Tentative Amended Safety Assessment

DEA Amides as Used in Cosmetics

July 8, 2011

All interested persons are provided 60 days from the above date to comment on this Tentative Safety Assessment and to identify additional published data that should be included or provide unpublished data which can be made public and included. Information may be submitted without identifying the source or the trade name of the cosmetic product containing the ingredient. All unpublished data submitted to CIR will be discussed in open meetings, will be available at the CIR office for review by any interested party and may be cited in a peer-reviewed scientific journal. Please submit data, comments, or requests to the CIR Director, Dr. F. Alan Andersen.

The 2011 Cosmetic Ingredient Review Expert Panel members are: Chairman, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D; James G. Marks, Jr., M.D., Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is F. Alan Andersen, Ph.D. This report was prepared by Monice M. Fiume, Senior Scientific Analyst/Writer, and Bart Heldreth, Chemist, CIR.

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ABSTRACT

The CIR Expert Panel re-reviewed the safety of cocamide DEA, and also assessed the safety of 32 DEA amides as used in cosmetics. Cocamide DEA is reported to function in cosmetics as a surfactant-foam booster or a viscosity increasing agent; most of the amides included in the re-review have these same functions, although a few may function differently. The Panel reviewed available animal and clinical data, as well as information from previous CIR reports; while these ingredients are not salts and do not readily dissociate in water, amidases present in human skin could potentially convert these amides to DEA and the corresponding fatty acids. The Panel concluded that the DEA amides named in this safety assessment are safe as used when formulated to be non-irritating. These ingredients should not be used in cosmetic products in which N-nitroso compounds are formed.

INTRODUCTION

The safety of cocamide DEA as used in cosmetics was last assessed in 1996. 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, and that cocamide DEA should not be used as an ingredient in cosmetic products in which *N*-nitroso compounds are formed.[1] (Cocamide DEA was originally reviewed in 1986. At that time, the Panel concluded that cocamide DEA was safe as used in cosmetic formulations, and that it should not be used as an ingredient in cosmetic products containing nitrosating agents).[2]

The Panel has determined that the following 32 DEA amides are closely related to Cocamide DEA and that the available safety data may be extended to support the safety of their use in cosmetics:

Almondamide DEA
Apricotamide DEA
Avocadamide DEA
Babassuamide DEA
Behenamide DEA
Capramide DEA
Cornamide DEA
Cornamide/Cocamide DEA
Hydrogenated Tallowamide DEA
Isostearamide DEA*
Lanolinamide DEA
Lauramide DEA*
Lauramide/Myristamide DEA
Lecithinamide DEA
Linoleamide DEA*
Minkamide DEA
Myristamide DEA*
Oleamide DEA
Olivamide DEA*
Palm Kernelamide DEA
Palmamide DEA
Palmitamide DEA
Ricebranamide DEA
Ricinoleamide DEA
Sesamide DEA
Shea Butteramide/Castoramide DEA
Soyamide DEA
Stearamide DEA*
Tallamide DEA
Tallowamide DEA
Undecylenamide DEA
Wheat Germamide DEA

In addition, the ingredients marked with an asterisk (*) previously have been reviewed by the CIR Expert Panel. Lauramide DEA, linoleamide DEA, and oleamide DEA were reviewed in 1986, at which time the Panel concluded that these ingredients are safe as used, and that they should not be used in products containing nitrosating agents.[2] In 1995, the Expert Panel concluded that isostearamide DEA, myristamide DEA, and stearamide DEA are safe for use in rinse-off products.[3] In leave-on products, these ingredients are safe for use at concentrations that will limit the release of free ethanolamines to 5%, with a maximum use concentration of 40%.

The ingredients included in this review consist of DEA and one or more components. The safety of many of these components has been reviewed by the CIR. The conclusions of the previously reviewed ingredients, and of the components that have been reviewed, are provided in Table 1.

CHEMISTRY

Definition and Structure

The DEA amides consist of covalent, tertiary amides, whereby two of the nitrogen substituents are ethanol (or at least an ethanol residue) and the third is a carbonyl attached substituent. For example, behenamide DEA is a tertiary amide wherein two of the nitrogen substituents are ethanol and the third is a 22 carbon, carbonyl attached chain (Figure 1). These ingredients are not salts and do not readily dissociate in water. However, amidases, such as fatty acid amide hydrolase which is known to be present in human skin, could potentially convert these amides to DEA and the corresponding fatty acids.[4-6]

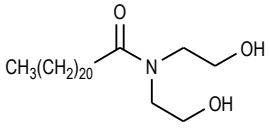


Figure 1. Behenamide DEA

The structures and definitions of cocamide DEA and all the DEA amides are provided in Table 2, and available chemical and physical properties are provided in Table 3.

Method of Manufacture

Specific methods of manufacture of most of the ingredients included in this assessment were not found.

Cocamide DEA

Cocamide DEA is produced by a condensation reaction at a 1:1 or 1:2 molar ratio of a mixture of methyl cocoate, coconut oil, whole coconut acids, or stripped coconut fatty acids to DEA.

From the Final Report on the Safety Assessment of Cocamide, Lauramide, Linoleamide, and Oleamide DEA[2]

Cocamide DEA has been produced by the reaction of refined coconut oil with diethanolamine in the presence of sodium methoxide (catalyst), yielding cocamide DEA, 10% glycerine, and 5% coconut fatty acid amide.
From the Amended Final Report on the Safety Assessment of Cocamide DEA.[1]

Lauramide DEA

Lauramide DEA is produced by a condensation reaction at a 1:1 or 1:2 molar ratio of a mixture of lauric and myristic acid to DEA.
From the Final Report on the Safety Assessment of Cocamide, Lauramide, Linoleamide, and Oleamide DEA[2]

Lauramide DEA is produced by the condensation of lauric acid methyl ester with DEA at elevated temperature and in the presence of a catalyst.[7]

Oleamide DEA

Oleamide DEA is produced by a condensation reaction at a 1:1 or 1:2 molar ratio of a mixture of oleic acid to DEA.
From the Final Report on the Safety Assessment of Cocamide, Lauramide, Linoleamide, and Oleamide DEA[2]

Linoleamide DEA

Linoleamide DEA is produced by a condensation reaction at a 1:1 or 1:2 molar ratio of a mixture of linoleic acid or its methyl ester to DEA.
From the Final Report on the Safety Assessment of Cocamide, Lauramide, Linoleamide, and Oleamide DEA[2]

Impurities

In the manufacture of the 1:2 mixture of fatty acid to DEA, ethylene glycol and free DEA residues are present. The 1:1 mixture contains much less free amine. Alkanolamides manufactured by base-catalyzed condensation of DEA and the methyl ester of long chain fatty acids are susceptible to nitrosamine formation.
From the Final Report on the Safety Assessment of Cocamide, Lauramide, Linoleamide, and Oleamide DEA[2]

Cocamide DEA

Various grades of cocamide DEA are available. Cocamide DEA contains 4.0-8.5% free DEA.
From the Amended Final Report on the Safety Assessment of Cocamide DEA.[1]

In the National Toxicology Program (NTP) studies, cocamide DEA contained approximately 18.2% free DEA by weight, alkanolamides of unsaturated acids, and amine salts of the acids. *N*-Nitrosodiethanolamine (NDELA) was detected at a concentration of 219 ppb.[8]
Commercial samples of cocamide DEA were analyzed for DEA.[9] The amount of DEA in the 9 samples ranged from 3.2-14.0%. NDELA was not found in any of the samples.

Lauramide DEA

Various grades of lauramide DEA are available for cosmetic use. The free amine value is 10-35.
From the Final Report on the Safety Assessment of Cocamide, Lauramide, Linoleamide, and Oleamide DEA[2]

In the NTP studies, the purity of lauramide DEA was approximately 90% for lauric acid DEA condensate, with approximately 5% amine (probably DEA) and approximately 5% other organic impurities.[7] NDELA was detected at a concentration of 3600 ppb. The report also stated that, based on data provided by the manufacturer, lauramide DEA contained 0.83% free DEA by weight, and approximately 9% other organic impurities.
Commercial samples of lauramide DEA were analyzed for DEA.[9] The amount of DEA in the 9 samples ranged from 1.2-12.4%. NDELA was not found in any of the samples.

Stearamide DEA

Stearamide DEA is characterized by 9-12% free fatty acids (as oleic acid) and 2-6% free amines (as DEA).
From the Final Report on Isostearamide DEA & MEA, Myristamide DEA & MEA, and Stearamide DEA & MEA[3]

Oleamide DEA

Oleamide DEA contains 6.0-7.5% free fatty acids (as oleic acid).
From the Final Report on the Safety Assessment of Cocamide, Lauramide, Linoleamide, and Oleamide DEA[2]

In the NTP studies of oleamide DEA, the oleic acid DEA condensate content was 47.5%.[10] Impurities were identified as other fatty acid alkanolamides (approximately 30%), other fatty acids, and unidentified impurities. Free DEA was estimated at 0.19%; NDELA was detected at a concentration of 68 ppb.

Linoleamide DEA

Commercial sample of linoleamide DEA were analyzed for DEA, and 4.3-5.0% was detected.[9] NDELA was not found in any of the samples.

USE

Cosmetic

Cocamide DEA is reported to function in cosmetics as a surfactant-foam booster or a viscosity increasing agent.[11] Most of the other DEA amides are reported to have these same functions, although a few are reported to function as a hair conditioning agent, skin conditioning agent, surfactant-cleansing or surfactant-emulsifying agent, or as an opacifying agent.

Voluntary Cosmetic Registration Program (VCRP) data obtained in 2011 indicate that cocamide DEA is used in 710 cosmetic formulations, the majority (596) of which are rinse-off formulations.[12] According to data submitted in response to a survey conducted by the Personal Care Products Council (Council), cocamide DEA is used at concentrations of 0.5-7%.[13,14] The highest concentration of cocamide DEA reported to be used in leave-on products is 6%. Lauramide DEA is reported to be used in 281 cosmetic formulations at 0.2-9%; the use of lauramide DEA at 9% is the highest concentration of use in a leave-on product reported for any of the DEA amides. Linoleamide DEA has the highest concentration of use reported, 12%, and that is in rinse-off formulations. The remaining DEA amides have less than 35 reported uses, and the majority of the ingredients are not reported to be in use. Concentration and frequency of use data for in-use DEA amides are provided in Table 4a. Ingredients not reported to be in use, according to VCRP data and the Council survey, are listed in Table 4b.

Cocamide and lauramide DEA are reported to be used in baby products, and some of the dialkanolamides are used in products that come in contact with the mucous membranes. Additionally, some of the dialkanolamides are reported to be present in hair sprays or fragrance formulations, and effects on the lungs that may be induced by aerosolized products containing these ingredients are of concern. The particle size of aerosol hair sprays and pump hair sprays is around 38 μm and >80 μm, respectively, and is large compared to respirable particle sizes (≤10 μm). Therefore, because of their size, most aerosol particles are deposited in the nasopharyngeal region and are not respirable.

Fatty acid dialkanolamides are listed in Annex III of the European Cosmetics Directive, which is a list of substances cosmetic products must not contain except subject to the restrictions laid down.[15] The restrictions for these ingredients are: maximum secondary amine content of 0.5% in the finished product; do not use with nitrosating systems; maximum secondary amine content of 5% for raw materials; maximum nitrosamine content of 50 μg/kg; and keep in nitrite free containers. The ingredients listed in Annex III with these restrictions, as well as additional EC information,[16] are provided in Table 5.

Non-Cosmetic

Many of the ingredients included in this safety assessment have use as indirect food additives.[17]

Cocamide DEA

Cocamide DEA is used as a corrosion inhibitor in metalworking fluids and in polishing agents.
From the Amended Final Report on the Safety Assessment of Cocamide DEA[1]

TOXICOKINETICS

Absorption, Distribution, Metabolism and Excretion

[^{14}C]Lauramide DEA partitioned well into rat and human liver slices, and the absorbed radioactivity was mostly unchanged lauramide DEA. In the media, 18-42% of the radioactivity was present in the form of metabolites. Using microsomes to compare hydroxylation, lauramide DEA 12-hydroxylase activity in human liver microsomes was similar to that in rat liver microsomes, but three times the rate observed in rat kidney microsomes.

