# FINAL REPORT

# Isostearamide DEA & MEA
# Myristamide DEA & MEA
# Stearamide DEA & MEA
# Acid

## ABSTRACT

*Stearamide DEA & MEA, Isostearamide DEA & MEA, and Myristamide DEA & MEA are all ethanolamides of fatty acids that function as foam boosting surfactants and aqueous viscosity increasing agents in cosmetic products. All except Myristamide MEA are currently used in cosmetic formulations. The maximum concentration of use for these ingredients is 15% in anti-perspirants. There is little data available on toxicity of these ethanolamides. The limited clinical tests show some irritation with formulations containing Stearamide MEA, but no sensitization. Data are available on DEA & MEA and on the fatty acids, however, and these are summarized in this report. The principle toxicity concern is for the ethanolamines, DEA & MEA. Dermal and ocular irritation have been reported, and there is the potential for nitrosation in the presence of N-nitrosating agents. These data were previously reviewed with the conclusion that concentration and other limits are needed to assure their safe use in cosmetic formulations. Estimates of the amounts of ethanolamines that may be released on hydrolysis of Stearamide DEA & MEA, Isostearamide DEA & MEA, and Myristamide DEA & MEA were made and generally expected to be below the concentration limit of 5% previously established. Because only certain concentrations of Stearamide DEA & MEA, Isostearamide DEA & MEA, and Myristamide DEA & MEA were actually tested clinically, these concentrations were considered as the maximum values for which safety could be concluded. On the basis of the available information, it was concluded that Stearamide DEA & MEA, Isostearamide DEA & MEA, and Myristamide DEA & MEA are safe for use in rinse-off products. In leave-on products, it was concluded these ingredients are safe for use at concentrations that limit the release of free ethanolamines to 5%, but that the maximum concentration of Stearamide MEA, Isostearamide MEA, and Myristamide MEA should be 17% and the maximum concentration of Stearamide DEA, Isostearamide DEA, and Myristamide DEA should be 40%. In addition, it was concluded that these ingredients should not be used in cosmetic products in which N-nitroso compounds may be formed.*

## INTRODUCTION

The following report is a review of the safety data on Isostearamide DEA and MEA, Myristamide DEA and MEA, and Stearamide DEA and MEA, which are used in cosmetics as foam boosting surfactants and as aqueous viscosity increasing agents. Chemically, these ingredients are the ethanolamides of Isostearic, myristic, and stearic acid. These basic components were reviewed previously by the Cosmetic Ingredient Review (CIR) Expert Panel and Final Reports have been published (Elder, 1983a; Elder, 1983b; Elder, 1987). The following conclusions were made by the Expert Panel:

*Triethanolamine (TEA), Diethanolamine (DEA) and, Monoethanolamine (MEA) are safe for use in cosmetic formulations designed for discontinuous, brief use followed by thorough rinsing from the surface of the skin. In products intended for prolonged contact with the skin, the concentration of ethanolamines should not exceed 5%. MEA should be used only in rinse-off products. TEA and DEA should not be used*

*in products containing N-nitrosating agents (Elder, 1983a).*

*Isostearic, Myristic, and Stearic Acids are safe in the present practices of use and concentration in cosmetics (Elder, 1983b; Elder, 1987).*

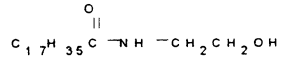
Since there are limited safety data specifically on Isostearamide DEA and MEA, Myristamide DEA and MEA, and Stearamide DEA and MEA, the relevant data from the Final Reports on TEA, DEA, MEA, and Isostearic, myristic, and stearic acid have been extracted and summarized in this review as a basis for the assessment of safety of these six ingredients.

The Expert Panel has reviewed other diethanolamides of fatty acids, specifically Cocamide DEA, Lauramide DEA, Linoleamide DEA, and Oleamide DEA (Elder, 1986). These ingredients were found to be safe for use as cosmetic ingredients, with the caveat that they should not be used in products containing nitrosating agents. Summaries of the data used to reach this conclusion are included at the end of this report.

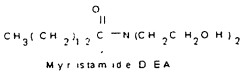
# CHEMISTRY

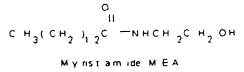
## Definition and Structure

Isostearamide DEA (CAS No. 52794-79-3) and Isostearamide MEA (CAS No. 54536-43-5) are mixtures of ethanolamides of Isostearic Acid (q.v.). Isostearamide DEA has the empirical formula: C22H45NO3, and Isostearamide MEA conforms to the following formula (Wenninger and McEwen, 1993):

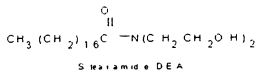


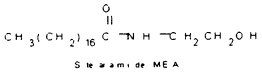
Myristamide DEA (CAS No. 7545-23-5) and Myristamide MEA (CAS No. 142-58-5) are mixtures of ethanolamides of myristic acid conforming to the formulas (Wenninger and McEwen, 1993):




Stearamide DEA (CAS No. 93-82-3) and Stearamide MEA (CAS No. 111-57-9) are mixtures of ethanolamides of stearic acid that conform to the following formulas (Wenninger and McEwen, 1993):




## Chemical and Physical Properties

Myristamide DEA is a white to off-white waxy solid that is a condensation product of myristic acid and diethanolamine. It is soluble in alcohol, chlorinated hydrocarbons and aromatic hydrocarbons and is dispersible in water, mineral spirits, kerosene, white mineral oils, and natural fats and oils. A 10% aq. dispersion of Myristamide DEA has a pH range of 9.5 to 10.5. This ingredient has a melting range of 40-54°C, an alkali value of 26-50, and a maximum acid value of 1 (Nikitakis and McEwen, 1990).

