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Safety Assessment of Ethanolamides as Used in Cosmetics

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Abstract

The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) rereviewed the safety of 28 ethanolamides and found them safe in the present practices of use and concentration when they are formulated to be nonirritating, and that these ingredients should not be used in cosmetic products in which *N*-nitroso compounds may be formed. Most of the ethanolamides are reported to function in cosmetics as hair-conditioning agents, skin-conditioning agents, and surfactant—foam boosters. The Panel reviewed available animal and clinical data, as well as information from previous CIR reports.

Keywords

ethanolamides, safety, cosmetics

Introduction

This safety assessment reviews the safety of isostearamide monoethanolamine (MEA), myristamide MEA, and stearamide MEA, as used in cosmetics. The following 25 ingredients, which are secondary carboxamides comprising the amidation products of alkyl carboxylic acids and ethanolamines, are also included in this safety assessment, for a total of 28 ingredients defined in the International Cosmetic Ingredient Dictionary and Handbook as ingredients:

acetamide MEA,
azelamide MEA,
babassuamide MEA,
behenamide MEA,
C16-22 acid amide MEA,
cocamide MEA,
cocamide methyl MEA,
cocamidopropyl betainamide MEA chloride,
hydroxystearamide MEA,
lactamide MEA,
lauramide MEA,
linoleamide MEA,
oatamide MEA,
oleamide MEA,
oliveamide MEA,
palm kernelamide MEA,
palmamide MEA,
palmitamide MEA,
pantothenamide MEA,
peanutamide MEA,
ricinoleamide MEA,
sunfloweramide MEA,
tallowamide MEA,
trideceth-2 carboxamide MEA, and
undecylenamide MEA,

Most of the ethanolamides are reported to function in cosmetics as hair-conditioning agents, skin-conditioning agents, and surfactant—foam boosters.

Several ingredients on this list have previously been reviewed by the Cosmetic Ingredient Review (CIR). In 1995, CIR published a safety of isostearamide MEA, myristamide MEA, and stearamide MEA[1] and concluded that these 3 ingredients were safe for use in rinse-off products. In leave-on products, these ingredients were safe for use at concentrations that will limit the release of free ethanolamine to 5% but

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with a maximum use concentration of 17% for isostearamide, myristamide, and stearamide MEA. In that assessment, test data were used to establish limits for use concentrations because concentration of use data was not available. The report further stated that these ingredients should not be used in cosmetic products in which *N*-nitroso compounds may be formed.

In 1993, the Panel concluded that acetamide MEA is safe as used as a cosmetic ingredient at concentrations not to exceed 7.5% in leave-on products, based on sensitization test data, and is safe in the present practices of use in rinse-off products; cosmetic formulations containing acetamide MEA should not contain nitrosating agents or significant amounts of free acetamide.[2] In that assessment, acetamide MEA was reported to be used at up to 25% in rinse-off products. This conclusion was reaffirmed.[3] Cocamide MEA was reviewed in 1999; the Panel concluded that cocamide MEA is safe as used in rinse-off cosmetic products and safe at concentrations of up to 10% in leave-on products.[4] Cocamide MEA was reported to be used at up to 25% in 1984, but the types of products, that is, rinse-off or leave-on, were not specified. The Panel also noted that cocamide MEA should not be used as an ingredient in cosmetic products containing *N*-nitrosating agents or in product formulations intended to be aerosolized. The leave-on concentration limit was derived from the concentration found safe at the time for cocamide diethanolamine (DEA); the inhalation caveat was based on concerns of inhalation toxicity of ethanolamine. These conclusions will be superseded by the conclusion reached in this safety assessment.

The structures and definitions of the ethanolamides are provided in Table 1. The conclusions of the previous reports, as well as those for relevant acids that have been previously reviewed by CIR, are provided in Table 2.

The data in this report apply to the safety of the 3 ingredients previously reviewed and the additional 25 ingredients that are secondary carboxamides, consisting of the amidation products of alkyl carboxylic acids and ethanolamine.

Chemistry

The ethanolamides consist of covalent, secondary amides, whereby one of the nitrogen substituents is ethanol and the second is a carbonyl attached substituent. For example, myristamide MEA is a secondary amide wherein one of the nitrogen substituents is ethanol and the second is a 14 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 (FAAH) which is known to be present in human skin, could potentially convert these amides to ethanolamine and the corresponding fatty acids.[5-7] Secondary amides do tend to react with nitrosating agents to form nitrosamides. Chemical and physical properties of ethanolamides are summarized in Table 3.

Method of Manufacture

Ethanolamine reacts with long-chain fatty acid esters in a 1:1 mole ratio to produce a 90+% pure, crystalline ethanolamide mixture.[8] Two different routes of synthesis of ethanolamides are common: direct acylation with free fatty acids and transacylation using fatty acid esters (often enzymatically).[9,10] Ethanolamides can be produced via enzymatic amidification; monoacylated ethanolamine can be isolated from the reaction mixture. The reaction is carried out using an equimolar ratio of fatty acid and ethanolamine. The enzyme is filtered upon completion of the reaction, and the product is dissolved in a mixture of methanol and chloroform. The solvent is then eliminated by evaporation, and the resulting solid is the amide.