Mice and rats were exposed dermally to 5-800 mg/kg and 25 or 400 mg/kg [^{14}C]lauramide DEA, respectively. In rats, absorption was similar for each dose when calculated as a percentage of dose, and absorption was greater in mice (50-70% of the applied dose) than in rats (20-24%). In rats, the parent compound and the half-acid amide metabolites were detected in the plasma. Repeated application of 25 mg/kg/day lauramide DEA did not appear to affect absorption or excretion. In rats dosed orally with 1000 mg/kg [^{14}C]lauramide DEA, after 72 h, 4% of the dose was recovered in the tissues and 79% in the urine; at 6 h, no DEA, DEA metabolites, or unchanged lauramide DEA were found in the urine; only very polar metabolites were found. With intravenous (i.v.) dosing, a 50 mg/kg dose of lauramide DEA was quickly metabolized and eliminated by mice; approximately 95% of the dose was excreted in the urine in 24 h. More than 80% of a 25 mg/kg dose was excreted in the urine by rats in 24 h.

In Vitro

Lauramide DEA

Human liver slices, and liver slices from diethylhexyl phthalate-(DEHP) induced and untreated male F344 rats, were incubated with [^{14}C]lauramide DEA.[18] Lauramide DEA "partitioned well" into the liver slices, and approximately 70% of the radioactivity absorbed into the slices in 4 h. The absorbed radioactivity was present mostly as lauramide DEA. In the media from liver slice incubations, 18-42% of the radioactivity was present in the form of metabolites. The analytes present in the incubation media included half-acid amides, parent lauramide DEA, and three other metabolites that are products of ω- and ω-1 to 4 hydroxylation.

The in vitro metabolism of [^{14}C]lauramide DEA, randomly labeled on the DEA moiety, was examined in liver and kidney microsomes from rats and humans to determine the extent of hydroxylation, and to determine the products formed.[19] Incubation of lauramide DEA with liver microsomes from control and DEHP-treated rats produced two major high performance liquid chromatography peaks that were identified as 11-hydroxy- and 12-hydroxy-lauramide DEA. Treatment with DEHP increased the 12-hydroxylation rate 5-fold, while the 11-hydroxylase activity was unchanged. Upon comparison of lauramide DEA hydroxylation rates using human liver microsomes from the rates measured using rat liver and kidney microsomes, the lauramide DEA 12-hydroxylase activity in human liver microsomes was similar to the activity in liver microsomes from control rats. The 12-hydroxylase activity in liver microsomes was 3 times greater than that observed in rat kidney microsomes.

Dermal

Non-Human

Lauramide DEA

Groups of four male B6C3F$_1$ mice and four F344 rats were dosed dermally with [^{14}C]lauramide DEA that was randomly labeled on the DEA moiety.[18] The vehicle was ethanol. A non-occlusive application was made to a 0.5 sq. in. area of skin of mice and to a 1 sq. in. area of skin of rats. At the end of the study, the excised skin was rinsed with ethanol. Absorption was calculated from the total disposition of radioactivity in the tissues, urine, feces, and dose site. In mice dosed with 5-800 mg/kg [^{14}C]lauramide DEA, 50-70% of the applied radioactivity was absorbed at 72 h, and absorption was similar for all the doses. Approximately 32-55% of the radioactivity was excreted in the urine. In rats dosed with 25 or 400 mg/kg lauramide DEA, 21-26% of the radioactivity penetrated the skin in 72 h, and 3-5% was recovered at the site of application. Approximately 20-24% of the radioactivity was recovered in the urine. The tissue/blood ratio was greatest in the liver and kidney. Lauramide DEA and the half-acid amide metabolites were detected in the plasma, with maximum levels found 24 h after dosing.

The researchers also applied 25 mg/kg/day lauramide DEA, 5 applications/wk for 3 wks, to a group of 5 rats to examine the effects of repeated administration on absorption and excretion. The rate of absorption of lauramide DEA did not vary much at the different collection time points, and the amounts excreted were similar at each collection period.

Oral

Non-Human

Lauramide DEA

Three male F344 rats were dosed orally with [^{14}C]lauramide DEA that was randomly labeled on the DEA moiety, 16-18 µCi/dose, and that was formulated with an appropriate amount of unlabeled lauramide DEA and water to give delivery of the target dose in a volume of 5 ml/kg bw.[18] After oral dosing with 1000 mg/kg [^{14}C]lauramide DEA, approximately 10, 60,and 79% of the dose was recovered in the urine after 6, 24, and 72 h, respectively. Approximately 4% of the dose was recovered in the tissues after 72 h, with almost 3% found in adipose tissue and 1.3% in the liver. At 6 h, no DEA, DEA metabolites, or unchanged lauramide DEA were present in the urine; only very polar metabolites were found. The researchers postulated that the metabolites were carboxylic acids, and that the acid function was formed from the lauryl chain.

Intravenous

Non-Human

Lauramide DEA

Three male B6C3F$_1$ mice and four F344 rats were dosed i.v. with [^{14}C]lauramide DEA that was randomly labeled on the DEA moiety, 3-5 µCi and 16-17 µCi, respectively, and that was formulated to deliver a target dose in a volume of 4 ml/kg in mice and 1 ml/kg in rats.[18] The dose for mice was 50 mg/kg and the dose for rats was 25 mg/kg. In B6C3F$_1$ mice, lauramide DEA was quickly metabolized and eliminated. At 24 h after dosing, approximately 95% of the dose was excreted, with 90% found in the urine; the highest concentrations and total amounts of the lauramide DEA were in adipose tissue. In F344 rats, 50% of the dose was excreted in the urine within the first 6 h, and more than 80% was excreted in the urine by 24 h. The rats were killed at 72 h after dosing, and only 3% of the dose was recovered in the tissues; 1% of the dose was in the adipose tissue and 0.67% was found in the liver.

TOXICOLOGICAL STUDIES

Acute dermal testing with 50% lauramide DEA and undiluted and 10% aq linoleamide DEA, and acute oral testing with several fatty acid DEA amides, did not result in significant toxicity.

In repeated dose dermal studies with cocamide, lauramide, and oleamide DEA in mice and/or rats, irritation was observed at the site of application. Increases in liver and kidney weights were observed in most studies, while decreases in body weight were observed sporadically. The incidence of renal tubule regeneration was greater in female rats dosed with 100-400 mg/kg cocamide DEA when compared to controls. A formulation containing 3% linoleamide DEA was not a cumulative systemic toxicant in a 13-wk dermal study; dermal irritation was observed.

With repeat oral dosing of lauramide DEA, the no-observed effect level (NOEL) was 0.1% in a study with SPF rats and 250 mg/kg/day in a study using Wistar rats. The NOEL for Beagle dogs fed lauramide DEA for 12 wks was 5000 ppm.

Data on the reproductive and developmental toxicity of the DEA amides were not found. Available reproductive and developmental toxicity data on DEA and some of the fatty acids and other components from previous CIR reports were reviewed, and no significant effects were noted.

Single Dose (Acute) Toxicity

Dermal

Lauramide DEA

In an acute dermal toxicity study using guinea pigs, 50% lauramide DEA in corn oil was non-toxic.
From the Final Report on the Safety Assessment of Cocamide, Lauramide, Linoleamide, and Oleamide DEA[2]

Linoleamide DEA

Linoleamide DEA, tested as 10% aq. and undiluted, was nontoxic in acute studies with guinea pigs.
From the Final Report on the Safety Assessment of Cocamide, Lauramide, Linoleamide, and Oleamide DEA[2]

Oral

Cocamide DEA

In an acute oral toxicity test in male and female Sprague-Dawley rats, undiluted cocamide DEA had an LD_{50} of 12.2 g/kg.
From the Final Report on the Safety Assessment of Cocamide, Lauramide, Linoleamide, and Oleamide DEA[2]

The acute oral toxicity of cocamide DEA was determined using groups of 3 male and 3 female Wistar rats. Three or more animals per group died with doses of ≥6.3 g/kg.[20]

Lauramide DEA

In rats, the oral LD_{50} of 25% lauramide DEA in corn oil was >5 g/kg, of 10% aq. was 2.7 g/kg, of a shampoo formulation containing 8% lauramide DEA was 9.63 g/kg, and of a bubble bath containing 6% lauramide DEA was >15 g/kg.
From the Final Report on the Safety Assessment of Cocamide, Lauramide, Linoleamide, and Oleamide DEA[2]

Stearamide DEA

The oral LD_{50} of a mixture containing 35-40% stearamide DEA was >20 g/kg in CFW mice.
From the Final Report on Isostearamide DEA & MEA, Myristamide DEA & MEA, and Stearamide DEA & MEA[3]

Oleamide DEA

In rats, the oral LD_{50} of undiluted oleamide DEA was 12.4 ml/kg.

From the Final Report on the Safety Assessment of Cocamide, Lauramide, Linoleamide, and Oleamide DEA[2]

Linoleamide DEA

In rats, the oral LD_{50} of undiluted and 10% aq. linoleamide DEA was >5 g/kg, and the LD_{50} of a product containing 1.5% linoleamide DEA was 3.16 g/kg.

From the Final Report on the Safety Assessment of Cocamide, Lauramide, Linoleamide, and Oleamide DEA[2]

Repeated Dose Toxicity

Dermal

Cocamide DEA

A shaving cream containing 1.92% cocamide DEA was applied to the intact or abraded skin on the back of 8 New Zealand White (NZW) rabbits. Applications of 500 mg/kg of the test product were made 5x/wk for 4 wks. Dermal irritation was observed at both intact and abraded application sites. No systemic effects attributed to dosing were observed.

From the Final Report on the Safety Assessment of Cocamide, Lauramide, Linoleamide, and Oleamide DEA[2]

The repeated-dose dermal toxicity of cocamide DEA (containing 18.2% free DEA by wt) was evaluated using mice and rats. Groups of 10 male and 10 female $B6C3F_1$ mice were dosed with 50, 100, 200, 400, or 800 mg/kg bw cocamide DEA in ethanol (20-320 mg/ml), 5 exposures/wk, for 14 wks.[8] Vehicle only was applied to the negative control group. All animals survived until study termination. Dermal irritation was observed at the application site of males and females of the 800 mg/kg dose group. Epidermal and sebaceous gland hyperplasia, parakeratosis, chronic active inflammation, and ulceration were observed; severity generally increased with increased dose. Final mean body weights and mean body weight gains were similar for test and control animals. The absolute and relative liver and kidney weights to body weights of males and females of the 800 mg/kg group, relative liver weights to body weights of females of the 400 mg/kg group, and absolute and relative lung weights to body weights of females of the 800 mg/kg group were significantly greater than for those of the controls. The epididymal spermatozoal concentration was significantly greater in males of the 800 mg/kg dose group.

Groups of 20 male and 20 female F344/N rats were dosed dermally with 25, 50, 100, 200, or 400 mg/kg/bw cocamide DEA in ethanol (30-485 mg/ml), 5 exposures/wk, for 14 wks; 10 rats per group were used for clinical chemistry and hematology evaluation.[8] Vehicle only was applied to the negative control group. All animals survived until study termination. Dermal irritation was observed at the application site of 2 males and one female of the 100 mg/kg group and in nearly all males and females of the 200 and 400 mg/kg dose groups. Lesions included epidermal and sebaceous gland hyperplasia, parakeratosis, chronic active inflammation, and ulceration; incidence and severity generally increased with increasing dose. Final mean body weights and mean body weight gains of males and females of the 200 and 400 mg groups were significantly less than those of the controls. Kidney weights of females of the 50 mg/kg group were significantly greater than those of the controls. Decreases in epididymal weights in 200 and 400 mg/kg males were attributed to decreased body weights. Changes in some hematology and clinical chemistry parameters were noted and the researchers stated there was an indication of altered lipid metabolism, as evidenced by decreased cholesterol and triglyceride concentrations. The incidences of renal tubule regeneration were greater in females of the 100 dose group, and the incidences and severities were greater in females of the 200 and 400 mg/kg dose groups, as compared to controls.

