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Amended Final Report on the Safety Assessment of Cocamide DEA[1]

Abstract: Cocamide DEA is a mixture of ethanolamides of Coconut Acid that is used as a surfactant-foam booster and viscosity-increasing agent–aqueous in cosmetic products. Production formulation data submitted to the Food and Drug Administration in 1994 indicated that this ingredient was used in 745 products. The Cosmetic Ingredient Review (CIR) Expert Panel had previously evaluated the safety of Cocamide DEA, Lauramide DEA, Linoleamide DEA, and Oleamide DEA in cosmetics and concluded that they were safe as cosmetic ingredients at the concentrations that were currently being used (≤50%). CIR's decision to reevaluate the safety of Cocamide DEA in cosmetics is based on occupational studies indicating that this ingredient may have sensitization potential; however, the Expert Panel has determined that these studies are not relevant to cosmetic use. Furthermore, the Panel agreed that its original conclusion on Cocamide DEA should be clarified relative to use of this ingredient in rinse-off and leave-on products. Clarification of the original conclusion is based on the results of a skin irritation test in which 15 volunteers were tested with a surfactant solution containing 10% Cocamide DEA, the highest concentration tested in predictive patch tests. Additional comments that were made during the Panel's review of other data in the present report include that the severe ocular irritation reactions induced by a chemical (pH 9–10.5) containing >64% Cocamide DEA were likely a result of pH; that the renal effects noted in Fischer 344 rats in the National Toxicology Program (NTP) subchronic dermal toxicity study may be species-related and not test substance-related; and with reference to an ongoing NTP two-year chronic study that was initiated in 1993, that the results will be reviewed when the study is available. On the basis of the animal and clinical data presented in the present report, the Expert Panel concluded that Cocamide DEA is safe as used in rinse-off products and safe at concentrations ≤10% in leave-on cosmetic products. It was also concluded that Cocamide DEA should not be used as an ingredient in cosmetic products in which *N*-nitroso compounds are formed. **Key Words:** Cocamide DEA—Toxicity—Irritation—Sensitization—Mutagenicity—Cosmetic use—Carcinogenicity.

The Cosmetic Ingredient Review (CIR) Expert Panel had previously evaluated the safety of Cocamide DEA, Lauramide DEA, Linoleamide DEA, and Oleamide DEA in cosmetics and concluded that they were safe as cosmetic ingredients at the concentrations that were being used (≤50%) (Elder, 1986). The CIR's decision to reevaluate the safety of Cocamide DEA in cosmetics was based on occupa-

[1] Reviewed by the Cosmetic Ingredient Review Expert Panel.

Address correspondence and reprint requests to Dr. F. A. Andersen at Cosmetic Ingredient Review, 1101 17th Street NW, Suite 310, Washington, D.C. 20036, U.S.A.

tional studies indicating that this ingredient may have sensitization potential. This amendment covers only Cocamide DEA and updates the limited sensitization data on this ingredient that are included in the original report. Other current studies on the toxicity of Cocamide DEA have been incorporated as well. The CIR is also in the process of evaluating the safety (separate review) of Stearamide MEA, Stearamide DEA, Isostearamide MEA, Isostearamide DEA, Myristamide MEA, and Myristamide DEA in cosmetics and has previously evaluated the safety of triethanolamines, as well as other monoethanolamines and diethanolamines.

CHEMISTRY

Chemical and Physical Properties

Cocamide DEA (CAS Nos. 61791-31-9 and 68603-42-9) is a mixture of ethanolamides of Coconut Acid that conforms generally to the formula shown in Fig. 1, where RCO represents the fatty acids derived from coconut oil (Wenninger and McEwen, 1993). Other names for this chemical include amides, coco, *N,N*-bis(2-hydroxyethyl)-; *N,N*-bis(2-hydroxy-ethyl)coco amides; *N,N*-bis(2-hydroxyethyl)coco fatty acid amide; coco amides, *N,N*-bis(2-hydroxyethyl)-; coconut diethanolamide; coconut fatty acid diethanol-amide; cocoyl diethanolamide; and diethanolamide coconut fatty acid condensate (Wenninger and McEwen, 1993). Various grades (2:1, 1:1, and modified) of Cocamide DEA are commercially available. The 1:1 grade is defined as a 1:1 molar reaction product of diethanolamine and methyl cocoate, coconut oil, whole coconut fatty acids, or stripped coconut fatty acids, yielding the high purity amide. The 2:1 grade results from the use of 2 mol of diethanolamide, yielding the amide and ethylene glycol. In modified grades, other ingredients, such as soaps or detergents, have been added to alter the properties of the product in some applications (Cosmetic, Toiletry, and Fragrance Association [CTFA], 1983). Properties of Cocamide DEA are listed in Table 1.