Myristamide MEA is a pale straw to tan colored wax with a faintly soapy odor. It is soluble in water and a 1% aq. solution has a pH range of 8.0-10.0. The melting range of this ingredient is 89-93°C, the maximum acid value is 7.0, the maximum free amine is 1.5%, and the maximum moisture is 0.7% (Nikitakis and McEwen, 1990).

Stearamide DEA is a white to pale yellow, wax-like solid. It is dispersible in water and is soluble in most organic solvents. The pH range of a 1% aq. dispersion ranges from 9 to 10. This compound is characterized by 9-12% free fatty acids (as oleic acid) and 2-6% free amines (as diethanolamine). The maximum amount of moisture for this compound is 1.5%, and the maximum amounts of arsenic and lead are

3 ppm and 20 ppm, respectively (Nikitakis and McEwen, 1990).

Stearamide MEA is also a wax-like solid, with a white to cream color. It has a faint characteristic odor and is soluble in hot alcohol, chlorinated solvents, fats and oils, and is dispersible in water. A 10% aq. dispersion has a pH range of 9.0 to 10.5. The melting point of this ingredient is 86-90°C. It has 0.8% maximum free fatty acids (as stearic acid), 0.5-2.0% free amine (as monoethanolamine), and 54.0-58.0% total fatty acids (as stearic acid). The acid value of separated fatty acids is 200-210. The maximum moisture value is 0.5, and the maximum amounts of arsenic and lead are 3 ppm and 20 ppm, respectively (Nikitakis and McEwen, 1990).

### Analytical Methods

Stearamide MEA and DEA can be separated using high-performance liquid chromatography by employing a porous micro-spherical poly(styrene-divinylbenzene) gel as the stationary phase (Nakae and Kunihiro, 1978).

## USE

### Cosmetic

#### United States

Isostearamide DEA and MEA, Myristamide DEA and MEA, and Stearamide DEA and MEA are used as a foam boosting surfactants and as aqueous viscosity increasing agents in cosmetic formulations (Wenninger and McEwen, 1992). The product formulation data submitted to the Food and Drug Administration (FDA) in 1995 reported that Isostearamide DEA was used in 23 products, Isostearamide MEA in one product, Myristamide DEA in six products, Stearamide DEA in 19 products, and Stearamide MEA in 22 products. There was no listing for Myristamide MEA (Table 1) (FDA, 1995).

The concentrations at which these ingredients are used are unknown because concentration of use values are no longer reported to the FDA by the cosmetic industry (Federal Register, 1992). However, data submitted to CIR by the Cosmetic, Toiletry, and Fragrance Association [CTFA] reported that Isostearamide DEA, Myristamide DEA, and Stearamide DEA and MEA are used in anti-perspirants at a concentration of 15%, in shampoos at a concentration of 6%, in shower gels at a concentration of 5%, and in perms and relaxers at a concentration of 2% (CTFA, 1995). Additionally, product formulation data submitted to the FDA in 1984 stated that Isostearamide DEA, Myristamide DEA, and Stearamide DEA were used at concentrations up to 10% and that Stearamide MEA was used at concentrations up to 25% (FDA, 1984).

### International

Isostearamide DEA, Myristamide DEA, and Stearamide DEA and MEA are approved for use in Japan (Rempe and Santucci, 1992).

The European Union limits the use of fatty acid dialkanolamides to a maximum dialkanolamine content of 0.5% in finished products. These types of ingredients are not to be used with nitrosating systems. Maximum dialkanolamine content in raw material should not exceed 5%, and the maximum allowable N-nitrosodialkanolamine content is 50 µg/kg (EEC Cosmetics Directive, 1993).

## BIOLOGY

### Absorption, Distribution, Metabolism, and Excretion

*MEA is the only naturally occurring ethanolamine in mammals and is excreted in the urine. Much of the available scientific literature on the metabolism of the ethanolamines is concerned with the effect on phospholipid biosynthesis following intraperitoneal and*

TABLE 1

COSMETIC PRODUCT FORMULATION DATA (FDA, 1995)

| Product Category | Total No. Formulations in Category | Total No. of Formulations Containing Ingredient |
|---|---|---|
| | **ISOSTEARAMIDE DEA** | |
| Other bath preparations | 144 | 3 |
| Other eye makeup preparations | 130 | 1 |
| Shampoos (non-coloring) | 916 | 3 |
| Foundations | 333 | 3 |
| Makeup bases | 159 | 3 |
| Makeup fixatives | 11 | 3 |
| Other makeup preparations | 155 | 2 |
| Moisturizing | 873 | 4 |
| Other skin care preparations | 782 | 1 |
| **1995 Total** | | **23** |
| | **ISOSTEARAMIDE MEA** | |
| Shampoos (non-coloring) | 916 | 1 |
| **1995 Total** | | **1** |
| | **MYRISTAMIDE DEA** | |
| Other bath preparations | 144 | 1 |
| Shampoos (non-coloring) | 916 | 4 |
| Bath soaps and detergents | 339 | 1 |
| **1995 Total** | | **6** |
| | **STEARAMIDE DEA** | |
| Hair conditioners | 639 | 4 |
| Shampoos (non-coloring) | 916 | 1 |
| Foundations | 333 | 4 |
| Makeup bases | 159 | 1 |
| Other makeup preparations | 155 | 2 |
| Cleansing preparations | 771 | 1 |
| Face and neck (excluding shaving preparations) | 261 | 1 |
| Body and hand (excluding shaving preparations) | 987 | 3 |
| Moisturizing | 873 | 2 |
| **1995 Total** | | **19** |