Lauramide DEA

The dermal toxicity of lauramide DEA was evaluated in two 13-wk studies using Sprague-Dawley rats. A 0.45% aq. solution of a cream cleanser containing 4.0% lauramide DEA, tested in 15 females, and a medicated liquid cleanser containing 5.0% lauramide DEA, tested in 10 males and 10 females, did not have any systemic toxic effects.

From the Final Report on the Safety Assessment of Cocamide, Lauramide, Linoleamide, and Oleamide DEA[2]

The repeated-dose dermal toxicity of lauramide DEA (90% purity; 0.83% free DEA by wt) was evaluated in mice and rats. Groups of 10 male and 10 female $B6C3F_1$ mice were dosed with 50, 100, 200, 400, or 800 mg/kg bw lauramide DEA in ethanol, 5 exposures/wk, for 14 wks.[7] Vehicle only was applied to the negative control group. All animals survived until study termination. Dermal irritation was observed at the application site in males and females dosed with 400 or 800 mg/kg lauramide DEA. Final mean body weights and mean body weight gains were similar for test and control animals. The absolute kidney weights of males of the 100, 400 and 800 mg/kg bw groups, the relative kidney to body weights of all dosed males, and the liver weights of females of the 200, 400, and 800 mg/kg bw groups, were statistically significantly greater than those of the control mice. The absolute thymus weights of males of the 400 and 800 mg/kg groups were significantly less than those of the controls. There were no statistically significant differences in reproductive tissue evaluation or estrous cycle between the treated and control groups. At the application site, incidences of non-neoplastic lesions of the skin, including hyperplasia of the epidermis and sebaceous gland, chronic inflammation, parakeratosis, and ulceration, were increased in males and females dosed with ≥200 mg/kg lauramide DEA.

Groups of 20 male and 20 female F344/N rats were dosed dermally with 25, 50, 100, 200, or 400 mg/kg bw lauramide DEA in ethanol, 5 exposures/wk for 14 wks; 10 rats per group were used for clinical pathology.[7] Vehicle only was applied to the negative control group. All animals survived until study termination. Dermal irritation was observed at the application site of males dosed with ≥100 mg/kg and in females dosed with 200 or 400 mg/kg lauramide DEA. Final mean body weights and mean body weight gains of males of the 200 and 400 mg/kg bw group were statistically significantly less than those of the control group. Kidney weights of females dosed with 200 or 400 mg/kg bw were statistically significantly greater, and absolute liver weights of males dosed 400 mg/kg lauramide DEA were statistically significantly less, than those of the control groups. There were no statistically significant differences in reproductive tissue evaluation or estrous cycle between the treated and control groups. At the application site, incidences of non-neoplastic lesions of the skin, including hyperplasia of the epidermis and sebaceous gland, chronic inflammation, parakeratosis, and ulceration, were statistically significantly increased with increasing dose.

Oleamide DEA

The repeated-dose dermal toxicity of oleamide DEA (47.5% oleic acid DEA condensate content; 0.19% free DEA) was evaluated using mice and rats. Groups of 10 male and 10 female $B6C3F_1$ mice were dosed with 50, 100, 200, 400, or 800 mg/kg bw oleamide DEA in ethanol (20-320 mg/ml), 5 exposures/wk, for 13 wks.[10] Vehicle only was applied to the negative control group. All animals, except one high dose male, survived until study termination. Final mean body weights and body weight gains of males of the 800 mg/kg group and females of the 400 mg/kg group were statistically significantly less than those of controls. Dermal irritation was observed at the application site of all treated males and for most females dosed with ≥100 mg/kg oleamide DEA. Lesions included epidermal hyperplasia, parakeratosis, suppurative epidermal and chronic active dermal inflammation, sebaceous gland hypertrophy, and ulceration; severity generally increased with increased dose. Heart weights of females of the 200 mg/kg and males and females of the 400 and 800 mg/kg groups, kidney weights of males of the 50, 100, and 400 mg/kg groups, and liver weights of all dose groups were statistically significantly greater than those of controls. The incidences of hematopoietic cell proliferation of the spleen of males of the 800 mg/kg group and females of

the 400 and 800 mg/kg groups were statistically significantly greater than the controls. Sperm motility and vaginal cytology parameters of dosed mice were similar to those of the controls.

Groups of 20 male and 20 female F344/N rats were dosed dermally with 25, 50, 100, 200, or 400 mg/kg bw oleamide DEA in ethanol (30-485 mg/ml), 5 exposures/wk for 13 wks; 10 rats per group were used for clinical chemistry and hematology evaluation.[10] Vehicle only was applied to the negative control group. All animals survived until study termination. Dermal irritation was observed at the application site of most males dosed with ≥100 mg/kg and all females dosed with ≥50 mg/kg oleamide DEA. Lesions included epidermal hyperplasia, parakeratosis, suppurative epidermal and chronic active dermal inflammation, and sebaceous gland hypertrophy; severity generally increased with increased dose. The final mean body weights and mean body weight gains of males of the 200 and 400 mg/kg groups and mean body weight gains of females of the 400 mg/kg group were statistically significantly less than controls; some associated lower organ weights were observed. Kidney weights were statistically significantly greater for females of the 200 and 400 mg/kg groups as compared to controls. Some increases in segmented neutrophil counts and alkaline phosphatase concentrations were reported. There were no biologically significant differences in sperm motility or vaginal cytology parameters between treated and control rats.

Linoleamide DEA

The dermal toxicity of a shampoo formulation containing 3.0% linoleamide DEA was evaluated in a 13-wk study. The test article was applied as a 2.5% solution, a 25% solution, or a 25% solution that was rinsed after 15 min, to groups of 10 male and 10 female Sprague-Dawley rats. Dermal irritation was observed, but the formulation containing 3% linoleamide DEA was not a cumulative systemic toxicant.

From the Final Report on the Safety Assessment of Cocamide, Lauramide, Linoleamide, and Oleamide DEA[2]

Oral

Lauramide DEA

The oral toxicity of lauramide DEA was evaluated in two 13-wk dietary studies. In the first study, 0-2% lauramide DEA was evaluated using groups of 15 male and 15 female SPF rats. A reduction in growth was associated with reduced feed intake at doses of ≥0.5% lauramide DEA. There were no treatment-related gross or microscopic lesions. The no-effect dose was 0.1% lauramide DEA. In the second study, groups of 20 male and 20 female Wistar rats were fed 0-250 mg/kg/day. No adverse effects were reported, and the no-effect dose for rats was 250 mg/kg/day. Groups of 4 male and 5 female Beagle dogs were fed 0-5000 ppm lauramide DEA for 12 wks. No adverse effects were reported, and the no-effect dose for dogs was 5000 ppm lauramide DEA.

From the Final Report on the Safety Assessment of Cocamide, Lauramide, Linoleamide, and Oleamide DEA[2]

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Data on the reproductive and developmental toxicity of the DEA amides were not found. Since DEA may be present as an impurity in the DEA amides, and since amidases in the skin might convert some of the DEA amide to DEA and the corresponding fatty acid, summary data from the reports on DEA and the other "components" of these dialkanolamides is being provided.

DEA: Hair dyes containing up to 2% DEA were applied topically to the shaved skin of groups of 20 gravid rats on days, 1, 4, 7, 10, 13, 16, and 19 of gestation, and the rats were killed on day 20 of gestation. No developmental or reproductive effects were observed.[21]

In a study in which gravid mice were dosed dermally with 20-320 mg/kg DEA from day 6 of gestation through PND 21, no effects on skeletal formation were observed, but dose-dependent effects on some growth and developmental parameters were observed. In a study in which parental mice were treated dermally with 20-320 mg/kg DEA for 4 wks prior to mating, sperm motility was decreased in a dose-dependent manner. In rats and rabbits, dermal dosing with up to 1500 mg/kg/day and 350 mg/kg/day DEA, respectively, during gestation, did not have any fetotoxic or teratogenic effects. The NOEL for embryonal/fetal toxicity was 380 mg/kg/day for rats and 350 mg/kg/day for rabbits.[22]

In an oral reproductive study in which rats were dosed with up to 1200 mg/kg/day DEA on days 6-15 of gestation, maternal mortality was observed at doses of ≥50 mg/kg; the NOEL for embryonal/fetal toxicity was 200 mg/kg/day. In a study in which gravid rats were dosed orally with up to 300 mg/kg/day DEA, the dams of the 300 mg/kg group were killed due to excessive toxicity; the LD_{50} was calculated to be 218 mg/kg. The LOAEL for both maternal toxicity and teratogenicity was 125 mg/kg/day.[22]

In a reproductive study in which rats were exposed by inhalation to DEA on days 6-15 of gestation, the NOAEC for both maternal and developmental toxicity was 0.05 mg/l, and the NOAEC for teratogenicity was >0.2 g/ml.[22]

Lecithin: In oral studies, ≤1600 mg/kg lecithin was not a reproductive toxicant in mice or rats and ≤47 mg/kg was not a reproductive toxicant in rabbits. In an i.v. reproductive study, the lowest toxic daily i.v. dose for rats was >1000 mg/kg. Lecithin, ≤3.0 mM, had no significant effect on human sperm motility.[23]

Palm Oil: Crude palm oil was not a reproductive toxicant in a study in which male and female Wistar/NIN inbred weanling rats were fed a diet containing this ingredient (10%) prior to mating. Mean litter sizes were comparable between test and control groups. No significant changes were found in liver or kidney weight in adult animals. Neither untreated palm oil (15%) nor 15% heated palm oil in the diet induced anomalies with respect to fertility and in utero growth when fed to male and female Sprague-Dawley SPF rats prior to mating. In a study investigating the effects of palm oil on sexual maturation and endocrine function, vaginal opening was observed significantly earlier (compared to 5% corn oil control) in weanling rats fed 20% palm oil in the diet. No significant differences were observed in endocrine function.[24]

Palm Kernel Oil: In the second generation resulting from the mating of adult Mongolian gerbils fed a diet containing 8.75% w/w palm kernel oil, no statistically significant differences were found with respect to the following: frequency of litters, mean litter size, total of newborns, and suckling death. Animals receiving a basal diet served as the control.[24]

Ricinus Communis (Castor) Seed Oil: Groups of mice and rats fed diets containing 0.62%, 1.25%, 2.5%, 5.0%, and 10% castor oil continuously for 13 wks had a slight decrease in epididymal weight (6% to 7%) in mid and high-dose groups of male rats; however, this finding was not dose-related. No effects on any other male reproductive endpoint (testes weight and epididymal sperm motility, density, or testicular spermatid head count) or female reproductive endpoint (estrous cycle length, or time spent in each phase of the cycle) were noted. Castor oil served as the vehicle control in a study evaluating the effect of long-term treatment with ICI 182,780 (an anti-estrogen) on the rat testis. In the control group, four male Sprague-Dawley rats were injected subcutaneously with castor oil (0.2 ml) once per week and then killed 100 days after the first injection. Spermatogenesis appeared normal in each of the four control rats.[25]

Sesamum Indicum (Sesame) Seed Oil: Although not teratogenic, oral dosing with sesame oil (4 ml doses) increased the incidence of resorptions in rats when compared to controls. In a 42-week two-generation reproduction study involving rats, sesame oil (vehicle control, dose volume not stated) did not induce any adverse effects on reproductive performance, fertility, or reproductive organ weights of male or female rats through 2 consecutive generations. Oral dosing with sesame oil (vehicle control, single intragastric dose [not stated]) on day 9 of gestation also had no adverse effect on the fetal survival rate or crown-rump length in mice. Dosing with sesame oil subcutaneously (s.c.) did not adversely affect the development of mice receiving doses (0.05 ml injections) beginning at 3 to 5 days of age or induce teratogenic effects in their offspring. In a study involving rats, dosing with sesame oil s.c. (0.05 ml injections) did not have an adverse effect on the following when compared to untreated controls: uterine and ovarian weight (female rats) and weight of the testes, prostate, and seminal vesicles (male rats). Dosing with sesame oil intraperitoneally (0.4 ml) was associated with a marked increase in the incidence of deciduomas in mice.[26]

Tall Oil Acid: No treatment-related effects were observed in rats used in rats fed diets containing 5% and 10% tall oil acid in a two-generation study.[27]

GENOTOXICITY

Cocamide DEA, lauramide DEA, and oleamide DEA were, generally, non-genotoxic in a number of assays. Exceptions were an increase in the frequency of micronucleated erythrocytes in mice by cocamide DEA and the induction of SCEs in CHO cells by lauramide DEA.