Methods of Manufacture

Cocamide DEA is produced by the condensation of diethanolamine with coconut fatty acids or their esters (Nikitakis and McEwen, 1990). It has also been produced by the reaction of refined coconut oil with diethanolamide in the presence of sodium methoxide (catalyst), yielding Cocamide DEA, 10% glycerine, and 5% coconut fatty acid ester amide (Nurse, 1980).

Impurities

Alkanolamines manufactured by base-catalyzed condensation of diethanolamine and the methyl ester of long chain fatty acids are susceptible to nitrosamine

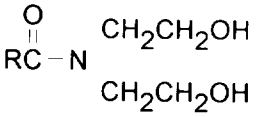

FIG. 1. Chemical formula for Cocamide DEA (Wenninger and McEwen, 1993). RCO represents the fatty acids derived from coconut oil.

TABLE 1. *Properties of Cocamide DEA*[a]

Form	Liquid
Color	Amber
Odor	Faint
pH (10% aqueous solution)	9.5–10.5
Solubility	Soluble in water
Acid value	3.0 maximum
Free diethanolamine	4.0–8.5%

[a] From Nikitakis and McEwen (1990).

formation. Consequently, methods for the analysis of nitrosamines in alkanolamides, including Cocamide DEA, have been developed (Rosenberg et al., 1979; 1980*a*; 1980*b*; Elder, 1983; 1984; European Chemical Industry Ecology and Toxicology Centre [ECETOC], 1991). *N*-nitrosodiethanolamine (<1 ng/g [ppb]–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 (Lijinsky et al., 1972; Fan et al., 1977; Schmeltz and Wenger, 1979). *N*-nitrosodiethanolamine is rapidly absorbed across human trunk skin in vitro (Franz et al., 1993). More recent data indicate that when leave-on products, such as deodorants, skin lotions, and sunscreens, were analyzed, *N*-nitrosodiethanolamine was detected in three of 62 samples (maximum concentration = 53 μg/kg). In the same survey, the maximum concentration in shampoos was 41 μg/kg (ECETOC, 1990). The results of surveys conducted by the Food and Drug Administration (FDA) are summarized in Table 2 (Havery and Chou, 1994).

The results of a risk assessment of *N*-nitrosodiethanolamine indicated that the liver tumor risk from exposure to 0.0002 μg/kg/day of this chemical from personal care products would be 0.16×10^{-7}–0.16×10^{-8} (ECETOC, 1990). Additionally,

TABLE 2. *N-nitrosodiethanolamine (NDELA) in personal care products analyzed by the FDA*[a]

Year purchased	No. of samples	% Positive samples	NDELA range (ppb)
1977	32	31	35–130,000
1978	174	33	20–42,000
1979	87	32	40–25,000
1980	53	57	30–4,910
1981	47	30	110–23,000
1982	18	0	—[b]
1983	22	23	350–4,800
1984	12	17	140–1,800
1985	2	—[c]	0–700
1986	2	—[c]	—[b]
1987	6	0	—[b]
1989	2	—[c]	—[b]
1991	8	63	120–1,080
1992	12	67	210–2,960

[a] From Havery and Chou (1994).
[b] None detected.
[c] Less than three samples.

using drinking water carcinogenicity studies of rats, the Environmental Protection Agency (EPA) determined that the excess cancer risk to humans following daily exposure to 1 μg/kg for a lifetime would be 1×10^{-4} (EPA, 1988). Therefore, if one assumes a straight-line relationship at very low doses, the risk from exposure to 0.0002 μg/kg/day would be on the order of 0.2×10^{-7} (ECETOC, 1990).

Reactivity

Cocamide DEA is very stable in neutral, moderately alkaline, or acid systems, but it is subject to hydrolysis at high concentrations of mineral acids and alkali (CTFA, 1983).

Analytical Methods

Cocamide DEA has been identified by infrared spectroscopy (Nikitakis and McEwen, 1990). Methods for the normal and reverse-phase high-pressure liquid-chromatography analyses of Cocamide DEA have been published (Nakae and Kunihiro, 1978; Nakamura et al., 1980.

USE

Purpose in Cosmetics

Cocamide DEA functions as a surfactant-foam booster and viscosity-increasing agent–aqueous in cosmetic products (Wenninger and McEwen, 1992).