| Product Category | Total No. Formulations in Category | Total No. of Formulations Containing Ingredient |
|---|---|---|
| | STEARAMIDE MEA | |
| Hair conditioners | 693 | 6 |
| Permanent waves | 423 | 2 |
| Hair dyes and colors (all types requiring caution statements and patch tests) | 1437 | 8 |
| Bath soaps and detergents | 339 | 1 |
| Deodorants (underarm) | 293 | 1 |
| Other personal cleanliness products | 317 | 1 |
| Cleansing preparations | 771 | 2 |
| Face and neck (excluding shaving preparations) | 261 | 1 |
| **1995 Total** | | **22** |

*intracerebral administration of MEA to animals or in vitro effects on mammalian tissue. In general, it was documented that MEA was converted to phosphatidylethanolamine in all the tissues, and into phosphatidylcholine in some tissues Elder, 1983a).*

*In general, fatty acids are absorbed, digested, and transported in animals and humans. Radioactivity from labeled fatty acids administered orally, intravenously, intraperitoneally, and intraduodenally has been found in various tissues and in blood and lymph. ß-Oxidation of the fatty acids involves serial oxidation and reduction reactions yielding acetyl-CoA. Placental transfer of fatty acids has been documented in several species and fetal lipid metabolism has been studied. High intake of dietary saturated fatty acids has been associated with the incidence of atherosclerosis and thrombosis (Elder, 1987).*

# ANIMAL TOXICOLOGY

## Oral Studies

### Acute Toxicity

*The oral LD50s of DEA and MEA for rats range from 0.71 ml/kg to 2.83 g/kg and 1.72 g/kg to 2.74 g/kg, respectively (Elder, 1983a).*

*In rats, the oral LD50 for Isostearic acid was estimated to be >32 ml/kg (Elder, 1983b). Little acute toxicity was observed in studies with myristic and stearic acid at concentrations up to 10 g/kg, or with cosmetic formulations containing stearic acid at concentrations of 2.8-13% at a dose of 15-19 g/kg body weight (Elder, 1987).*

The oral LD50 of a mixture containing 35-40% Stearamide DEA was >20 g/kg for CFW mice (Leberco Laboratories, 1971a). For a formulation containing 17.0% Stearamide MEA, the LD50 for rats was >5.0 g/kg (CTFA, 1975a).

### Short-Term Toxicity

*In 2-wk toxicity studies, F344/N rats and B6C3F1 mice were given 630, 1250, 2500, 5000, and 10000 ppm DEA in drinking water. All female rats in the two highest dose groups and two male rats in the 10000 ppm group died before the end of the study. Surviving rats in the higher concentration groups had reduced weight gains. The following effects were also observed in dosed rats: poorly regenerative, microcytic anemia, increased kidney weights, renal tubular cell necrosis, and decreased renal function. Male rats also had degenerated seminiferous tubules of the testis. In studies with mice, there was a dose-dependent*

*increase in liver weight, and cytologic alteration and necrosis of individual hepatocytes were found in the highest dose group (NTP, 1992).*

## Subchronic and Chronic Toxicity

*In subchronic oral studies with rats, DEA and MEA produced lesions limited mainly to the liver and kidneys. In general, DEA was more toxic to rats than MEA. It was suggested that this may be because MEA has a normal function in the lipid metabolism of the body and DEA is structurally similar enough to MEA to act in competition with it and interfere with lipid metabolism (Elder, 1983a).*

*In drinking water studies, rats were given 320-5000 ppm (males) or 160-2500 ppm (females) DEA, and mice were given 630-10000 ppm (males and females) DEA for 13 wks. Deaths occurred in the three highest dose groups of mice, and two rats in the high dose group also died. Reduced body weight gains occurred among the animals surviving the higher concentrations. Dosed rats had poorly regenerative, microcytic anemia, increased kidney weights, renal tubular cell necrosis, decreased renal function, increased incidences or severity of nephropathy, tubular necrosis, and mineralization. Male rats also had degenerated seminiferous tubules of the testis, and sperm motility and count were decreased. In both male and female rats, demyelination in the medulla oblongata and spinal cord were observed (NTP, 1992).*

*No toxic effects were observed in a two year study of dogs fed 0.0975% g/kg/day MEA (Elder, 1983a).*

*When stearic acid was tested in subchronic feeding studies with rats, doses ranging from 5-50% caused thrombosis, aortic atherosclerosis, anorexia, and mortality. Similar effects were observed in chronic feeding studies with rats at doses of 50 g/kg/day and 3000 ppm in the diet (Elder, 1987).*

# Dermal Studies

## Acute Toxicity

*Mild to moderate erythema but no edema was observed when rabbits were treated on both intact and abraded skin with undiluted (88.1% and 91.8% active) TEA (Elder, 1983a).*

*Intradermal injections of 10-100 mM stearic acid in olive oil produced mild erythema and slight induration to the skin of guinea pigs and rabbits (Elder, 1987).*