In Vitro

Cocamide DEA

Cocamide DEA was not mutagenic in an Ames assay (0.1-200 µg/plate), did not induce mutations in L5178Y mouse lymphoma cells (1.25-50 nl/ml), nor SCEs (0.5-30 µg/ml) or chromosomal aberrations (16-50 µg/ml) in CHO cells; all tests were performed with and without metabolic activation.[8] However, at the end of a 14-wk repeated dose study (described earlier), significant increases in the frequencies of micronucleated normochromatic erythrocytes were found in peripheral blood of male and female mice.

Lauramide DEA

Lauramide DEA was not mutagenic or genotoxic in multiple Ames assays, a DNA damage assay using *Bacillus subtilis*, an in vitro transformation assay using Syrian golden hamster embryo cells, or an in vivo transformation assay using hamster embryo cells. Lauramide DEA was mutagenic in the spot test with two strains of *S. typhimurium*, but quantitative results were not provided.

From the Final Report on the Safety Assessment of Cocamide, Lauramide, Linoleamide, and Oleamide DEA[2]

Lauramide DEA (0.3-1000 µg/plate) was not mutagenic in the Ames test with or without metabolic activation, and it was negative in a L5178Y mouse lymphoma assay (2.5-60 µg/ml), did not increase the number of chromosomal aberrations in CHO cells (1.5-100 µg/ml), with or without metabolic activation, and was not clastogenic in a mouse micronucleus test (50-800 mg/kg).[7] Lauramide DEA (2.49-49.7 µg/ml) induced SCEs in CHO cells, in the presence and the absence of metabolic activation.

Oleamide DEA

Oleamide DEA was not mutagenic in an Ames test (0.1-200 µg/plate) and did not induce mutations in L5178Y mouse lymphoma cells (1.25-20 nl/ml), with or without metabolic activation.[10]

CARCINOGENICITY

The carcinogenic potential of dermally applied cocamide, lauramide, and oleamide DEA was evaluated in B6C3F$_1$ mice and F344/N rats by the NTP. (The doses tested are included in parentheses). Cocamide DEA produced clear evidence of carcinogenic activity in male and female mice (100-200 mg/kg) based on increased incidences of hepatic and renal tubule neoplasms, equivocal evidence in female rats (50-100 mg/kg) based on a marginal increase in the incidences of renal tubule neoplasms, and no evidence in male rats (50-100 mg/kg). Lauramide DEA produced some evidence of carcinogenic activity in female mice (100-200 mg/kg, based on increased incidences of hepatocellular neoplasms, and no evidence in male mice (100-200 mg/kg) or male and female rats (50-100 mg/kg). Oleamide DEA produced no evidence of carcinogenic activity in male or female mice (15-30 mg/kg) or male or female rats (50-100 mg/kg).

Dermal

Table 6 summarizes the conclusions of the NTP dermal studies on lauramide DEA, oleamide DEA, and cocamide DEA. (The results from the DEA carcinogenicity study are also provided in this table).

Cocamide DEA

The carcinogenic potential of dermally applied cocamide DEA (containing 18.2% free DEA by wt) was assayed by the NTP, using B6C3F$_1$ mice and F344/N rats.[8] Groups of 50 male and 50 female mice were dosed dermally with 0, 100, or 200 mg/kg cocamide DEA in ethanol, 5 days/wk, for 104-105 wks. There were no statistically significant differences in survival between the test animals and the controls. Mean body weights of 100 and 200 mg/kg females were less than controls from wks 93 and 77, respectively. Dermal irritation was observed at the application site of 200 mg/kg males. The incidences of epidermal and sebaceous gland hyperplasia and hyperkeratosis were statistically significantly greater in all dose groups compared to the controls, and in the in 200 mg/kg dose group, the incidences of ulceration in males and inflammation and parakeratosis in females were increased. The incidences of hepatic neoplasms were statistically significantly greater in dosed male and female mice compared to controls. The incidences of eosinophilic foci in dosed groups of males were increased compared to controls, and the incidence of nephropathy was statistically significantly less than that of the controls. The incidences of renal tubule adenoma and of renal tubule adenoma or carcinoma (combined) in 200 mg/kg males were statistically significantly greater than controls and exceeded the historical control ranges for these neoplasms. In the thyroid gland, the incidences of follicular cell hyperplasia in all dosed groups of males and females were statistically significantly greater than the controls. The researchers concluded there was *clear evidence of carcinogenic activity* in male B6C3F$_1$ mice, based on increased incidences of hepatic and renal tubule neoplasms, and in female B6C3F$_1$ mice, based on increased incidences of hepatic neoplasms. The researchers hypothesized these increases were associated with the concentration of free DEA present as a contaminant in the DEA condensate.

In the rats, groups of 50 males and 50 females were dosed dermally with 0, 50, or 100 mg/kg bw cocamide DEA in ethanol (0, 85, or 170 mg/ml, respectively), 5 days/wk for 104 wks. Survival and mean body weights were similar in test and control animals. Dermal irritation was observed at the application site of 100 mg/kg females. The incidences of epidermal and sebaceous gland hyperplasia, parakeratosis, and hyperkeratosis were statistically significantly greater in all dose groups compared to the controls; the severity of the lesions generally increased with increasing dose and ranged from minimal to mild. Incidences of renal tubule hyperplasia in dosed females and of renal tubule adenoma or carcinoma (combined) in females of the 50 mg/kg group were statistically significantly greater than in the controls. Incidences of nephropathy were similar between test and control rats; severity in females increased with increasing dose. In the forestomach, the incidences of chronic, active inflammation, epithelial hyperplasia, and epithelial ulcer were statistically significantly increased in 100 mg/kg females. The incidence of pancreatic acinar atrophy was statistically significantly greater in the 100 mg/kg males than in the controls. The researchers concluded there was *no evidence of carcinogenic activity* in male F344/N rats dosed dermally with 50 or 100 mg/kg cocamide DEA. There was *equivocal evidence of carcinogenic activity* in female F344/N rats, based on a marginal increase in the incidences of renal tubule neoplasms.

Lauramide DEA

The NTP evaluated the carcinogenic potential of lauramide DEA (90% purity; 0.83% free DEA by wt) using B6C3F$_1$ mice and F344/N rats.[7] Groups of 50 male and 50 female mice were dosed dermally with 0, 100, or 200 mg/kg/day lauramide DEA in ethanol (0, 50, or 100 mg/ml, respectively), 5 days/wk, for 105-106 wks. There were no clinical findings attributable to lauramide DEA. In female mice, the incidence of hepatocellular adenoma and carcinoma (combined) were statistically significantly increased in all dose groups, of hepatocellular adenoma was statistically significantly increased in females of the 100 mg/kg group, and of eosinophilic foci was statistically significantly increased in the 200 mg/kg group. The incidences of these lesions in male mice were not statistically significantly different from controls. Incidences of non-neoplastic lesions of the skin at the site of application were statistically significantly increased in treated males and females; the lesions were mostly epidermal and sebaceous gland hyperplasia. The incidence of focal hyperplasia of thyroid gland follicular cells was statistically significantly greater in males of the 200 mg/kg group compared to controls; there were not corresponding increases in the incidences of follicular cell neoplasms. There was *no evidence of carcinogenic activity* in male mice. There was *some evidence of carcinogenic* activity in female B6C3F$_1$ mice based on increased incidences of hepatocellular neoplasms; the researchers hypothesized these increases were associated with free DEA, which was present as a contaminant.

Groups of 50 male and 50 female rats were dosed dermally with 0, 50, or 100 mg/kg bw lauramide DEA in ethanol (0, 85, or 170 mg/ml, respectively), 5 days/wk, for 104-105 wks. Survival and mean body weights of test animals were similar to controls. The only treatment-related clinical finding was minimal to moderate irritation at the application site; epidermal and sebaceous gland hyperplasia, hyperkeratosis, and chronic inflammation were statistically significantly increased compared to controls. The incidence of neoplasms was similar for treated and control rats. The incidence of forestomach ulcer in the 100 mg/kg group males, of inflammation of the nasal mucosa in all test males, and of chronic inflammation of the liver in 100 mg/kg females was statistically significantly lower than in the controls. There was *no evidence of carcinogenic activity* of lauramide DEA in male or female F344/rats.

Oleamide DEA

The NTP also examined the carcinogenic potential of dermally applied oleamide DEA (47.5% oleic acid DEA condensate content; 0.19% free DEA) using B6C3F$_1$ mice and F344/N rats.[10] Groups of 55 male and 55 female mice were dosed dermally with 0, 15, or 30 mg/kg oleamide DEA in ethanol (0, 7.5, or 15 mg/ml, respectively), 5 days/wk, for 105 wks; 5 males and 5 females per group were used for a 3-mos interim evaluation. Survival was similar for treated and control mice. Mean body weights of females of the 30 mg/kg group were less than controls as of wk 76 of the study. Increased incidence of dermal irritation was observed at the application site of males of the 30 mg/kg dose group. The incidences of epidermal and sebaceous gland hyperplasia were statistically significantly increased in all male and female dose groups, as compared to controls, at both the 3-mos and 2-yr evaluation. Additional dermal lesions were observed, but a dose-related increase in neoplasms was not observed. The incidence of malignant lymphoma in female mice increased with increasing dose, and the increase was statistically significant in the high dose group. However, the researchers noted that the incidence in the high-dose group was similar to the incidences observed in other studies that used ethanol as the vehicle. There was *no evidence of carcinogenic activity* in male or female mice dosed dermally with ≤30 mg/kg oleamide DEA.

The researchers also dosed groups of 50 male and 50 female rats dermally with 0, 50, or 100 mg/kg oleamide DEA in ethanol (0, 85, or 170 mg/ml, respectively), 5 days/wk, for 104 wks. Survival was similar for treated and control rats. Mean body weights of males of the 100 mg/kg group were slightly less than controls throughout the study, while in the females of this dose group, a decrease in body weights was observed from wk 24 on. Mild to moderate irritation was observed at the application site of doses rats. Skin lesions observed at the application site, including statistically significant increases in epidermal and sebaceous hyperplasia, were considered indicative of local irritation, with no neoplastic or preneoplastic changes. The researchers did not consider increased incidences of lesions in the forestomach, testis, and thyroid gland test article-related. There was *no evidence of carcinogenic activity* in male or female rats dosed dermally with ≤100 mg/kg oleamide DEA.