Scope and Extent of Use in Cosmetics

Concentration of use values are no longer reported to the FDA by the cosmetics industry (Federal Register, 1992). However, 1984 product formulation data submitted to the FDA stated that Cocamide DEA was used at concentrations ≤50% (FDA, 1984). The product formulation data submitted to the FDA in 1994 indicate that Cocamide DEA is used in 745 cosmetic product formulations, as shown in Table 3 (FDA, 1994).

International Use

Cocamide DEA is included in the CTFA *List of Japanese Cosmetic Ingredients* that are known to be approved for cosmetic use in Japan. The inclusion of any ingredient in the CTFA list guarantees neither that the ingredient is safe for use as a cosmetic ingredient nor that the use of the substance as a cosmetic ingredient complies with the laws and regulations governing such use in Japan (Rempe and Santucci, 1992). Cocamide DEA is not included among the ingredients listed as prohibited from use in cosmetic products marketed in the European Economic Community (EEC, 1993).

TABLE 3. *Product formulation data on Cocamide DEA*[a]

Product category	Total no. of formulations in category	Total no. of formulations containing ingredient
Other baby products	23	1
Bath oils, tablets, and salts	149	14
Bubble baths	214	47
Bath capsules	4	2
Other bath preparations	132	13
Other fragrance preparations	136	1
Hair conditioners	614	3
Rinses (noncoloring)	58	1
Shampoos (noncoloring)	852	256
Tonics, dressings, and other hair grooming aids	563	8
Other hair preparations	376	9
Hair dyes and colors (all types requiring caution statement and patch test)	1,458	229
Hair shampoo (coloring)	15	2
Hair bleaches	115	3
Other hair coloring preparations	73	2
Other makeup preparations	146	1
Basecoats and undercoats	48	1
Nail creams and lotions	21	1
Bath soaps and detergents	343	46
Deodorants (underarm)	273	4
Douches	16	5
Other personal cleanliness products	321	26
Shaving cream	147	4
Other shaving preparation products	54	1
Cleansing	746	25
Body and hand preparations (excluding shaving)	984	2
Paste masks (mud packs)	282	1
Other skin care preparations	790	5
Suntan gels, creams, and liquids	218	1
No. of uses listed under trade name		29
1994 Totals		745

[a] From the FDA (1994).

Surfaces to Which Applied

Cosmetic products containing Cocamide DEA are applied to most parts of the body and may come in contact with the ocular and nasal mucosae.

Frequency and Duration of Application

Product formulations containing Cocamide DEA may be used on a daily basis and are expected to remain in contact with the skin for extended periods of time. Each product has the potential for being applied many times over a period of several years.

Noncosmetic Use

Cocamide DEA, a fatty acid diethanolamide, is used as a corrosion inhibitor in metalworking fluids (De Boer et al., 1989) and in polishing agents (Flyvholm,

1991). Additionally, fatty acid diethanolamides are widely used in light-duty and dishwashing detergent formulations (Swern, 1979). Fatty acid diethanolamides are regulated by the FDA as food additives permitted for direct addition to food for human consumption and as indirect food additives. Indirect food additive uses cited in the Code of Federal Regulations (CFR) include use in adhesive coatings and components (21 CFR 175.105), paper and paperboard components (21 CFR 176.180 and 176.210), polymers (21 CFR 177.1200 and 177.2800) and adjuvants (21 CFR 178.3130). Cocamide DEA is also regulated by the FDA as a "secondary direct food additive" to be used as a delinting agent for cottonseed (Federal Register, 1982).

TOXICOLOGY

Subchronic Dermal Toxicity

The subchronic dermal toxicity of Cocamide DEA was evaluated using five groups of 10 male and 10 female Fischer 344 rats. Initial body weights were not stated; however, body weight gain was reported for experimental and control groups. In the five experimental groups, Cocamide DEA was applied to the skin for ≤13 consecutive weeks at doses of 25, 50, 100, 200, and 400 mg/kg using dosing solutions (95% ethanol vehicle) at concentrations of 30, 61, 121, 243, and 485 mg/ml, respectively. For clinical pathology evaluations, blood samples were obtained from an additional group of rats (10 males, 10 females) on days 4 and 24; the rats were killed on day 24. Blood samples were also obtained from rats in the control and five dose groups at the end of the study, after which the rats were necropsied and tissues processed for histopathological examination. There were no deaths in experimental or control groups at any time during the study. Group mean body weight depressions of ≥10% were noted in male rats from the 200 mg/kg dose group and male and female rats from the 400 mg/kg dose group. Skin irritation at the application site was observed in eight females and 10 males from the 200 mg/kg dose group and all rats from the 400 mg/kg dose group. In the 100 mg/kg dose group, skin irritation was observed in one female and two male rats. The principal microscopic skin changes were epidermal hyperplasia (≥25 mg/kg, both sexes), chronic-active inflammation (≥100 mg/kg, both sexes), parakeratosis and ulceration (≥200 mg/kg, both sexes; 100 mg/kg, males), and sebaceous gland hyperplasia (≥100 mg/kg, both sexes; 50 mg/kg, males). Parakeratosis was primarily responsible for the gross changes that were described as "skin crusts" (National Toxicology Program [NTP], 1993*a*).