## Short-Term Toxicity

*In 2-wk toxicity studies, F344/N rats were topically treated five times a week with 125 to 2000 mg/kg DEA and B6C3F1 mice were treated with 160 to 2500 mg/kg DEA. Deaths occurred among male rats and male and female mice of the highest dose groups and in female rats of the two highest dose groups. In the higher dose groups of both rats and mice, body weight gains were reduced. Rats had dose-dependent hematologic and renal function changes, ulcerative skin lesions at the site of application (accompanied by inflammatory cell infiltration), hyperkeratosis, and acanthosis (hyperplasia) of the epidermis. Hyperkeratosis, without ulceration, was observed in some of the rats. In mice, ulceration at the site of application and acanthosis, without ulceration or inflammatory cell infiltration, were observed (NTP, 1992).*

*When 18 mmol% myristic acid and stearic acid were applied to the external ears of rabbits for six weeks, slight irritation was observed with myristic acid and no irritation was observed with stearic acid. Slight local edema was observed among rabbits after 4 wks of topical application of product formulations containing 2.0% stearic acid (Elder, 1987).*

A formulation containing 17.0% Stearamide MEA was tested in a 4-wk dermal toxicity study using rabbits. The backs of nine New Zealand albino rabbits were clipped and 2.0 g/kg of a 10% aq. solution of the formulation was applied by gentle inunction five days a week for a total of 20 applications. The treatment sites were abraded on three of the animals, while the skin of the remaining six rabbits was left intact. A control group of rabbits was untreated. Observations for gross signs of dermal irritation and systemic toxicity were made daily, and hematology studies were conducted with blood samples taken 24 h after the first application. All of the animals were killed at the end of the study for necropsy.

No deaths occurred during the study. One of the rabbits had an overall weight loss of 3 g at the end of the study, but the weights of the other rabbits were similar to those of the controls. There were no treatment related clinical signs of toxicity. The only change in blood chemistry parameters occurred with the mean glucose value, which was significantly lower as compared to the concurrent control value. However, the investigators noted that this value was within the historical range for rabbits and was related primarily to low glucose values for two rabbits. Therefore, they considered this alteration to be due to chance randomization. No gross or microscopic lesions were found during necropsy and histopathologic evaluation (CTFA, 1975b).

## Subchronic and Chronic Toxicity

*Percutaneous application of 4 mg/kg/day MEA to rats resulted in non-specific histological changes in the heart and lungs. Hepatotoxic manifestations included fatty degeneration of the liver parenchyma and subsequent focal necrosis. In another study, no systemic toxicity was observed when a hair dye formulation containing 2.0% DEA was applied to the skin of rabbits for 13 wks (Elder, 1983a).*

*In 13-wk dermal toxicity studies, rats were treated with 32-500 mg/kg DEA and mice were treated with 80-1250 mg/kg DEA five times a week. Some of the animals from the high dose groups died before the end of the study. Surviving animals in the higher dose groups had reduced body weight gains. In studies with rats, dose-dependent changes in hematology and renal function were observed. Skin lesions, including ulceration and inflammation, hyperkeratosis, and acanthosis, were found at the sites of application. There was an increase in the liver weights of rats, but no associated histopathological changes were found. Demyelination in the brain and spinal cord, and nephropathy, renal tubular necrosis, and/or tubular mineralization were also found. In studies with mice, cytological alterations in the liver and/or hepatocellular necrosis, renal tubular epithelial necrosis, and cardiac myocyte degeneration were observed (NTP, 1992).*

*In a 13-wk dermal toxicity studies, two cosmetic product formulations containing up to 5% stearic acid produced moderate skin irritation in rats receiving 4.0 ml/kg and 227 mg/kg doses. All other physiological parameters were normal (Elder, 1987).*

A formulation containing 5.27% Stearamide MEA was tested in a 13-wk dermal toxicity study using female albino rats (number of animals not stated). Each animal was treated topically with the formulation five days a week. There was no evidence of toxicity during the study, and no treatment related gross or microscopic lesions were found during necropsy and microscopic examination (CTFA, 1982).

## Irritation and Sensitization

*DEA had little potential for rabbit skin irritation in acute and subchronic skin irritation tests. MEA was corrosive to rabbit skin at a 30% concentration in a single semi-occluded patch application and at concentrations of 10% and greater following 10 open applications over a period of 14 d. No data on sensitization were available on either DEA or MEA. However, in studies of TEA, no sensitization was observed in guinea pigs treated with undiluted TEA (Elder, 1983a).*

*Undiluted Isostearic acid caused minimal irritation to the skin of rabbits, whereas no irritation was noted when it was diluted to 15% in corn oil. Product formulations containing Isostearic acid produced minimal to moderate skin irritation, most probably by virtue of the*

*other ingredients present in the formulations (Elder, 1983b).*

*In single insult occlusive patch tests for primary irritation, commercial grades of stearic acid, at doses of 35-65%, produced no to moderate erythema and slight, if any, edema in the skin of rabbits. Slight increases in irritation were observed in repeated patch tests of myristic acid (Elder, 1987).*

*In maximization studies with two cosmetic product formulations containing 1.0% stearic acid, slight reactions were observed to challenge patches. These formulations were considered weak, grade I, sensitizers. In another maximization study, after intradermal induction and booster injections of a formulation containing 3.5% stearic acid, reactions to topical challenge applications of the formulation were few and minimal in intensity (Elder, 1987).*

A mixture containing 35-40% Stearamide DEA (0.5 g) was applied under occlusive patches to intact and abraded skin of three albino rabbits for 24 h. The sites were scored when the patches were removed and 48 h later. The primary irritation index for this mixture was 0 (Leberco Laboratories, 1971b).