IRRITATION AND SENSITIZATION

The dermal irritation of fatty acid DEA amides, in non-human and human testing, varied greatly with formulation and test conditions. Lauramide DEA and linoleamide DEA were not sensitizers in humans. Cocamide DEA, 0.01-10%, produced positive results in provocative sensitization studies. Lauramide DEA was not phototoxic in humans. The ocular irritation of fatty acid DEA amides varied greatly with formulation and test conditions

Dermal Irritation

Non-Human

Cocamide DEA

Cocamide DEA, 30% in propylene glycol, was a moderate skin irritant in an irritation study using an occlusive covering.
From the Final Report on the Safety Assessment of Cocamide, Lauramide, Linoleamide, and Oleamide DEA[2]

Lauramide DEA

The dermal irritation potential of lauramide DEA was evaluated in numerous tests using rabbits and guinea pigs. In immersion tests using guinea pigs, lauramide DEA, as 0.1-0.5% aq solutions of lauramide DEA was minimally to mildly irritating, a shampoo formulation containing 8% lauramide DEA, tested as a 0.5% solution, was a slight irritant, and a bubble bath containing 6% lauramide DEA, tested as a 0.5% aq. solution, was practically non-irritating. In rabbits, lauramide DEA, tested as a 1.25-10% aq solution, was practically non- to slightly irritating, while a 20% aq. solution was a severe irritant. In a 14-day cumulative irritation test using rabbits, a 1% aq. solution of lauramide DEA was not an irritant, a 5% solution was a moderate irritant, and a 25% solution was a severe irritant. Liquid soap formulations containing 10% lauramide DEA ranged from mildly to severely irritating in rabbit skin.
From the Final Report on the Safety Assessment of Cocamide, Lauramide, Linoleamide, and Oleamide DEA[2]

Stearamide DEA

A mixture containing 35-40% stearamide DEA had a primary irritation score of 0 in a dermal study using rabbits.
From the Final Report on Isostearamide DEA & MEA, Myristamide DEA & MEA, and Stearamide DEA & MEA[3]

Oleamide DEA

Oleamide DEA in propylene glycol was mildly irritating to rabbit skin when tested at 5% and moderately irritating, when tested at 70%.
From the Final Report on the Safety Assessment of Cocamide, Lauramide, Linoleamide, and Oleamide DEA[2]

Linoleamide DEA

Linoleamide DEA, tested as a 0.1-0.5% aq. solution, was non- to slightly irritating in immersion tests with guinea pigs, and a formulation containing 1.5% linoleamide DEA, tested as a 0.5% aq. solution, was a slight irritant in an immersion test. In primary irritation tests using rabbits, 5-10% aq. linoleamide DEA was non to mildly irritating, while an aq. solution of 20% linoleamide DEA was a severe dermal irritant in rabbits. A formulation containing 1.5% linoleamide DEA, tested as a 2.5% aq. solution, was a minimal dermal irritant in rabbits.
From the Final Report on the Safety Assessment of Cocamide, Lauramide, Linoleamide, and Oleamide DEA[2]

Ricinoleamide DEA

Undiluted PEG-20 glyceryl ricinoleate + ricinoleamide DEA was evaluated for dermal irritation in a Draize test using NZW rabbits.[28] A semi-occlusive patch with 0.5 g of the test material was applied to a 6 cm^2 shaved site on the dorsal area of the trunk for 4 h. No signs of irritation were observed, and the surfactant was non-irritating to rabbit skin.

Human

Cocamide DEA

The irritation potential of a solution containing 10% cocamide DEA and 20% sodium lauryl sulfate was evaluated in 15 subjects in conjunction with 5 other cosmetic-grade surfactant solutions. Adverse reactions were not observed. The researchers concluded that skin irritation was not simply related to the total concentration of the surfactants in contact with the skin, but rather the combination of surfactants present.
From the Amended Final Report on the Safety Assessment of Cocamide DEA[1]

An aq. solution of 12.5 mmol/l cocamide DEA was applied to the forearm of 15 volunteers.[29] Twice a day, 5 days/wk, 0.3 ml of the test material was applied for 45 min/exposure, using a plastic chamber, for a total of 28 applications. The mean transepidermal water loss (TEWL) with cocamide DEA was 7.0 g/m^2 l; as a point of comparison, the TEWL with 12.5 mmol/l sodium lauryl sulfate was 15.2 g/m^2 l.

The irritation potential of 0.5% aq. cocamide DEA was evaluated in a single insult occlusive patch test using 105 subjects, 14.3% of which were atopic patients.[30] A volume of 40 µl was applied using Haye's test chambers for 48 h, and the test site was evaluated erythema and edema 15 min and 24 h after patch removal. An untreated occlusive patch was used as a negative control. Cocamide DEA had a total average index of skin irritation (AII) of 0.065, and was non-irritating (AII < 0.5) based on an amended Draize scale.

Lauramide DEA

Numerous studies were conducted in humans to evaluate the dermal irritation potential of formulations containing lauramide DEA. In primary irritation tests (single patch) using 17-19 subjects of a shampoo containing 8% and a bubble bath containing 6% lauramide DEA, both tested as a 1.25% aq solution, and an unspecified product containing 5% lauramide DEA, tested as a 1% aq. solution, minimal to mild irritation was observed. In three cumulative irritation soap chamber tests using 12-15 subjects, liquid soap formulations containing 10% lauramide DEA, tested as 8% aq solutions, were essentially non- to mildly irritating. In a 21-day cumulative irritation study, a medicated liquid soap containing 5% lauramide DEA, tested as a 25% solution, was a moderate skin irritant. In use studies, a liquid soap containing 10% lauramide DEA,

evaluated in 114 subjects for 4 wks, was minimally irritating under normal use and an acne liquid cleanser containing 5% lauramide DEA, evaluated in 50 subjects with twice daily use for 6 wks, was a mild irritant.
From the Final Report on the Safety Assessment of Cocamide, Lauramide, Linoleamide, and Oleamide DEA[2]

Linoleamide DEA

In a primary irritation (single patch) study, a product containing 1.5% linoleamide DEA, tested as a 1.25% aq. solution in 20 subjects, was a mild skin irritant.
From the Final Report on the Safety Assessment of Cocamide, Lauramide, Linoleamide, and Oleamide DEA[2]

Sensitization

Human

Cocamide DEA

Numerous provocative studies were performed, mostly using patients with occupational exposure to cocamide DEA, to evaluate the sensitization potential of cocamide DEA. Concentrations of 0.01-10% were tested. Positive results were seen in all eight studies. However, during discussion by the Panel, it was noted 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 concerns.
From the Amended Final Report on the Safety Assessment of Cocamide DEA[1]

An in-use study was performed with a shampoo containing 2% cocamide DEA using 104 female subjects. The subjects were patch tested with 2% aq. shampoo before and 10 days after 87 days of using the shampoo. The shampoo containing 2% cocamide DEA was an irritant, but not a sensitizer.
From the Final Report on the Safety Assessment of Cocamide, Lauramide, Linoleamide, and Oleamide DEA[2]

Lauramide DEA

Six repeat insult patch tests (RIPTs) using 41-159 subjects were performed on formulations containing 4-10% lauramide DEA, as 0.25-1.25% solutions. Lauramide DEA was not a sensitizer in any of the studies.
From the Final Report on the Safety Assessment of Cocamide, Lauramide, Linoleamide, and Oleamide DEA[2]

Linoleamide DEA

In an RIPT conducted with 100% linoleamide DEA on 100 subjects, no irritation or sensitization reactions were observed. A dandruff shampoo containing 1.5% linoleamide DEA, tested as a 1% aq. solution in a RIPT using 101 subjects, was an irritant, but not a sensitizer.
From the Final Report on the Safety Assessment of Cocamide, Lauramide, Linoleamide, and Oleamide DEA[2]

Co-Reactivity

Cocamide DEA

Thirty-five patients that had positive patch tests to cocamidopropyl betaine, amidoamine, or both, were tested for co-reactivity with cocamide DEA.[31] Two of the patients (5.7%) had positive reactions to cocamide DEA.

Case Studies

Cocamide DEA

One patient with dermatitis on the hands and face, and two with dermatitis on the hands and forearms, were patch tested using the North American Contact Dermatitis Group standard tray and some additional chemicals.[32] The three patients had either personal or industrial exposure to cocamide DEA-containing products. All three had positive patch test results (2+) to cocamide DEA, and two had reactions to several other chemicals. In all patients, the dermatitis cleared with avoidance of DEA-containing products.

Undecylenamide DEA

One patient with dermatitis of the hands and axillae had positive test reaction to a liquid soap.[33] Subsequent testing with 0.1 and 1% aq. undecylenamide DEA, an ingredient in the soap, gave positive reactions. In 10 control subjects, testing with 0.1% undecylenamide DEA was negative.

Phototoxicity/Photosensitization

Human

Lauramide DEA

A liquid soap containing 10% lauramide DEA, tested as a 10% aq. solution in 25 subjects, was not phototoxic. In a photo-sensitivity study of a liquid soap containing 10% lauramide DEA, tested as a 1% aq. solution in 25 subjects, slight irritation was seen in 9 subjects at induction and 4 at challenge, but the test substance was not a photosensitizer.
From the Final Report on the Safety Assessment of Cocamide, Lauramide, Linoleamide, and Oleamide DEA[2]

Ocular Irritation

In Vitro

Cocamide DEA

The ocular irritation potential of cocamide DEA was evaluated in the EpiOcular tissue model, and the irritation classification was compared to the results of a Draize test.[34] In the assay, a 10% solution was classified as a non- to minimal ocular irritant. This result was similar to a non-irritant score obtained in the Draize test.

Myristamide DEA

The irritation potential of various concentrations of myristamide DEA was evaluated in a neutral red assay. The IC_{50} values in Chinese hamster fibroblast V79 cells, rabbit corneal cells, and human epidermal keratinocytes were 15.2, 23.9, and 6.2 µg/ml, respectively. The DS_{20} (concentration predicted to produce a Draize score of 20/110) was 14.4% w/w myristamide DEA.

From the Final Report on Isostearamide DEA & MEA, Myristamide DEA & MEA, and Stearamide DEA & MEA[3]

Non-Human

Cocamide DEA

A substance composed of >64% cocamide DEA and <29% DEA was a severe irritant in rabbit eyes.
From the Amended Final Report on the Safety Assessment of Cocamide DEA[1]

Cocamide DEA, 30% in propylene glycol, was at least a mild eye irritant in rabbits.
From the Final Report on the Safety Assessment of Cocamide, Lauramide, Linoleamide, and Oleamide DEA[2]

Lauramide DEA

Five ocular irritation studies were performed in rabbits with lauramide DEA at concentrations of 1-25% One percent aq. lauramide DEA was mildly irritating, 5% was slightly to moderately irritating, 10-20% was moderately irritating, and 25% was moderately to severely irritating. One bubble bath formulation containing 6% lauramide DEA was practically non-irritating, while another was moderately irritating, and three shampoo formulations containing 8% lauramide DEA were non- to moderately irritating. In a mucous membrane irritation test, a soap containing 10% lauramide DEA was significantly more irritating than water to vaginal mucosa of rabbits.
From the Final Report on the Safety Assessment of Cocamide, Lauramide, Linoleamide, and Oleamide DEA[2]

Stearamide DEA

A mixture containing 35-40% stearamide DEA was not-irritating to rabbit eyes.
From the Final Report on Isostearamide DEA & MEA, Myristamide DEA & MEA, and Stearamide DEA & MEA[3]

Isostearamide DEA

A formulation containing 8.0% isostearamide DEA was a moderate irritant in rabbit eyes.
From the Final Report on Isostearamide DEA & MEA, Myristamide DEA & MEA, and Stearamide DEA & MEA[3]

Oleamide DEA

Undiluted oleamide DEA was practically non-irritating to rabbit eyes.
From the Final Report on the Safety Assessment of Cocamide, Lauramide, Linoleamide, and Oleamide DEA[2]

Linoleamide DEA

Linoleamide DEA, 10% aq, was practically non-irritating to rabbit eyes, while the undiluted test article was minimally to moderately irritating. A product containing 1.5% linoleamide DEA, applied as a 25% aq solution, and a formulation containing 15% linoleamide DEA, were moderate eye irritants in rabbits, while a formulation containing 15% linoleamide DEA, applied as a 25% aq. solution, was mildly irritating.
From the Final Report on the Safety Assessment of Cocamide, Lauramide, Linoleamide, and Oleamide DEA[2]

Ricinoleamide DEA

Undiluted PEG-20 glyceryl ricinoleate + ricinoleamide DEA was evaluated for ocular irritation using NZW rabbits.[28] No signs of irritation were observed, and the surfactant was a non-irritant.

SUMMARY

This report assesses the safety of cocamide DEA and 32 additional DEA amides as used in cosmetics. Some of these ingredients have been previously reviewed by the CIR, and are included here to create a report on the complete family of ingredients.

Amidases, such as fatty acid amide hydrolase which is known to be present in human skin, could potentially convert the DEA amides to DEA and the corresponding fatty acids. The yield of DEA from metabolism of DEA amides in human skin is unknown.

The DEA amides generally have some amount of free DEA, and that amount can vary greatly by ingredient. For example, in the NTP studies, it was estimated that oleamide DEA contained 0.19% free DEA, while cocamide DEA contained 18.2% free DEA by weight.

Cocamide DEA is reported to function in cosmetic formulations as a surfactant-foam booster or a viscosity increasing agent. Most of the other DEA amides are reported to have these same functions, although a few are reported to function as a hair conditioning agent, skin conditioning agent, surfactant-cleansing or emulsifying agent, or an opacifying agent.