The results of hematological evaluations in the preceding study indicated a reduction in hemoglobin concentration in females from the 200 and 400 mg/kg dose groups and in males dosed with 400 mg/kg. A reduction in the hematocrit was noted in females of the three highest dose groups and in males of the 400 mg/kg dose group. Additionally, the red blood cell count was depressed in females of the 200 and 400 mg/kg dose groups. Perturbations in clinical chemistry values for serum albumin, cholesterol, and triglycerides were also observed in some of the dose groups, suggesting that Cocamide DEA may have an effect on the biochemical/metabolic functions of the liver. Renal tubule regeneration and renal mineralization were noted in all female dose groups. The severity of renal tubule re-

generation was greater in rats of the two highest dose groups (200 and 400 mg/kg), and the severity of renal mineralization was greater in rats of the three highest dose groups (100, 200, and 400 mg/kg). There seemed to be a correlation between dose-related increases (≥50 mg/kg) in absolute and relative kidney weights in females and Cocamide DEA–induced changes in the renal tubule (NTP, 1993*a*).

In a second study, the subchronic dermal toxicity of Cocamide DEA was evaluated using five groups of 10 male and 10 female B6C3F$_1$ mice. The untreated control group also consisted of 10 male and 10 female mice. Initial body weights were not stated; however, body weight gain was reported for experimental and control groups. Group mean body weights were said to have been similar to controls throughout the study. In the five experimental groups, Cocamide DEA was applied to the skin for ≤13 consecutive weeks at doses of 50, 100, 200, 400, and 800 mg/kg using dosing solutions (95% ethanol vehicle) at concentrations of 20, 40, 80, 160, or 320 mg/ml, respectively. At the end of the study, the animals were necropsied and tissues processed for histopathological evaluation. There were no deaths in experimental or control groups at any time during the study. Skin irritation at the application site was observed in all males and females of the 800 mg/kg dose group; gross skin lesions were noted in six of 10 males and five of 10 females. The principal microscopic changes in skin were epidermal and sebaceous gland hyperplasia (≥50 mg/kg, both sexes), chronic-active inflammation (≥200 mg/kg, males; ≥100 mg/kg, females), parakeratosis (≥200 mg/kg, males; ≥400 mg/kg, females), and ulceration (800 mg/kg, both sexes). Parakeratosis was primarily responsible for the gross changes that were described as "skin crusts" in males and females of the 800 mg/kg dose group. Weight increases in the liver, kidney, and lungs that were seen in experimental groups were considered treatment-related, but they occurred in the absence of pathological changes. Organ weight changes were present in ≥400 mg/kg dose groups (males) and in ≥200 mg/kg dose groups (females) (NTP, 1993*b*).

The following conclusions for the two preceding subchronic dermal toxicity studies of Cocamide DEA were made by the National Toxicology Program Working Group for Cocamide DEA (NTP, 1993*c*). The dermal application of Cocamide DEA was associated with microscopic lesions in the skin of male and female F344 rats and in the kidneys of female rats. Treatment-related microscopic lesions were observed in the skin of B6C3F$_1$ mice. In rats and mice, the skin lesions tended to have a dose response with regard to the incidence and severity of the changes. Renal tubule regeneration was particularly increased in female rats of the 200 and 400 mg/kg dose groups. Both studies were conducted under the direction and support of the NTP. The contents and conclusions have not been reviewed by the NTP staff, and therefore do not necessarily represent the position of the NTP.