The primary irritation index of a formulation containing 17.0% Stearamide MEA was 1.00/8 for a group of three rabbits (CTFA, 1975c).

## Phototoxicity and Photosensitization

*No data on phototoxicity were available on DEA or MEA; however, negative results were reported in a study of guinea pigs treated topically with a suntan lotion containing 1% TEA followed by exposure to UVA (Elder, 1983a).*

*Isostearic acid caused moderate irritation to the skin of rabbits in a phototoxicity study, but there was no statistically significant difference in the scores between the irradiated and the non-irradiated sites (Elder, 1983b).*

*Skin lotion formulations containing 2.8% stearic acid were not photosensitizing to the skin of guinea pigs (Elder, 1987).*

## Comedogenicity

*A product formulation both with and without 2.5% Isostearic acid was tested in a rabbit ear comedogenicity assay. The formulations without Isostearic acid was irritating but did not produce comedones; however, the formulation with Isostearic acid was both irritating and comedogenic (Elder, 1983b).*

## Ocular Irritation

*DEA and MEA were irritating to the eyes of rabbits at concentrations of 50% and 5%, respectively (Elder, 1983a).*

*Undiluted Isostearic acid produced no significant ocular irritation in Draize rabbit irritation tests, whereas variable degrees of irritation were produced by product formulations containing Isostearic acid (Elder, 1983b).*

*Myristic acid and stearic acid alone, as well as cosmetic product formulations containing either 1.5% myristic acid or 1-65% stearic acid produced no to minimal irritation after single and multiple installations into the conjunctival sacs of rabbits. Irritation was primarily in the form of very slight conjunctival erythema (Elder, 1987).*

The ocular irritation potential of a mixture containing 35-40% Stearamide DEA was tested using three albino rabbits. The right conjunctival sac of each rabbit was instilled with 0.1 g of the mixture and the left eye served as the control. Examinations of both eyes were conducted every 24 h for 4 days, and then at day 7. No irritation was observed (Leberco Laboratories, 1971c).

No signs of irritation were observed when a formulation containing 5.27% Stearamide MEA was instilled into the conjunctival sacs of six rabbits (CTFA, 1981a), and only minimal irritation was observed with a formulation containing 17.0% Stearamide MEA (CTFA, 1975d).

Moderate eye irritation was observed in Draize tests with formulations containing 8.0% Isostearamide DEA (CTFA, 1983a) and 17.0% Stearamide MEA (CTFA, 1975e).

Ikarashi et al. (1993) reported on cytotoxicity assays which have correlations between in vitro cytotoxicity and the results of in vivo Draize tests. Three different types of cell lines were used in the neutral red assay: Chinese hamster lung fibroblast V79 cells, primary rabbit corneal cells, and normal human epidermal keratinocytes. The cells were incubated with various concentrations of Myristamide DEA for 24 h, followed by incubation with neutral red, and the concentration inducing a 50% reduction in neutral red uptake (IC50) was determined for each cell line. The IC50 values for Myristamide DEA were 15.2 µg/ml for V79 cells, 23.9 µg/ml for rabbit corneal cells, and 6.2 µg/ml for human epidermal keratinocytes. In the Draize test, the DS20 (the concentration predicted to produce a Draize score of 20 (out of a maximum possible score of 110) was 14.5 w/w% Myristamide DEA.

### Inhalation Studies

*In short-terms studies, 200 ppm DEA vapor and 1400 ppm DEA aerosol caused respiratory difficulties and some deaths in rats. In longer-term studies, increased liver and kidney weights were reported. Continuous exposure to 5-6 ppm MEA vapor caused skin irritation and lethargy in dogs, guinea pigs, and rats. Mortality was observed among dogs exposed to 12-26 ppm MEA vapor and among rodents exposed to 66-75 ppm MEA vapor. Exposure to 66-102 ppm MEA caused behavioral changes and pulmonary and hepatic inflammation, hepatic and renal damage, and hematologic changes in dogs and rodents (Elder, 1983a).*

## TERATOGENICITY AND REPRODUCTION STUDIES

*No evidence of teratogenicity was observed when rats were treated topically with hair dyes containing 2.0% DEA or were fed a composite hair dye and base containing 22% MEA. There were no dose-related significant differences in male and female fertility, or teratogenic effects when up to 7800 ppm of a composite hair dye containing 22% MEA was fed to either male or female rats. When this same composite was administered by gavage to pregnant rabbits during gestation, no teratologic effects were observed (Elder, 1983a).*

## MUTAGENICITY

*The ethanolamines were non-mutagenic in the Ames test and TEA is also non-mutagenic to Bacillus subtilis. TEA did not cause DNA-damage inducible repair in an unscheduled DNA synthesis test (Elder, 1983a).*

*Stearic acid was inactive in aneuploidy induction tests and in the Ames test (Elder, 1987).*

## CARCINOGENICITY

*There was a higher incidence of malignant lymphoid tumors in female mice fed diets containing TEA for their whole lifespan than in male mice on the same diet or in control mice. However, TEA had no carcinogenic or cocarcinogenic activity when dermally applied to mice for 18 months (Elder, 1983a). DEA is currently under test in an carcinogenesis bioassay being conducted by the National Toxicology Program (NTP, 1994).*