VCRP data obtained in 2011 indicate that cocamide DEA is used in 710 cosmetic formulations, the majority of which are rinse-off formulations. With the exception of lauramide DEA, which is reported to be used in 281 cosmetic formulations, the remaining DEA amides have less than 35 uses, and most are not reported to be used. The reported concentration of use of the DEA amides ranges from 0.2-12%; the greatest leave-on concentration reported was 9%. Fatty acid dialkanolamides are allowed for use in products in Europe with restrictions; the restrictions address secondary amine content.

[^{14}C]Lauramide DEA partitioned well into rat and human liver slices, and the absorbed radioactivity was mostly unchanged lauramide DEA. In the media, 18-42% of the radioactivity was present in the form of metabolites. Using microsomes to compare hydroxylation, lauramide DEA 12-hydroxylase activity in human liver microsomes was similar to that in rat liver microsomes, but three times the rate observed in rat kidney microsomes.

Mice and rats were exposed dermally to 5-800 mg/kg and 25 or 400 mg/kg [^{14}C]lauramide DEA, respectively. In rats, absorption was similar for each dose when calculated as a percentage of dose, and absorption was greater in mice (50-70% of the applied dose) than in rats (20-24%). In rats, the parent compound and the half-acid amide metabolites were detected in the plasma. Repeated application of 25 mg/kg/day lauramide DEA did not appear to affect absorption or excretion. In rats dosed orally with 1000 mg/kg [^{14}C]lauramide DEA, 4% of the dose was recovered in the tissues and 79% in the urine after 72 h; at 6 h, no DEA, DEA metabolites, or unchanged lauramide DEA were found in the urine; only very polar metabolites were found. With i.v. dosing, a 50 mg/kg dose of lauramide DEA was quickly metabolized and eliminated by mice; approximately 95% of the dose was excreted in the urine in 24 h. More than 80% of a 25 mg/kg dose was excreted in the urine by rats in 24 h.

Acute dermal testing with 50% lauramide DEA and undiluted and 10% aq linoleamide DEA and acute oral testing with several fatty acid DEA amides did not result in significant toxicity.

In repeated dose dermal studies with cocamide, lauramide, and oleamide DEA in mice and/or rats, irritation was observed at the site of application. Increases in liver and kidney weights were observed in most studies, while decreases in body weight were observed sporadically. The incidence of renal tubule regeneration was greater in female rats dosed with 100-400 mg/kg cocamide DEA when compared to controls. A formulation containing 3% linoleamide DEA was not a cumulative systemic toxicant in a 13-wk dermal study; dermal irritation was observed.

With repeat oral dosing of lauramide DEA, the NOEL was 0.1% in the diet in a study with SPF rats and 250 mg/kg/day in a feeding study using Wistar rats. The NOEL for Beagle dogs fed lauramide DEA for 12 wks was 5000 ppm.

Data on the reproductive and developmental toxicity of the DEA amides were not found. Available reproductive and developmental toxicity data on DEA and some of the fatty acids from previous CIR reports were summarized, and no significant toxic effects were noted.

Cocamide DEA, lauramide DEA, and oleamide DEA were, generally, non-genotoxic in a number of assays. Exceptions were an increase in the frequency of micronucleated erythrocytes in mice by cocamide DEA and the induction of SCEs in CHO cells by lauramide DEA.

The carcinogenic potential of dermally applied cocamide, lauramide, and oleamide DEA was evaluated in B6C3F$_1$ mice and F344/N rats by the NTP. (The doses tested are included in parentheses). Cocamide DEA produced clear evidence of carcinogenic activity in male and female mice (100-200 mg/kg) based on increased incidences of hepatic and renal tubule neoplasms, equivocal evidence in female rats (50-100 mg/kg) based on a marginal increase in the incidences of renal tubule neoplasms, and no evidence in male rats (50-100 mg/kg). Lauramide DEA produced some evidence of carcinogenic activity in female mice (100-200 mg/kg), based on increased incidences of hepatocellular neoplasms, and no evidence in male mice (100-200 mg/kg) or male and female rats (50-100 mg/kg). Oleamide DEA produced no evidence of carcinogenic activity in male or female mice (15-30 mg/kg) or male or female rats (50-100 mg/kg).

The dermal irritation of fatty acid DEA amides, in non-human and human testing, varied greatly with formulation and test conditions. Lauramide DEA and linoleamide DEA were not sensitizers in humans. Cocamide DEA, 0.01-10%, produced positive results in provocative sensitization studies. Lauramide DEA was not phototoxic in humans. The ocular irritation of fatty acid also varied greatly with formulation and test conditions.

DISCUSSION

Cocamide DEA previously has been reviewed by the CIR. On consideration of the available new data and the likelihood that the available data would also support the safety of other related DEA amides, the Panel agreed to re-open the safety assessment of cocamide DEA to add 32 similar DEA amides. Some of the ingredients included in this re-review, specifically isostearamide DEA, lauramide DEA, linoleamide DEA, myristamide DEA, oleamide DEA, and stearamide DEA, themselves have been reviewed by the CIR. These previously reviewed ingredients are included in order to create a complete presentation of DEA amides used in cosmetics in one report. The conclusions regarding the safety of each of these ingredients were essentially the same, but the wording varied between reports; the conclusions on each of these ingredients will now be consistent.

While the Panel noted gaps in the available safety data for many of the DEA amides included in this group, the Panel was able to extrapolate the existing data, including the data from previous CIR assessments as well as data that has come available since those assessments have been published, to support the safety of all the DEA amides included in this safety assessment. Those data could be read-across to support the safety of these ingredients due to similar structure activity relationships and biological function.

A specific concern of the Panel was the lack of reproductive and developmental toxicity data for any of the DEA amides. Since DEA may be present as an impurity in the DEA amides, and since amidases in the skin might convert some of the DEA amide to DEA and the corresponding fatty acid, the Panel determined that data from the CIR safety assessment on DEA as well as from assessments on the other "components" could be used to resolve this issue. The Panel considered that ample data were available demonstrating that DEA is not a reproductive or developmental toxicant.

The Panel was also concerned with levels of free DEA that could be present as an impurity in DEA amides. It was the opinion of the Panel that the "clear evidence of carcinogenic activity" of cocamide DEA reported for male and female mice and the "equivocal evidence of carcinogenic activity" of cocamide DEA reported in female rats, as well as "some evidence of carcinogenic activity" of lauramide DEA in female mice, was due to the presence of free DEA. This opinion was supported by the fact that in carcinogenicity studies on cocamide DEA, lauramide DEA, and oleamide DEA, the level of carcinogenic activity in the DEA amides corresponded to the amount of free DEA found in the test substance.

The Panel was also concerned that free DEA present as an impurity in the DEA amides could be converted (nitrosated) into *N*-nitrosamines that may be carcinogenic. Because of the potential for this process to occur, DEA amides should not be used in cosmetic products in which N-nitroso compounds are formed.

For the reasons described above, the Panel stated that the amount of free DEA available in DEA amides must be limited to no more than that considered safe by the Panel, as described in the CIR report on DEA. (The CIR report on DEA includes a discussion regarding carcinogenic potential of DEA in animals compared to the relevance in humans).

The Expert Panel was concerned that the potential exists for dermal irritation with the use of products formulated using DEA amides. The Expert Panel specified that products must be formulated to be non-irritating.

DEA amides are used in cosmetic products that may be inhaled during use. In practice, however, the particle sizes produced by cosmetic aerosols are not respirable.

CONCLUSION

The CIR Expert Panel concluded that the cocamide-DEA and the 32 DEA amides, listed below, are safe when formulated to be non-irritating. Were ingredients in this group not in current use (as indicated by *) to be used in the future, the expectation is that they would be used at concentrations that

would be formulated to be non-irritating. The Expert Panel cautions that products containing these ingredients should be formulated to avoid the formation of nitrosamines. The ingredients reviewed in this safety assessment are:

Almondamide DEA*
Apricotamide DEA*
Avocadamide DEA*
Babassuamide DEA*
Behenamide DEA*
Capramide DEA
Cornamide DEA*
Cornamide/Cocamide DEA*
Hydrogenated Tallowamide DEA*
Isostearamide DEA
Lanolinamide DEA*
Lauramide DEA
Lauramide/Myristamide DEA
Lecithinamide DEA*
Linoleamide DEA
Minkamide DEA*
Myristamide DEA
Oleamide DEA
Olivamide DEA*
Palm Kernelamide DEA
Palmamide DEA*
Palmitamide DEA*
Ricebranamide DEA*
Ricinoleamide DEA*
Sesamide DEA*
Shea Butteramide/Castoramide DEA*
Soyamide DEA
Stearamide DEA
Tallamide DEA*
Tallowamide DEA*
Undecylenamide DEA*
Wheat Germamide DEA*

TABLES

Table 1. Conclusions of previously reviewed ingredients and components

Ingredient	Conclusion	Reference
	PREVIOUSLY REVIEWED INGREDIENTS	
Cocamide DEA	safe as used in rinse-off products; safe at concentrations ≤10% in leave-on products; should not be used as an ingredient in cosmetic products in which *N*-nitroso compounds are formed	1
Isostearamide DEA	safe for use in rinse-off products; in leave-on products, safe for use at a concentration that will limit the release of free ethanolamines to 5%, with a maximum use concentration of 40%	3
Lauramide DEA	safe as used; should not be used in products containing nitrosating agents	2
Linoleamide DEA	safe as used; should not be used in products containing nitrosating agents	2
Myristamide DEA	safe for use in rinse-off products; in leave-on products, safe for use at a concentration that will limit the release of free ethanolamines to 5%, with a maximum use concentration of 40%	3
Oleamide DEA	safe as used; should not be used in products containing nitrosating agents	2
Stearamide DEA	safe for use in rinse-off products; in leave-on products, safe for use at a concentration that will limit the release of free ethanolamines to 5%, with a maximum use concentration of 40%	3
	COMPONENTS	
DEA (likely an impurity)	**current Tentative conclusion:** DEA and its salts, except for DEA lauraminopropionate, are safe in the present practices of use and concentration when formulated to be non-irritating; these ingredients should not be used in cosmetic products in which N-nitroso compounds are formed; the available data are insufficient to conclude that DEA-Lauraminopropionate is safe under the intended conditions of use	22
Butyrospermum Parkii (Shea) Butter	safe as used	35
Coconut Acid	safe as used	35
Corn Acid	safe as used	35
Elaeis Guineensis (Palm) Kernel Oil Elaeis Guineensis (Palm) Oil	safe as used	35
Isostearic Acid	safe as used	36
Lanolin Acid	safe as used in topical applications	37
Lauric Acid	safe as used	38
Lecithin	safe as used in rinse-off products; safe for use in leave-on products at concentrations of ≤15%; and the data were **insufficient to determine the safety for use in products where lecithin is likely to be inhaled**; should not be used in cosmetic products in which N-nitroso compounds may be formed	23
Mink Oil	safe as used	39
Myristic Acid	safe as used	40
Olea Europaea (Olive) Fruit Oil	safe as used	35
Oleic Acid	safe as used	38
Orbignya Oleifera (Babassu) Oil	safe as used	35
Palmitic Acid	safe as used	38
Persea Gratissima (Avocado) Oil	safe as used	35
Prunus Amygdalus Dulcis (Sweet Almond) Oil	safe as used	35
Prunus Armeniaca (Apricot) Kernel Oil	safe as used	35
Rice Bran Acid	safe as used	35
Ricinoleic Acid	safe as used	25
Ricinus Communis (Castor) Seed Oil	safe as used	25
Sesamum Indicum (Sesame) Oil	safe as used	35
Soy Acid	safe as used	35
Stearic Acid	safe as used	38
Tall Oil Acid	safe as used	27
Tallow	safe as used	41
Wheat Germ Acid	safe as used	35
Zea Mays (Corn) Oil	safe as used	35