Ocular Irritation

The ocular irritation potential of a chemical substance (pH 9–10.5) composed of Cocamide DEA (>64%) and diethanolamine (<29%) was evaluated using three New Zealand white rabbits. The chemical was tested at a concentration of 1% according to a modified Draize eye irritation test procedure. Thus, the effective

test concentrations of Cocamide DEA and diethanolamine were >0.6% and >0.3%, respectively. The test substance (0.1 ml) was instilled into the right conjunctival sac of each rabbit; untreated eyes served as controls. Ocular irritation reactions were scored at 1 h and 1, 2, 3, 4, and 7 days postinstillation according to the Draize scale: 0–110. The highest mean Draize score (57.67) was reported on day 3. On day 7, a mean Draize score of 37 was reported. It was concluded that the test material was a severe ocular irritant, owing to continued corneal damage in a significant number of rabbits (three of three) through day 7 (Pharmichem Testing Services, Inc., 1981).

Cytotoxicity

The in vitro cytotoxicity of Cocamide DEA was evaluated using Chinese hamster fibroblasts (V79 cells) obtained from the Japanese Cancer Research Resources Bank, rabbit corneal cells (RC cells) from the Japanese white rabbit, and normal human epidermal keratinocytes (NHEK). Cocamide DEA was dissolved in a solution of 50% ethanol in phosphate-buffered saline at a concentration of 100 mg/ml and diluted with medium immediately before testing. The concentration of ethanol in the exposure medium did not exceed 0.5%. Cell cultures were incubated with the test substance for 24 h, after which the medium was removed and replaced with medium containing neutral red (50 μg/ml). The cells were then incubated for an additional 3 h. The absorbance of the extracted dye was measured using a microplate reader equipped with a 540-nm filter. The relative toxicity of Cocamide DEA was established by determining the concentration that induced a 50% reduction in neutral red uptake compared with that observed in the control culture (IC_{50}). The IC_{50} values for the three cell types were 27 μg/ml (V79 cells), 39.8 μg/ml (RC cells), and 7.8 μg/ml (NHEK cells). In order to compare the in vitro results with in vivo (Draize ocular irritation test) data, the DS_{20} value was determined. In vivo Draize ocular irritation test data were taken from the publication by Watanabe et al. (1989). The DS_{20} is defined as a prediction of the chemical concentration that would result in a Draize test score of 20; specifically, the DS_{20} is extrapolated from the dose-response curve giving a Draize test score of 20. The DS_{20} for Cocamide DEA was 11% (w/w) (Ikarashi et al., 1993).

Mutagenicity

The mutagenicity of Cocamide DEA in dimethyl sulfoxide [DMSO] was evaluated according to a modification of the Ames test procedure (Haworth et al., 1983) using strains TA100 and TA1535 of *Salmonella typhimurium*. Assays were conducted with and without metabolic activation at doses ≤10,000 μg/plate. Cocamide DEA was not mutagenic in the presence or absence of metabolic activation (NTP, 1994*c*). Cocamide DEA also was not mutagenic in strains TA97, TA98, TA100, and TA1535 of *Salmonella typhimurium* when tested, with and without metabolic activation, according to a modification of the same test procedure. Cocamide DEA was tested at doses ≤200 μg/plate (Zeiger et al., 1988).

In one set of assays, Cocamide DEA in DMSO induced sister chromatid exchanges in Chinese hamster ovary cells with metabolic activation but did not

induce chromosomal aberrations with or without metabolic activation (NTP, 1985). More recent results indicate that Cocamide DEA did not induce chromosomal aberrations or sister chromatid exchanges with or without metabolic activation (NTP, 1994*a*). When Cocamide DEA (in ethanol) was tested in L5178Y mouse lymphoma forward mutation assays, both negative and inconclusive results were noted with and without metabolic activation (NTP, 1994*d*).

Carcinogenicity

An NTP 2-year chronic study on Cocamide DEA, initiated in 1993, is in progress (NTP, 1994*b*). Based on the results of subchronic dermal toxicity studies (included in this report), the National Toxicology Program Pathology Working Group for Cocamide DEA suggested that this ingredient be tested at doses ≤100 mg/kg (rats) and 400 mg/kg (mice) in the 2-year chronic study (NTP, 1993*c*).