*No evidence of carcinogenicity was observed in studies of rats fed 3000 ppm stearic acid for 30 wks or 50 g/kg/day stearic acid for 24 wks. In subcutaneous studies, a low incidence of carcinomas, sarcomas, and lymphomas were observed in mice receiving repeated subcutaneous injections of up to 82 mg stearic acid (Elder, 1987).*

## CLINICAL STUDIES

### Dermal Irritation and Sensitization

*Clinical skin testing of TEA and cosmetic products containing TEA and DEA resulted in mild skin irritation at concentrations above 5%. There was very little skin sensitization. A dyeless base formulation containing 11.47% MEA and a hair preparation containing 1.6%*

*DEA and 5.9% MEA were irritating to human skin in patch tests (Elder, 1983a).*

*In studies of Isostearic acid, no signs of irritation were observed after a 24 h single insult skin patch with undiluted Isostearic acid. Product formulations containing up to 4% Isostearic acid produced, at most, minimal irritation when similarly tested. In another study, there was no evidence that 35% Isostearic acid in mineral oil was an irritant, sensitizer, or photosensitizer. Isostearic acid at 10% in mineral oil was similarly non-irritating and non-sensitizing. Product formulations containing 2.5-2.85% Isostearic acid produced no evidence of contact sensitization when tested in repeated insult patch tests (Elder, 1983b).*

*Primary and cumulative irritation studies of 100% myristic acid and up to 40% stearic acid in mineral oil were negative. Mild to intense erythema in single insult occlusive patch tests, soap chamber tests, and 21-day cumulative irritation studies were produced by cosmetic product formulations containing up 8% myristic acid and up to 13% stearic acid. These reactions were generally not related to the fatty acid concentrations in the formulations (Elder, 1987).*

*In clinical repeated insult patch tests (open, occlusive, and semi-occlusive), maximization tests, and prophetic patch tests with cosmetic product formulations containing up to 13% stearic acid, no primary or cumulative irritation or sensitization was reported. A few subjects reacted to a few, isolated induction patches. Slight, if any, reactions were observed after challenge patching at original or adjacent sites on the upper backs or forearms of some subjects. Intensity of observed reactions to the formulations was not directly related to the concentrations of the fatty acid ingredients (Elder, 1987).*

A single insult 24-h patch test of a 1.0% aq. formulation containing 17.0% Stearamide MEA was conducted using 19 subjects. Seven subjects had questionable reactions and three had mild reactions (CTFA, 1981b). In a similar study of a 0.5% formulation containing 8.0% Isostearamide DEA, six of 18 subjects developed a questionable reactions to the formulation and one subject developed a mild reaction (CTFA, 1983b).

The cumulative irritation potential of a formulation containing 5.0% Stearamide MEA was conducted using 14 volunteers. Occlusive patches of 0.2 ml of the formulation were applied to the back of each panelist for 23 h for 21 consecutive days. Test sites were scored 24 h after each application. The composite total score was 156/882. The investigators concluded that this formulation was slightly irritating (Hill Top Research, 1977).

A formulation containing 5.27% Stearamide MEA was tested in a repeated insult patch test using 100 volunteers. The formulation (0.1 ml) was applied under occlusive patches to the backs of each subject for 24 h on Mondays, Wednesdays, and Fridays for 3 wks. After a 2-wk non-treatment period, challenge patches of the formulation were applied to previously untreated sites. One subject had a questionable reaction following the fifth induction patch, but there was no evidence of sensitization in any of the subjects (CTFA, 1981c).

## Photosensitization

*There was no phototoxicity and photosensitization reactions with products containing up to 20.04% TEA (Elder, 1983a). Cosmetic product formulations containing up to 13% stearic acid produced no photosensitization in human subjects. There were slight reactions to a few induction patches (Elder, 1987).*

## Inhalation

*MEA inhalation by humans has been reported to cause immediate allergic responses of dyspnea and asthma and clinical symptoms of acute liver damage and chronic hepatitis (Elder, 1983a).*

# SAFETY ASSESSMENT OF OTHER DIETHANOLAMIDES

*Cocamide DEA, Lauramide DEA, Linoleamide DEA, and Oleamide DEA are fatty acid diethanolamides that were reviewed by the CIR Expert Panel in an earlier safety assessment (Elder, 1986). They are similar to the ingredients reviewed in this report both in their chemistry and use in cosmetics.*

*In general, these four fatty acid alkanolamides were slightly toxic to non-toxic to rats in formulation and inert vehicles via acute oral administration. Lauramide DEA was the most toxic with an LD50 of 2.7 g/kg. Lauramide DEA was not a significant oral toxin in rats or dogs when administered orally at concentrations of up to 2% of the diet in a subchronic study. Subchronic oral toxicity data were not available for Cocamide DEA, Linoleamide DEA, and Oleamide DEA. However, noting the low toxicity demonstrated by Lauramide DEA and the low acute oral toxicity of all four ingredients, the CIR Expert Panel agreed that the three ingredients were probably not toxic after oral administration. Low toxicity was further supported by the chemical and structural similarities of the four ingredients.*

*In acute dermal studies, 50% Lauramide DEA and 100% Linoleamide DEA were nontoxic. In various cosmetic formulations, Cocamide DEA, 1.92%, Lauramide DEA, ≤5%, and Linoleamide DEA, 3.0% in a ≤25% solution which was rinsed after 15 min, were not dermal toxins in subchronic animal studies. Oleamide DEA was not tested for dermal toxicity.*