Table 2. Definitions and Structures

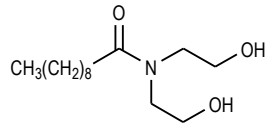
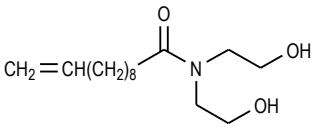
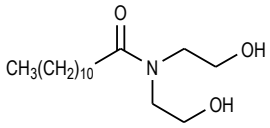
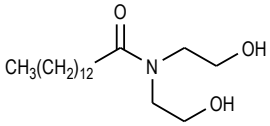
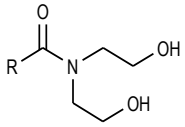
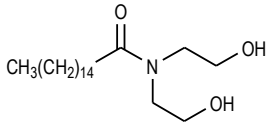
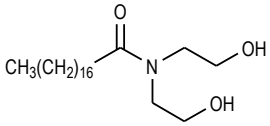
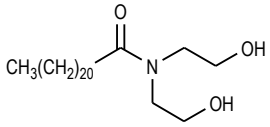
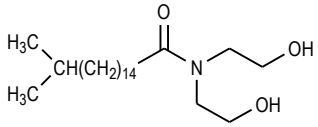
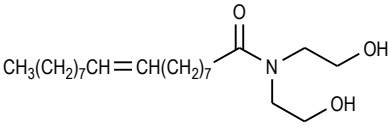
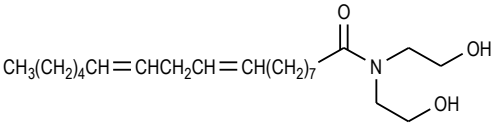
Ingredient CAS No.	Definition	Function(s)	Formula/structure
-Alkyl amides			
Capramide DEA 136-26-5	a mixture of ethanolamides of capric acid	Surf. - Foam Boosters; Visc. Incr. Ag. - Aq.	
Undecylenamide DEA 60239-68-1 25377-64-4	a mixture of ethanolamides of undecylenic acid	Hair Cond. Ag.; Surf. - Foam Boosters; Visc. Incr. Ag. - Aq.	
Lauramide DEA 120-40-1	a mixture of ethanolamides of lauric acid	Surf. - Foam Boosters	
Myristamide DEA 7545-23-5	a mixture of ethanolamides of myristic acid	Surf. - Foam Boosters; Visc. Incr. Ag. - Aq.	
Lauramide/ Myristamide DEA	a mixture of ethanolamides of a blend of lauric and myristic acids	Surf. - Foam Boosters; Visc. Incr. Ag. - Aq.	 wherein RC(O) represents a 12 or 14 carbon fatty acid residue
Palmitamide DEA 7545-24-6	a mixture of ethanolamides of palmitic acid.	Surf. - Foam Boosters; Visc. Incr. Ag. - Aq.	
Stearamide DEA 93-82-3	a mixture of ethanolamides of stearic acid.	Surf. - Foam Boosters; Visc. Incr. Ag. - Aq.	
Behenamide DEA 70496-39-8	a mixture of ethanolamides of behenic acid	Hair Cond. Ag.; Surf. - Foam Boosters; Visc. Incr. Ag. - Aq.	
-Branched			
Isostearamide DEA 52794-79-3	a mixture of ethanolamides of isostearic acid	Surf. - Foam Boosters; Visc. Incr. Ag. - Aq.	 one example of an “iso”
-Partially unsaturated			
Oleamide DEA 5299-69-4 93-83-4	a mixture of ethanolamides of oleic acid	Surf. - Foam Boosters; Visc. Incr. Ag. - Aq.	
Linoleamide DEA 56863-02-6	a mixture of ethanolamides of linoleic acid	Hair Cond. Ag.; Surf. - Foam Boosters; Visc. Incr. Ag. - Aq.; Hair Cond. Ag.; Surf. - Foam Boosters; Visc. Incr. Ag. - Aq.	

Table 2. Definitions and Structures

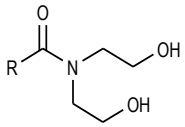
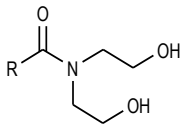
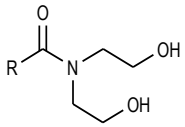
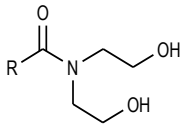
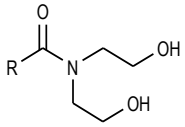
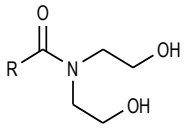
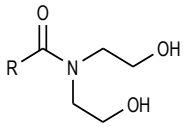
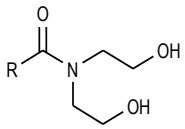
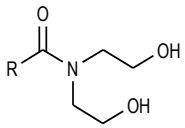
Ingredient CAS No.	Definition	Function(s)	Formula/structure
-Natural source mixtures			
Almondamide DEA 124046-18-0	a mixture of ethanolamides of the fatty acids derived from almond oil	Surf. - Foam Boosters; Visc. Incr. Ag. - Aq.	 wherein RC(O) represents the fatty acid residues derived from almond oil
Apricotamide DEA 185123-36-8	a mixture of ethanolamides of the fatty acids derived from Prunus Armeniaca (Apricot) Kernel Oil	Surf. - Foam Boosters; Visc. Incr. Ag. - Aq.	 wherein RC(O) represents the fatty acid residues derived from Prunus Armeniaca (Apricot) Kernel Oil
Avocadamide DEA 124046-21-5	a mixture of ethanolamides of the fatty acids derived from Persea Gratissima (Avocado) Oil	Surf. - Foam Boosters; Visc. Incr. Ag. - Aq.	 wherein RC(O) represents the fatty acid residues derived from Persea Gratissima (Avocado) Oil
Babassuamide DEA 124046-24-8	a mixture of ethanolamides of the fatty acids derived from Orbignya Oleifera (Babassu) Oil	Hair Cond. Ag.; Surf. - Foam Boosters; Visc. Incr. Ag. - Aq.	 wherein RC(O) represents the fatty acid residues derived from Orbignya Oleifera (Babassu) Oil
Cocamide DEA 61791-31-9	a mixture of ethanolamides of coconut acid	Surf. - Foam Boosters; Visc. Incr. Ag. - Aq.	 wherein RC(O) represents the fatty acid residues derived from coconut acid
Cornamide DEA	a mixture of ethanolamides of corn acid	Surf. - Foam Boosters; Visc. Incr. Ag. - Aq.	 wherein RC(O) represents the fatty acid residues derived from corn acid
Cornamide/ Cocamide DEA	the diethanolamide of a mixture of coconut acid and the fatty acids obtained from Zea Mays (Corn) Oil	Surf. - Foam Boosters; Visc. Incr. Ag. - Aq.	 wherein RC(O) represents the fatty acid residues derived from coconut acid and Zea Mays (Corn) Oil
Hydrogenated Tallowamide DEA 68440-32-4	a mixture of ethanolamides of the fatty acids derived from hydrogenated tallow	Surf. - Foam Boosters; Visc. Incr. Ag. - Aq.	 wherein RC(O) represents the fatty acid residues derived from hydrogenated tallow
Lanolinamide DEA [85408-88-4]	a mixture of ethanolamides of Lanolin Acid	Surf. - Foam Boosters; Visc. Incr. Ag. - Aq.	 wherein RC(O) represents the fatty acid residues derived from lanolin acid

Table 2. Definitions and Structures

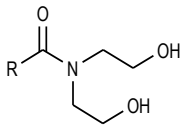
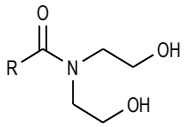
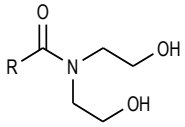
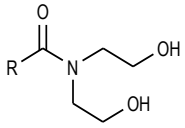
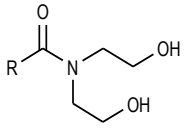
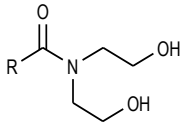
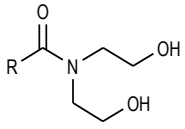
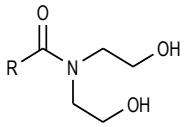
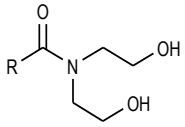
Ingredient CAS No.	Definition	Function(s)	Formula/structure
Lecithinamide DEA	the mixture of reaction products of DEA and the fatty acids of lecithin.	Hair Cond. Ag.; Surf. - Foam Boosters; Visc. Incr. Ag. - Aq.	 wherein RC(O) represents the fatty acid residues derived from lecithin
Minkamide DEA 124046-27-1	a mixture of ethanolamides of the fatty acids derived from mink oil.	Surf. - Foam Boosters; Visc. Incr. Ag. - Aq.	 wherein RC(O) represents the fatty acid residues derived from mink oil
Olivamide DEA 124046-30-6	a mixture of ethanolamides of the fatty acids derived from olive oil	Surf. - Foam Boosters; Visc. Incr. Ag. - Aq.	 wherein RC(O) represents the fatty acid residues derived from olive oil
Palm Kernelamide DEA 73807-15-5	a mixture of ethanolamides of the fatty acids derived from Elaeis Guineensis (Palm) Kernel Oil	Surf. - Foam Boosters; Visc. Incr. Ag. - Aq.	 wherein RC(O) represents the fatty acid residues derived from Elaeis Guineensis (Palm) Kernel Oil
Palmamide DEA	a mixture of ethanolamides of the fatty acids derived from Elaeis Guineensis (Palm) Oil	Surf. - Foam Boosters; Visc. Incr. Ag. - Aq.	 wherein RC(O) represents the fatty acid residues derived from Elaeis Guineensis (Palm) Oil
Ricebranamide DEA	a mixture of ethanolamides of rice bran acid	Surf. - Foam Boosters; Visc. Incr. Ag. - Aq.	 wherein RC(O) represents the fatty acid residues derived from rice bran acid
Ricinoleamide DEA 40716-42-5	a mixture of ethanolamides of ricinoleic acid	Surf. - Foam Boosters; Visc. Incr. Ag. - Aq.	 wherein RC(O) represents the ricinoleic acid residue
Sesamide DEA 124046-35-1	a mixture of diethanolamides of the fatty acids derived from Sesamum Indicum (Sesame) Oil	Surf. - Foam Boosters; Visc. Incr. Ag. - Aq.	 wherein RC(O) represents the fatty acid residues derived from Sesamum Indicum (Sesame) Oil
Shea Butteramide/Castoramide DEA	a mixture of diethanolamides of the fatty acids derived from Butyrospermum Parkii (Shea Butter) and Ricinus Communis (Castor) Seed Oil	Visc. Incr. Ag. - Aq.	 wherein RC(O) represents the fatty acid residues derived from Butyrospermum Parkii (Shea Butter) and Ricinus Communis (Castor) Seed Oil

Table 2. Definitions and Structures

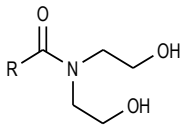
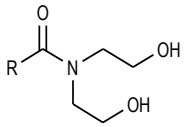
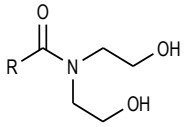
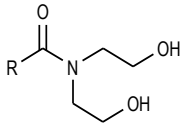
Ingredient CAS No.	Definition	Function(s)	Formula/structure
Soyamide DEA 68425-47-8	a mixture of ethanolamides of soy acid	Surf. - Foam Boosters; Visc. Incr. Ag. - Aq.	 wherein RC(O) represents the fatty acid residues derived from soy acid
Tallamide DEA 68155-20-4	a mixture of ethanolamides of the fatty acids derived from tall oil acid	Surf. - Foam Boosters; Visc. Incr. Ag. - Aq.	 wherein RC(O) represents the fatty acid residues derived from tall oil acid
Tallowamide DEA 68140-08-9	a mixture of ethanolamides of tallow acid	Surf. - Foam Boosters; Visc. Incr. Ag. - Aq.	 wherein RC(O) represents the fatty acid residues derived from tallow acid
Wheat Germamide DEA 124046-39-5	a mixture of diethanolamides of wheat germ acid	Surf. - Foam Boosters; Visc. Incr. Ag. - Aq.	 wherein RC(O) represents the fatty acid residues derived from wheat germ acid