CLINICAL ASSESSMENT OF SAFETY

Skin Irritation

The skin irritation potential of six cosmetic-grade surfactant solutions was evaluated using 15 volunteers. One of the solutions consisted of 20% sodium lauryl sulfate and 10% Cocamide DEA and another consisted of 20% sodium lauryl sulfate. Two of the remaining solutions also contained 20% sodium lauryl sulfate and another surfactant. In a pilot study, three of the subjects were each patch-tested with the six solutions (six semiocclusive patches/subject). Each solution (200 μl) was applied to the external upper arm for 4 h; sites were rinsed with water after patch removal. Insufficient skin irritation was observed in the pilot study. In the main study, the remaining 12 subjects were patch-tested (occlusive patches) with the six surfactant solutions according to the same procedure. Reactions were scored 1 h, 24 h, 48 h, and 72 h after patch removal according to the following scale: 0 (no erythema) to 4 (severe erythema). In order to protect against hyperreactivity, a seventh occlusive patch containing 20% sodium lauryl sulfate was applied and removed after 1 h. According to the investigators, all patches would have been removed if a score >1 was reported; however, none of the subjects reacted adversely. Sodium lauryl sulfate (20% solution) induced erythema in eight subjects. Decreased erythema was noted 1 h after application of the solution containing 20% sodium lauryl sulfate and 10% Cocamide DEA, and complete skin recovery was observed at 48 h. The remaining four subjects were insensitive to treatment with the surfactants. Based upon the results for the sodium lauryl sulfate/Cocamide DEA solution and other surfactant solutions, it was concluded that skin irritation was not related simply to the total concentration of surfactants in contact with the skin, but rather to the combination of surfactants that was present (Dillarstone and Paye, 1993).

Skin Sensitization

Skin sensitization findings are summarized in Table 4. Six allergic contact dermatitis patients, three of whom were atopic, were patch-tested with Cocamide

TABLE 4. *Skin sensitization potential of Cocamide DEA in humans*

Number of patients	Test procedure	Concentration tested	Results	References
Six allergic contact (hand/forearm) dermatitis patients with positive patch test reactions to products containing 5–100% Cocamide DEA that had been used regularly at work	24- to 48-h patch test (Finn chambers)	0.1–10% in petrolatum	0.1% (2/2 subjects: +); 0.2% (1/1 subject: + +); 0.3% (4/4 subjects: + to + +); 0.5% (3/3 subjects: + + to + + +); 1% (4/4 subjects: + to + +); 3% (2/2 subjects: + + to + + +); 10% (2/2 subjects: + + to + + +); The 2 patients who used hand protecting foams (100% Cocamide DEA) had + + reactions to this product; conclusion: Cocamide DEA-induced occupational allergic contact dermatitis	Pinola et al., 1993
20 patients (controls for preceding study)	24- to 48-h patch test (Finn chambers)	3% and 10% in petrolatum	3% (negative); 10% (10/20 subjects: slight irritant reactions)	Pinola et al., 1993
40 employees (metalworking factory) with hand/forearm dermatitis	48-h patch test (Finn chambers)	0.5% in petrolatum	One subject with contact sensitization	DeBoer et al., 1989
954 patients (670 men, 284 women) with occupational skin disease; contact dermatitis was most prevalent	Patch test	Not stated	Cocamide DEA responsible for 11.5% of females and 2.3% of males with occupational allergic contact dermatitis; conclusion: Cocamide DEA classified as a definitive occupational allergen	Wall and Gebauer, 1991
One patient (employed by printing company) with hand dermatitis induced by hand gel containing Cocamide DEA	Patch test	0.5% in petrolatum	+ + reaction	Nurse, 1980
One patient (dentist) with hand dermatitis induced by hand-washing liquids containing Cocamide DEA	Patch test (Finn chambers)	0.01–1%	Results with Cocamide DEA from 2 different products: 0.01% (negative); 0.032% (1+ and negative); 0.1% (2+ and 1+) 0.32% (2+ and 2+); 1% (3+ and 2+); conclusion: allergic patch test reactions to Cocamide DEA	Kanerva et al., 1993
One coal miner with hand/forearm dermatitis after exposure to hydraulic mining oil containing Cocamide DEA	Patch test	0.5% in petrolatum	+ reaction	Hindson and Lawlor, 1983
One patient with dermatitis (scalp) induced by shampoo	Patch test	0.5% in petrolatum	Positive results	deGroot et al., 1987