*Thirty percent Cocamide DEA in propylene glycol was at least a minimal eye irritant and a moderate skin irritant under occlusive conditions using rabbits. Lauramide DEA and Linoleamide DEA in inert vehicles and formulations were mild to moderate eye irritants, mild skin irritants in immersion tests, and mild to severe skin irritants in cumulative and closed patch tests. Undiluted Oleamide DEA was not an eye irritant, but 70% Oleamide DEA was a moderate skin irritant in single and cumulative applications.*

*Lauramide DEA did not demonstrate mutagenic activity in four separate Ames-type assays using Salmonella typhimurium, one DNA-damage assay using Bacillus subtilis, or two studies on in vitro transformation of hamster embryo cells. Lauramide DEA was mutagenic in an Ames test when assayed at 50 µg in a spot test. No data were available on the mutagenic or carcinogenic activity of Cocamide DEA, Linoleamide DEA, and Oleamide DEA.*

*Most of the clinical studies on Cocamide DEA, Lauramide DEA, and Linoleamide DEA were conducted with cosmetic soaps and shampoos containing these ingredients. Generally, these products were mild skin irritants but not sensitizers or photosensitizers. Linoleamide DEA, tested full strength, was not an irritant or sensitizer in a repeat insult patch test.*

*The Panel noted that nitrosamide contamination of these ingredients is possible in one of two ways: either by pre-existing contamination in the diethanolamine used to manufacture the diethanolamide or by nitrosamine formation via the presence of nitrosating agents in formulations containing a diethanolamide. Therefore, they decided that Cocamide DEA, Lauramide DEA, Linoleamide DEA, and Oleamide DEA were safe as cosmetic ingredients when free of nitrosamines and not used in cosmetic products containing nitrosating agents.*

# SUMMARY

Isostearamide DEA and MEA, Myristamide DEA and MEA, and Stearamide DEA and MEA are mixtures of the ethanolamides of Isostearic, Myristic and Stearic Acids, respectively, and are used in cosmetics as foam boosting surfactants and as aqueous viscosity increasing agents. Data submitted to CIR reported that Isostearamide DEA, Myristamide DEA, and Stearamide DEA and MEA are used at the following concentrations: in anti-perspirants at 15%, in shampoos at 6%, in shower gels 5%, and in perms and relaxers at 2%.

Stearamide DEA and MEA had little toxicity when tested in acute oral studies at concentrations up to 40%. Longer term studies on these types of mixtures were not available.

However, short-term and subchronic studies of DEA indicate that this component affects the kidneys and livers of rats and mice. In general, it appears that DEA is more toxic than MEA. Thrombosis, aortic atherosclerosis, anorexia, and mortality were observed in feeding studies of stearic acid.

In both short-term and subchronic dermal studies, no evidence of toxicity or irritation was observed with formulations containing Stearamide MEA. MEA alone caused non-specific microscopic lesions in the heart and lungs of rats, as well as hepatic lesions; however, formulation studies of this ingredient were negative. In studies of DEA, effects on the kidneys and livers of mice and rats were observed, as well as skin lesions at the sites of application.

Little dermal irritation was observed in studies of formulations containing Stearamide DEA. However, in studies of component parts, MEA, but not DEA, was corrosive to the skin of rabbits, and Isostearic and stearic acid were minimal to moderate irritants. Also, formulations containing stearic acid had a weak potential for sensitization.

Some ocular irritation was observed in formulation studies of Stearamide DEA and Isostearamide DEA, as well as in studies of the separate ethanolamines and long-chain fatty acids.

Exposure to DEA and MEA in vaporized or aerosolized form caused respiratory difficulties, behavioral changes, skin irritation, hepatic and renal damage, and hematologic effects in animals. Clinical inhalations studies of MEA report immediate allergic responses of dyspnea and asthma and clinical signs of acute hepatic damage and chronic hepatitis.

In reproduction and teratology studies using rats, MEA in the diet had no effect on male and female fertility or on fetal development. No teratogenic effects were observed in pregnant rats following topical exposure to hair dyes containing DEA during gestation, or in pregnant rabbits given a composite hair dye and base containing MEA by gavage.

No mutagenicity or carcinogenicity data specifically on the mixtures of ethanolamides of fatty acids were available. However, the ethanolamines and stearic acid were negative in mutagenicity assays. TEA in the diet increased the incidence of malignant tumors in female mice as compared to male mice on the same diet or in control mice. However, no carcinogenicity or cocarcinogenicity was found in dermal studies. There was no significant evidence of carcinogenicity in oral or subcutaneous studies of stearic acid.

In clinical irritation and sensitization studies, slight irritation but no sensitization was observed with formulations containing Stearamide MEA. Similar results were observed in studies of the ethanolamides and fatty acids alone.

In a earlier review of other diethanolamines, the CIR Expert Panel evaluated the safety of Cocamide DEA, Lauramide DEA, Linoleamide DEA, and Oleamide DEA. In general, these ingredients had little oral and dermal toxicity in studies using animals. Mild to moderate dermal and ocular irritation were observed with most of these ingredients. Lauramide DEA was negative in mutagenicity assays, but no mutagenic or carcinogenic data were available on the other ingredients. In clinical studies, these diethanolamines were mild skin irritants but not sensitizers or photosensitizers.