Table 3. Physical and chemical properties

Property	Value	Reference
	Cocamide DEA	
Physical Form	clear viscous liquid	1,8
Color	amber or yellow	1,8
Odor	faint coconut	1
Molecular Weight	280-290	8
Melting Point	23-35°C	1
Water Solubility	soluble in water	1
pH (10% aq. solution)	9.5-10.5	1
Acid Value	3.0 max	1
	Capramide DEA	
Molecular Weight	259.39	42
Density (predicted)	1.001 ± 0.06 g/cm^3	42
Boiling Point (predicted)	417.9 ±30.0°C	42
log P (predicted)	3.014 ±0.270	42
	Undecylenamide DEA	
Molecular Weight	271.40	42
Density (predicted)	1.002 ± 0.06 g/cm^3	42
Boiling Point (predicted)	440.4 ±40.0°C	42
	Lauramide DEA	
Physical Form	viscous liquid or waxy solid	7
Color	light yellow (liquid) or white to light yellow (solid)	2
Odor	faint, characteristic	2
Molecular Weight	287.44	42
Density	0.984 ± 0.06 g/cm^3 (at 20°C)	42
Refractive Index	1.4708 (n30/L)	2
Melting Point	37-47°C	2
Boiling Point	443.2 ± 0.270°C	42
Water Solubility	dispersible	2
pH (10% aq. dispersion)	9.8-10.8	2
Acid Value	0.1-14	2
Alkaline Value	6-200	2
log P (predicted)	4.033 ± 0.270 (at 25°C)	42
pK_a	14.13 (at 25°C)	42
pK_b	-0.85 (at 25°C)	
	Myristamide DEA	
Physical Form	waxy solid	3
Color	white to off-white	3
Melting Point	40-54°C	3
Water Solubility	dispersible	3
Other Solubility	soluble in alcohol, chlorinated hydrocarbons, and aromatic hydrocarbons; dispersible in mineral spirits, kerosene, white mineral oils, and natural fats and oils	3
pH (10% aq. dispersion)	9.5-10.5	3
log P (predicted)	5.025±0.270	42
Acid Value	1 (max)	3
Alkaline Value	26-50	3
	Palmitamide DEA	
Molecular Weight	343.54	42
Density (predicted)	0.959 ± 0.06 g/cm^3 (20°C)	42
Boiling Point (predicted)	492.5 ±30.0°C	42
log P (predicted)	6.071 ±0.270	42
	Stearamide DEA	
Physical Form	wax-like solid	3
Color	white to pale yellow	3
Molecular Weight	371.60	42
Density (predicted)	0.959 ± 0.06 g/cm^3 (20°C)	42
pH (1% aq. dispersion)	9-10	3
log P (predicted)	7.090 ±0.270	42
	Behenamide DEA	
Molecular Weight	427.70	42
Density (predicted)	0.935 ± 0.06 g/cm^3 (20°C)	42
Boiling Point (predicted)	562.1 ±30.0°C	42
log P (predicted)	9.128 ±0.270	42

Table 3. Physical and chemical properties (continued)

Property	Value	Reference
	Oleamide DEA	
Physical Form	liquid	2
Color	amber	2
Molecular Weight	387.68	10
Specific Gravity	0.99 (25/25°C)	2
Phase Transition	congeals at -8°C	2
Boiling Point (predicted)	525.6 ±45.0°C	42
Water Solubility	dispersible	2
Other Solubility	soluble in alcohols, glycols, ketones, esters, benzenes, chlorinated solvents, and aliphatic hydrocarbons	2
pH	9-10	2
log P (predicted)	6.681 ±0.275	42
	Linoleamide DEA	
Physical Form	syrup-like liquid or wax-like mass	2
Color	light yellow (liquid) or white to yellow (mass)	2
Odor	characteristic	2
Specific Gravity	0.972-0.982 (25°/25°C)	2
Water Solubility	slightly soluble	2
Boiling Point (predicted)	525.6 ±50.0°C	42
Other Solubility	soluble in ethanol, propylene glycol, and glycerin; insoluble in mineral oil	2
Acid Value	2.0 (max)	2
Alkaline Value	25-50 (calculated as DEA)	
log P (predicted)	6.277 ±0.275	42
	Ricinoleamide DEA	
Molecular Weight	385.58	42
Density (predicted)	1.007± 0.06 g/cm^3 (20°C)	42
Boiling Point (predicted)	560.5 ±50.0°C	42
log P (predicted)	4.867 ±0.289	42

Table 4a. Frequency and concentration of use according to duration and type of exposure

	Capramide DEA		Cocamide DEA		Isostearamide DEA	
	# of Uses[12]	*Conc of Use (%)*[13]	*# of Uses*[12]	*Conc of Use (%)*[13]	*# of Uses*[12]	*Conc of Use (%)*[13]
Totals*	**1**	**NR**	**710**	**0.5-7**	**2**	**NR**
Duration of Use						
Leave-On	*NR*	*NR*	*37*	*0.5-6*	*2*	*NR*
Rinse Off	*1*	*NR*	*596*	*1-7*	*NR*	*NR*
Diluted for Use	*NR*	*NR*	*77*	*0.46*	*NR*	*NR*
Exposure Type						
Eye Area	NR	NR	2	NR	NR	NR
Possible Ingestion	NR	NR	NR	NR	NR	NR
Inhalation	NR	NR	1	NR	NR	NR
Dermal Contact	NR	NR	338	0.5-6	2	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	1	NR	212	1-7	NR	NR
Hair-Coloring	NR	NR	147	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	197	2-4	NR	NR
Bath Products	NR	NR	77	6	NR	NR
Baby Products	NR	NR	10	2	NR	NR

	Lauramide DEA		Lauramide/Myristamide DEA		Linoleamide DEA	
	# of Uses[12]	*Conc of Use (%)*[13]	*# of Uses*[12]	*Conc of Use (%)*[13]	*# of Uses*[12]	*Conc of Use (%)*[13]
Totals*	**281**	**0.2-9**	**1**	**NR**	**32**	**1-12**
Duration of Use						
Leave-On	*21*	*0.2-9*	*NR*	*NR*	*3*	*NR*
Rinse-Off	*232*	*0.2-8*	*1*	*NR*	*19*	*1-12*
Diluted for Use	*28*	*2-8*	*NR*	*NR*	*10*	*3*
Exposure Type						
Eye Area	NR	NR	NR	NR	NR	NR
Possible Ingestion	NR	NR	NR	NR	NR	NR
Inhalation	12	0.3-9	NR	NR	1	NR
Dermal Contact	165	0.2-9	1	NR	21	1-3
Deodorant (underarm)	1	2	NR	NR	NR	NR
Hair - Non-Coloring	115	0.3-8	NR	NR	4	3-7
Hair-Coloring	2	0.2	NR	NR	7	7-12
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	111	0.2-4	NR	NR	7	7
Bath Products	28	2-8	NR	NR	10	3
Baby Products	1	NR	NR	NR	NR	NR

Table 4a. Frequency and concentration of use according to duration and type of exposure

	Myristamide DEA		Oleamide DEA		Palm Kernelamide DEA	
	# of Uses[12]	*Conc of Use (%)*[13]	*# of Uses*[12]	*Conc of Use (%)*[13]	*# of Uses*[12]	*Conc of Use (%)*[13]
Totals*	**NR**	**0.8**	**5**	**5**	**4**	**2**
Duration of Use						
Leave-On	*NR*	*NR*	*3*	*NR*	*NR*	*NR*
Rinse Off	*NR*	*0.8*	*2*	*5*	*4*	*2*
Diluted for Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	NR	NR	NR	NR	NR	NR
Possible Ingestion	NR	NR	NR	NR	NR	NR
Inhalation	NR	NR	NR	NR	NR	NR
Dermal Contact	NR	0.8	4	NR	NR	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	1	5	4	2
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	0.8	NR	NR	NR	NR
Bath Products	NR	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR

	Soyamide DEA		Stearamide DEA	
	# of Uses[12]	*Conc of Use (%)*[13]	*# of Uses*[12]	*Conc of Use (%)*[13]
Totals*	**1**	**NR**	**10**	**0.5**
Duration of Use				
Leave-On	*NR*	*NR*	*9*	*NR*
Rinse-Off	*1*	*NR*	*1*	*0.5*
Diluted for Use	*NR*	*NR*	*NR*	*NR*
Exposure Type				
Eye Area	NR	NR	NR	NR
Possible Ingestion	NR	NR	NR	NR
Inhalation	NR	NR	NR	NR
Dermal Contact	NR	NR	9	NR
Deodorant (underarm)	NR	NR	NR	NR
Hair - Non-Coloring	1	NR	1	0.5
Hair-Coloring	NR	NR	NR	NR
Nail	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR
Bath Products	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR

* Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types my not equal the sum of total uses.
NR – none reported

Table 4b. Ingredients not reported to be in use

Almondamide DEA
Apricotamide DEA
Avocadamide DEA
Babassuamide DEA
Behenamide DEA
Cornamide DEA
Cornamide/Cocamide DEA
Hydrogenated Tallowamide DEA
Lactamide DEA
Lanolinamide DEA
Lecithinamide DEA
Minkamide DEA
Olivamide DEA
Palmamide DEA
Palmitamide DEA
Ricebranamide DEA
Ricinoleamide DEA
Sesamide DEA
Shea Butteramide/Castoramide DEA
Tallamide DEA
Tallowamide DEA
Undecylenamide DEA
Wheat Germamide DEA

Table 5. Status for use in Europe

Fatty Acid Dialkanolamides – listed in Annex III - restrictions[15]
(maximum secondary amine content of 0.5% in the finished product; do not use with nitrosating systems; maximum secondary amine content of 5% for raw materials; maximum nitrosamine content of 50 µg/kg; keep in nitrite free containers)

Almondamide DEA
Apricotamide DEA
Avocadamide DEA
Babassuamide DEA
Behenamide DEA
Capramide DEA
Cocamide DEA
Cornamide DEA
Cornamide/Cocamide DEA
Hydrogenated Tallowamide DEA
Isostearamide DEA
Lanolinamide DEA
Lauramide DEA
Lauramide/Myristamide DEA
Lecithinamide DEA
Linoleamide DEA
Minkamide DEA
Myristamide DEA
Oleamide DEA
Olivamide DEA
Palm Kernelamide DEA
Palmamide DEA
Palmitamide DEA
Ricebranamide DEA
Ricinoleamide DEA
Sesamide DEA
Soyamide DEA
Stearamide DEA
Tallamide DEA
Tallowamide DEA
Undecylenamide DEA
Wheat Germamide DEA

Listed in EC Inventory – no annex specified[16]
Shea Butteramide/Castoramide DEA

Table 6. Conclusions of NTP dermal carcinogenicity studies

	Cocamide DEA[8]	**Lauramide DEA**[7]
amount of free DEA	**18.2%**	**0.83%**
B6C3F$_1$ mice	0, 100, or 200 mg/kg	0, 100, or 200 mg/kg
Males	***clear evidence*** *of carcinogenic activity*	*no evidence of carcinogenic activity*
Basis	increased incidences of hepatic and renal tubule neoplasms	
Females	***clear evidence*** *of carcinogenic activity*	*some evidence of carcinogenic activity*
Basis	increased incidences of hepatic neoplasms	increased incidences of hepatocellular neoplasms
F344/N rats	0, 50, or 100 mg/kg	0, 50, or 100 mg/kg
Males	*no evidence of carcinogenic activity*	*no evidence of carcinogenic activity*
Basis		
Females	***equivocal evidence*** *of carcinogenic activity*	*no evidence of carcinogenic activity*
Basis	marginal increase in the incidences of renal tubule neoplasms	

	Oleamide DEA[10]	**DEA**[43]
amount of free DEA	**0.19%**	**>99% pure**
B6C3F$_1$ mice	0, 15, or 30 mg/kg	0 , 40, 80, and 160 mg/kg
Males	*no evidence of carcinogenic activity*	***clear evidence*** *of carcinogenic activity*
Basis		increased incidences of liver neoplasms and renal tubule neoplasms
Females	*no evidence of carcinogenic activity*	***clear evidence*** *of carcinogenic activity*
Basis		increased incidence of liver neoplasms
F344/N rats	0, 50, or 100 mg/kg	0, 16, 32, and 64 mg./kg
Males	*no evidence of carcinogenic activity*	*no evidence of carcinogenic activity*
Basis		
Females	*no evidence of carcinogenic activity*	*no evidence of carcinogenic activity*
Basis		

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