DEA from 1985 to 1992 using Finn chambers. The patients had been exposed to Cocamide DEA during the use of liquid or foam products for handwashing/hand protection while at work. In addition to exposure from these products, one of the patients was exposed to a metalworking fluid containing Cocamide DEA. All of the patients had hand dermatitis, and two of the six also had dermatitis on the forearm. The average age of the patients at the onset of dermatitis was 32 years, and the mean duration of dermatitis before diagnosis was 21 months. Before 1989, the patients were tested with Cocamide DEA at concentrations ranging from 0.01 to 10%. However, in April of 1989 a commercial test preparation (0.5% Cocamide DEA in petrolatum) was used. The patch-test procedure (Estlander, 1990) involved the application of a Finn chamber to the back of each patient for an occlusion time of 24–48 h. Each chamber was secured with porous nonocclusive colorless tape. Reactions were scored at the time of patch removal and at 24 h and 48–120 h postremoval according to International Contact Dermatitis Research Group (ICDRG) recommendations: ?+ (doubtful reaction), + (weak, nonvesicular reaction), + + (strong edematous or vesicular reaction), and + + + [extreme reaction (Wilkinson et al., 1970)]. At least three of the readings were performed by a dermatologist, and reactions of + + or greater were considered positive. The six patients were also tested with 1% aqueous cocamidopropyl betaine, another coconut oil–derived product. Allergic patch-test reactions were confirmed using a dilution series. Twenty control patients were tested with a dilution series of Cocamide DEA, and one patient was tested with a dilution series of diethanolamine. One patient was also prick-tested, using a disposable needle, with 0.5% aqueous Cocamide DEA on the volar aspect of the forearm. Reactions (wheal and flare) were recorded after 15–20 min (Pinola et al., 1993).

The results of product patch tests (six patients) from the preceding experiment were as follows: + + reactions were observed in the two patients who used hand-protecting foam (100% Cocamide DEA), in the patient who used liquid soap (10% Cocamide DEA), and in the remaining three patients who used handwashing liquid (10% Cocamide DEA). Two of the remaining three also used handwashing liquids with different concentrations of Cocamide DEA; one of the two patients had + and + + reactions to 3% and 20% Cocamide DEA products, respectively, and the other had a + + reaction to the 5% Cocamide DEA product. The patient who used liquid soap was also patch-tested with metalworking fluid containing Cocamide DEA, and the results were: 1% Cocamide DEA, no reaction, 3% Cocamide DEA, + reaction, and 10% Cocamide DEA + + reaction. Patients patch-tested with Cocamide DEA concentrations ranging from 0.1% to 10% in petrolatum had the following reactions: 0.1% Cocamide DEA, + in two of two subjects; 0.2%, + + in one of one subject; 0.3%, + to + + + in four of four subjects; 0.5%, + + to + + + in three of three subjects; 1%, + to + + in four of four subjects; 3%, + + to + + + in two of two subjects; and 10%, + + to + + + in two of two subjects. All six patients had negative patch-test reactions to 1% aqueous cocamidopropyl betaine. Two of the six also had a negative prick-test reaction to 0.5% aqueous Cocamide DEA and a negative patch-test reaction to diethanolamine (0.0001–1%) in petrolatum, respectively. In the group of 20 control patients, there were no reactions to 3% Cocamide DEA in petrolatum, and 10

patients had slight irritant reactions to 10% Cocamide DEA in petrolatum. It was concluded that Cocamide DEA induced occupational allergic contact dermatitis in the six patients who were evaluated (Pinola et al., 1993).

An epidemiological study was conducted using 284 employees of metalworking factories in the Netherlands. The workers were exposed to metalworking fluids while at work. Dermatitis of the hands and/or forearms was observed in 40 of the 284 workers. The 40 workers were patch-tested with a series of common components of metalworking fluids and preservatives to which the workers had been exposed. Cocamide DEA was patch-tested at a concentration of 0.5% in petrolatum. The test substance was applied to the upper back of each subject via a chamber that was secured with tape. The patches were removed at 48 h and scored at 72 h according to the ICDRG recommendations. The patch-test and scoring procedures were the same for other metalworking fluid components and preservatives that were tested. Contact sensitization was observed in eight of the 40 patients; four patients were allergic to biocides and/or corrosion inhibitors. Only one patient had a contact sensitization reaction to 0.5% Cocamide DEA in petrolatum. Some of the other substances that induced contact sensitization included formaldehyde, nickel sulfate, and balsam of Peru (DeBoer et al., 1989).

From 1980 to 1987, 2,449 cases in Australia were referred for assessment of possible occupational skin disease and/or skin allergy (patch) testing. Dermatologists were the major source of referral. Definite occupational skin disease was diagnosed in 993 of the 2,449 cases; 439 cases were atopic. The overall duration of occupational skin disease, before initial diagnosis, varied from a few weeks to many years. Contact dermatitis was the most prevalent occupational skin disease diagnosed; however, 14.6% of the cases were diagnosed as noneczematous occupational skin disease. An attempt was made in 1988 to contact, interview, and reexamine all of the 993 documented occupational skin disease patients. Of the 993 subjects, 954 (670 men, 284 women) were patch-tested; the remainder were either deceased or could not be located. Positive patch tests were expressed as a percentage of the total number of subjects with allergic occupational contact dermatitis. Cocamide DEA was classified as a definitive occupational allergen; the ingredient patch-test concentration was not stated. More specifically, it was classified as an occupational allergen in the hairdressing, medical, fitter, food-handling, printing, and cleaning groups. Cocamide DEA was responsible for occupational allergic contact dermatitis in 11.5% of the women and 2.3% of the men. In female subjects, nickel was responsible for the highest percentage (25%) of positive patch tests. Chromate was responsible for the highest percentage (37%) of positive patch tests in male subjects (Wall and Gebauer, 1991).