# DISCUSSION

The Expert Panel noted the marked absence of safety data specifically on Isostearamide DEA and MEA, Myristamide DEA and MEA, and Stearamide DEA and MEA. Since the basic components of these ingredients (DEA, MEA, Isostearic Acid, Myristic Acid, and Stearic Acid) were already evaluated by the Panel in previous reviews, data on the component parts were used as a basis for the assessment of safety of these six ingredients. Additionally, the Expert Panel reviewed data on diethanolamides that were evaluated in an earlier CIR report. Excerpts from earlier Expert Panel discussions of the component ingredients are presented below in italics.

***DEA and MEA**: In regard to DEA, the Panel was concerned about its potential for nitrosation in the presence of N-nitrosating agents, as well as the dermal and ocular irritation potential of this ingredient. MEA was also both a dermal and ocular irritant in animal studies, and clinical studies with formulations containing MEA indicated that it is a human skin irritant. The longer MEA was in contact with the skin, the greater the likelihood of irritation. With these issues in mind, the Panel concluded that DEA and MEA were safe for use in cosmetic formulations designed for discontinuous, brief use followed by thorough rinsing from the surface of the skin. MEA should be used only in rinse-off products, and the concentration of DEA should not exceed 5% in products intended for prolonged contact with the skin. DEA should not be used in products containing N-nitrosating agents.*

***Isostearic Acid**: The Panel expressed concern regarding the production of comedones in the rabbit ear assay by a product formulation containing commercially available Isostearic Acid. The Panel recognized that the available tests were inadequate to predict the potential for human comedogenicity of an ingredient used in a product formulation. However, it was considered a potential health effect that should be considered when Isostearic Acid is used in cosmetic formulations. The Panel concluded that Isostearic Acid was safe as a cosmetic ingredient.*

***Myristic and Stearic Acid**: The Panel noted the lack of safety data, specifically on Myristic Acid. However, due to Myristic Acid's structural similarity to Stearic Acid, as well as to oleic, lauric, and palmitic acid (which were reviewed in the same report), the Panel felt that the conclusions reached for the other ingredients could be extrapolated to myristic acid. The Panel concluded that both Myristic and Stearic Acid were safe for use in cosmetics.*

***Cocamide DEA, Lauramide DEA, Linoleamide DEA, and Oleamide DEA**: The Expert Panel recognized that the only data on subchronic oral toxicity was on Lauramide DEA. However, noting the low toxicity demonstrated by this ingredient and the low acute oral toxicity of all four ingredients, they decided that Cocamide DEA, Linoleamide DEA, and Oleamide DEA were probably not significantly toxic after oral administration. The chemical and structural similarities of the four ingredients further support this view.*

*However, nitrosamine contamination of diethanolamine and fatty acid diethanolamides and nitrosamine formation in formulations were considered potential problems in using these ingredients. Thus, the Expert Panel concluded that Cocamide DEA, Lauramide DEA, Linoleamide DEA, and Oleamide DEA are safe as cosmetic ingredients, but should not be used in cosmetic products containing nitrosating agents.*

Because these ethanolamine-fatty acid esters may be hydrolyzed to the free ethanolamine and fatty acid, principal concerns were the ability of MEA and DEA to cause irritation and the potential for nitrosation in the presence of N-nitrosating agents. The release of Stearic Acid, Myristic Acid, and Isostearic Acid as a result of hydrolysis of the parent ingredients were considered to present a lesser cause for concern. In general the Panel believed that restrictions to address the concerns about free ethanolamines should be continued, specifically because MEA and DEA could be produced from the esters by hydrolysis.

Even in the event of complete hydrolysis of the ethanolamine-fatty acid ester present in a formulation at "x"%, however, it is expected that no more than 0.33"x"% of free DEA or 0.22"x"% of free MEA would be released. Given that use concentrations are expected to be only up to 10% for the DEA-fatty acid esters and 25% for the MEA-fatty acid esters, and that partial hydrolysis is more likely to occur, the yield of free ethanolamine is not likely to be greater than 5% in a formulation, which is the concentration limit previously recommended by this Panel for free amines.

The Panel noted its earlier conclusion that MEA should be used only in rinse-off products. There were data available in this report on irritation produced by Stearamide MEA suggesting it to be less irritating than Stearic Acid or MEA alone; in addition, it was not sensitizing. The likelihood is that these data are relevant to the other MEA containing ingredients as well. Therefore, the Expert Panel concluded that there was no need

to restrict the MEA-fatty acid esters to rinse-off products. The ethanolamines are clearly irritants and can easily be produced from these esters by hydrolysis. However, the Expert Panel believed a 5% concentration limitation is still appropriate.

The Expert Panel also recognized that these ingredients were only tested up to a concentration of 40% for the DEA-fatty acids and 17% for the MEA-fatty acids. For that reason the Panel believes these concentrations to represent the highest concentrations for which it can be certain these ethanolamine-fatty acid esters can be used safely.

Combining all of these concerns, and recognizing that rinse-off use presented little concern, the Expert Panel arrived at a maximum concentrations for both the ethanolamine-fatty acid esters and for release of free ethanolamines when these esters are used in cosmetic formulations.

# CONCLUSION

Based upon the data included in this report and those data summarized from previous CIR reports, the Expert Panel concludes that Isostearamide DEA and MEA, Myristamide DEA and MEA, and Stearamide DEA and MEA are safe for use in rinse-off products. In leave-on products, these ingredients are safe for use at concentrations that will limit the release of free ethanolamines to 5%, but with a maximum use concentration of 17% for Isostearamide, Myristamide, and Stearamide MEA and of 40% for Isostearamide, Myristamide, and Stearamide DEA. These ingredients should not be used in cosmetic products in which N-nitroso compounds may be formed.

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