Acetamide MEA. Acetamide MEA is prepared by the reaction of acetic acid with ethanolamine. Additional methods of production, involving acetamide and ethylene oxide, ethanolamine, and acetyl chloride, have been reported.[2]

Impurities

Acetamide MEA. Analysis of 4 lots of acetamide MEA by gas chromatography-mass spectrometry indicated the presence of 0.0006% to 0.0029% ethanolamine and 0.0006% to 0.0030% acetamide. Using high-performance liquid chromatography, *N*-nitrosodiethanolamine was not detected (limit of detection = 0.05 ppm) in acetamide MEA.[2]

Myristamide MEA. The maximum free amine content of myristamide MEA is 1.5%.[1]

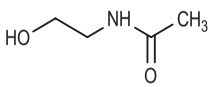
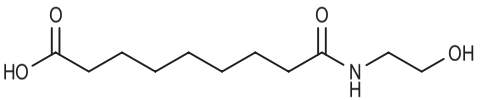
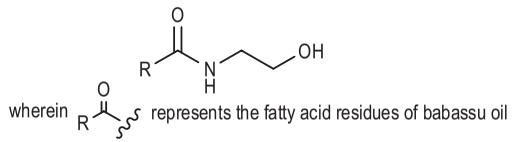
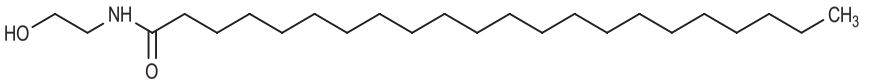
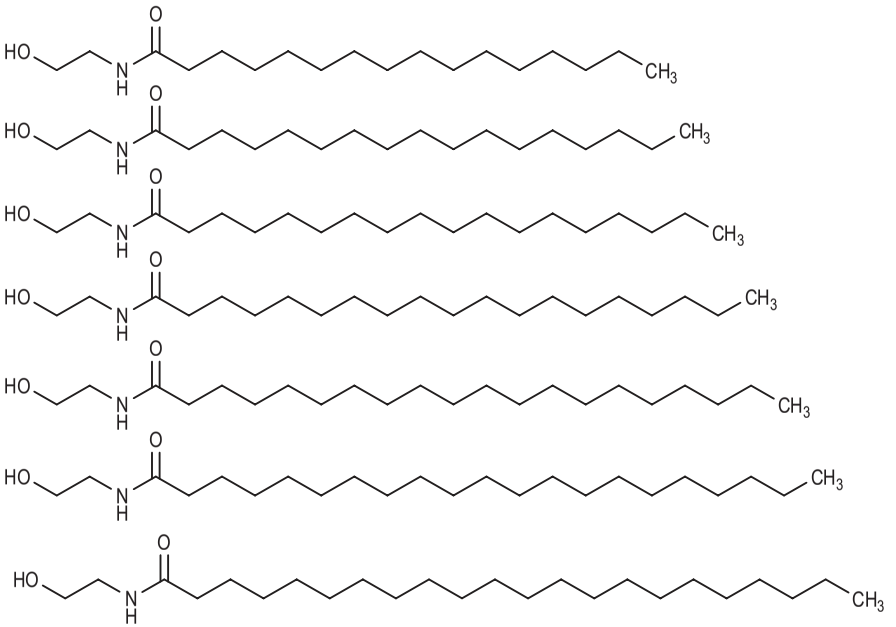
Stearamide MEA. Stearamide MEA has 0.8% maximum free fatty acids (as stearic acid), 0.5% to 2.0% free amine (as ethanolamine), and 54.0% to 58.0% total fatty acids (as stearic acid).[1]

