6 subjects reacted mildly at challenge; all reactions considered irritant; an irritant, not a sensitizer	123
RIPT	99	Bubble bath	6% induction–1.25% aqueous solution; challenge 0.5% aqueous solution	53 1+ (max 3) reactions to induction patches; 4 1+ reactions at challenge; no reactions when subjects were rechallenged; not a sensitizer	124
RIPT	86	Medicated liquid cleanser	5% tested as 0.5% aqueous solution	2 mild reactions during induction; 1 mild reaction at challenge; no reaction at rechallenge; not a sensitizer	125
RIPT	52	Skin cleanser	4% tested as 0.25% aqueous solution	13 barely perceptible reactions during induction; 2 barely perceptible reactions at challenge; reactions considered irritant; not a sensitizer	126
Phototoxicity	25	Liquid soap	10% tested as 10% aqueous soluton	No irritation immediately following irradiation; very slight irritation 24 and 48 h after irradiation; not a phototoxin	129
Photosensitivity	25	Liquid soap	10% tested as 1% aqueous solution	9 subjects had slight irritation during induction; 4 subjects reacted slightly at challenge; reactions considered irritant; not a photosensitizer	129

TABLE 6. (Continued)

Ingredient	*Test type*[a]	*No. of subjects*	*Vehicle/product type*	*Ingredient concentration/ test solution concentration*	*Comments*	*Reference*
Lauramide DEA	In-use study	114	Liquid soap	10%—normal use for 4 weeks	Minimal clinical or subjective irritation observed; minimal irritant under normal use conditions	131
	In-use study	~50	Acne liquid cleanser	5% twice daily for 6 weeks	Mild irritant	132
Linoleamide DEA	RIPT	102	None	100%	No reactions to induction or challenge patches; not an irritant or sensitizer	127
	Primary irritation; single patch[c]	20	Unspecified product	1.5% tested as 1.25% aqueous solution	PII = 1.15 (max 4); mild skin irritant	120
	RIPT	101	Dandruff shampoo	1.5% tested as 1% aqueous soluton	30 slight to moderate reactions during induction; 8 mild reactions at challenge; all reactions considered irritant; an irritant, not a sensitizer	128

[a]See text for more details.
[b]Not specified.
[c]Dotted line separates assays performed with pure ingredient (inert vehicle) from assays performed with the ingredient in formulation.

the diet in a subchronic study. Subchronic oral toxicity studies were not available for Cocamide DEA, Linoleamide DEA, and Oleamide DEA. Cocamide DEA, Lauramide DEA, and Linoleamide DEA were not dermal toxins in acute and subchronic animal studies. Oleamide DEA was not tested for dermal toxicity.

Cocamide DEA in propylene glycol was a minimal eye irritant and a moderate skin irritant in rabbits. Lauramide DEA and Linoleamide DEA in inert vehicles and formulations were mild to moderate eye irritants and mild to severe skin irritants; the skin irritancy was most pronounced in cumulative and closed patch tests. Undiluted Oleamide DEA was not an eye irritant and was a moderate skin irritant in single and cumulative applications.

Lauramide DEA did not demonstrate mutagenic activity in four separate Ames-type assays using *Salmonella typhimurium*, a DNA-damage assay using *Bacillus subtilis*, or two studies on in vitro transformation of hamster embryo cells. Slight mutagenic activity was reported for Lauramide DEA in a spot test. No data were available on the mutagenic or carcinogenic activity of Cocamide DEA, Linoleamide DEA, and Oleamide DEA. Cocamide DEA and Lauramide DEA are currently undergoing long-term carcinogenicity testing by NTP. (These data will be evaluated by the CIR Expert Panel when they become available.)

The clinical information on these ingredients was confined to Cocamide DEA, Lauramide DEA, and Linoleamide DEA, and all but one test were conducted with cosmetic soaps and shampoos containing the ingredient. Generally, these products were mild skin irritants but not sensitizers or photosensitizers. The one ingredient, Linoleamide DEA, tested full strength was not an irritant or sensitizer in a repeat insult patch test.

DISCUSSION

The Cosmetic Ingredient Review Expert Panel recognizes a lack of subchronic oral data on three ingredients in this group. However, the low animal subchronic oral toxicity demonstrated by Lauramide DEA and the low acute oral toxicity of the four ingredients indicate that Cocamide DEA, Linoleamide DEA, and Oleamide DEA probably are not significantly toxic after oral administration. Low toxicity is further supported by the chemical and structural similarities of the four ingredients evaluated in this report.

Nitrosamine contamination of diethanolamine and fatty acid diethanolamides and nitrosamine formation in formulations are potential problems in using these diethanolamides. The diethanolamides used in cosmetic products should be free of nitrosamines, and the finished product should not contain nitrosating agents as ingredients.

CONCLUSION

Based on the available information, the CIR Expert Panel concludes that Cocamide DEA, Lauramide DEA, Linoleamide DEA, and Oleamide DEA are safe as cosmetic ingredients at currently used concentrations. These chemicals should not be used as ingredients in cosmetic products containing nitrosating agents.

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