Case Reports

Case reports are summarized in Table 4. Positive patch-test reactions to hand-washing liquids (diluted to 10%) containing Cocamide DEA (Nurse, 1980; Kanerva et al., 1993) and to 0.5% Cocamide DEA (Nurse, 1980; Hindson and

Lawlor, 1983; deGroot et al., 1987) have been reported in case studies on dermatitis patients. The patients were exposed to Cocamide DEA either in an occupational setting (product use or accidental exposure to fluids) or during product use at home.

SUMMARY

Cocamide DEA (CAS Nos. 61791-31-9 and 68603-42-9) is a mixture of ethanolamides of coconut acid that is produced by the condensation of diethanolamine with coconut fatty acids or their esters. It functions as a surfactant-foam booster and viscosity-increasing agent in cosmetic products. Product formulation data submitted to the Food and Drug Administration in 1994 indicated that Cocamide DEA was used in 745 cosmetic product formulations. In subchronic dermal toxicity studies conducted by the NTP, Cocamide DEA was tested at doses ≤400 mg/kg in F344 rats and ≤800 mg/kg in B6C3F$_1$ mice. It was concluded that the dermal application of Cocamide DEA was associated with microscopic lesions in the skin of B6C3F$_1$ mice and F344 rats (both sexes) and in the kidneys of female F344 rats. A mixture (pH 9–10.5) diluted to 0.6% Cocamide DEA was severely irritating to the eyes of New Zealand White rabbits.

Cocamide DEA was not mutagenic with or without metabolic activation in strains TA97, TA98, TA100, and TA1535 of *Salmonella typhimurium*. Both positive and negative results were reported for Cocamide DEA in sister chromatid exchange assays (with metabolic activation) involving Chinese hamster ovary cells. Cocamide DEA did not induce chromosomal aberrations in Chinese hamster ovary cells. In L5178Y mouse lymphoma forward mutation assays, both negative and inconclusive results were noted with and without metabolic activation. An NTP 2-year chronic study on Cocamide DEA, initiated in 1993, is ongoing. Adverse reactions were not observed in a skin irritation test in which 15 volunteers were patch-tested with a solution containing 10% Cocamide DEA. However, regarding the sensitization potential of Cocamide DEA, a number of studies in the published literature indicate that this ingredient induces occupational allergic contact dermatitis.

DISCUSSION

The CIR Expert Panel had previously evaluated the safety of Cocamide DEA, Lauramide DEA, Linoleamide DEA, and Oleamide DEA in cosmetics and concluded that these ingredients were safe as cosmetic ingredients at the concentrations that were being used (≤50%). The Panel has also reviewed current occupational sensitization data on Cocamide DEA but does not consider these data relevant to cosmetic use. However, the Panel's original conclusion on Cocamide DEA has been clarified relative to use of this ingredient in rinse-off and leave-on cosmetic products. Clarification of the original conclusion is based on the results of a skin irritation test in which 15 volunteers were tested with a surfactant solution containing 10% Cocamide DEA, the highest concentration tested in predictive patch tests. Additional comments that were made during the Panel's review of other data included in this report are that the severe ocular irritation

reactions induced by a chemical (pH 9–10.5) containing >64% Cocamide DEA were likely a result of pH; that the renal effects noted in Fischer 344 rats in the NTP subchronic dermal toxicity study may be species-related and not test substance–related; and, with reference to an ongoing NTP 2-year chronic study on Cocamide DEA initiated in 1993, that the results will be reviewed when the study is available. Based on the data now available, the Expert Panel believes that there is a need to recognize that while occupational exposure to Cocamide DEA can result in sensitization, cosmetic use does not present the same concern.

CONCLUSION

On the basis of the animal and clinical data included in this report, the Expert Panel concludes that Cocamide DEA is safe as used in rinse-off products and safe at concentrations ≤10% in leave-on cosmetic products. Cocamide DEA should not be used as an ingredient in cosmetic products in which *N*-nitroso compounds are formed.

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