Use

Cosmetic

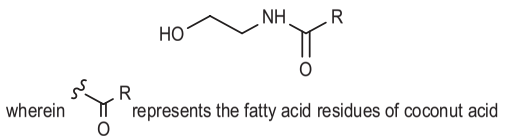
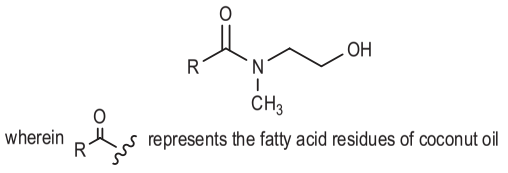
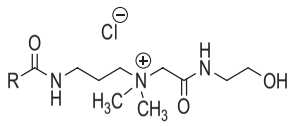
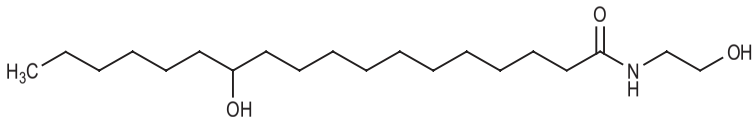
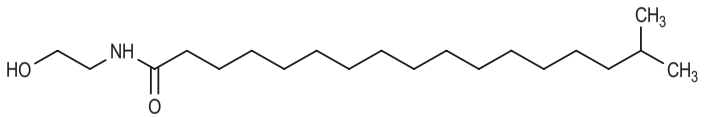
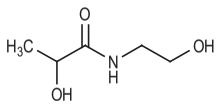
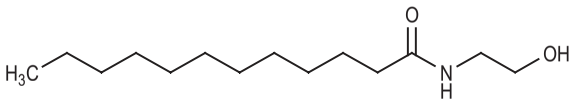
Most of the ethanolamides are reported to function in cosmetics as hair-conditioning agents, skin-conditioning agents, and surfactant—foam boosters; a few are reported to have other uses.[11] The Food and Drug Administration (FDA) collects information from manufacturers on the use of individual ingredients in cosmetics as a function of cosmetic product category in its Voluntary Cosmetic Registration Program (VCRP). The VCRP data obtained from the FDA in 2011 report that stearamide MEA is used in 10 cosmetic formulations, myristamide MEA is used in 1 formulation, and isostearamide MEA does not have any uses reported.[12] Other ethanolamides included in this safety assessment have many more reported uses. For example, cocamide MEA has the highest frequency of use, with 1122 reported uses; only 33 of those uses are in leave-on products. Trideceth-2 carboxamide MEA has 189 reported uses, and acetamide MEA is reported to be used in 148 formulations.

Table 1. Definitions and Structures.

Ingredient; CAS no.	Definition	Reported function[11]	Structure
Acetamide MEA; 142-26-7	The ethanolamide of acetic acid	Hair cond ag; skin cond ag—humectant; surf—foam booster; viscosity increasing ag—aq	
Azelamide MEA	The ethanolamide of azelaic acid	Surf—foam booster; viscosity increasing ag—aq	
Babassuamide MEA; 69227-24-3	A mixture of ethanolamides of the fatty acids derived from *Orbignya oleifera* (babassu) oil	Hair cond ag; surf—foam booster; surf—solubilizing ag; viscosity increasing ag—aq	
Behenamide MEA; 94109-05-4	The ethanolamide of behenic acid	Hair cond ag	
C16-22 acid amide MEA	A mixture of ethanolamides of C16-22 fatty acids	Surf—cleansing ag	

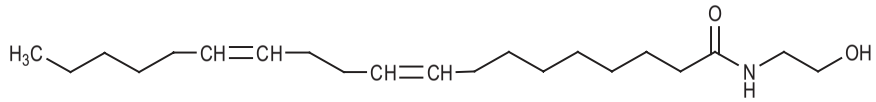
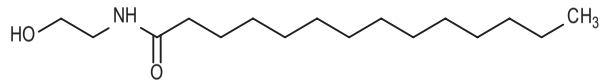
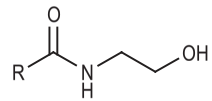
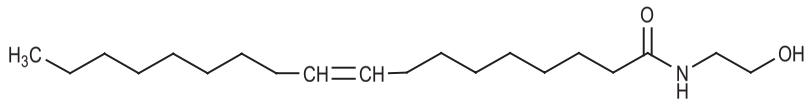
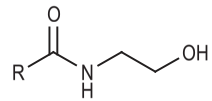
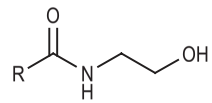
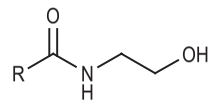
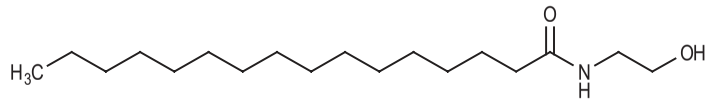
(continued)

Table 1. (continued)

Ingredient; CAS no.	Definition	Reported function[11]	Structure
Cocamide MEA; 68140-00-1	A mixture of ethanolamides of *Cocos nucifera* (coconut) acid	Surf—foam booster; viscosity increasing ag—aq	
Cocamide methyl MEA	A mixture of tertiary, *N* methyl ethanolamides of the fatty acids derived from *Cocos nucifera* (coconut) oil	Surf—foam booster; viscosity controlling ag	
Cocamidopropyl betainamide MEA chloride; 164288-56-6	A mixture of *N*′-betaine ethanolamides of the fatty acids derived from coconut oil	Surf—cleans. agent; surf—foam booster	
Hydroxystearamide MEA; 106-15-0	The 12-hydroxy substituted derivative of stearamide MEA	Surf—foam booster; viscosity increasing ag—aq	
Isostearamide MEA; 54536-43-5	The ethanolamide of isostearic acid	Surf—foam booster; viscosity increasing ag—aq	One example of an "iso" 
Lactamide MEA; 5422-34-4	The ethanolamide of lactic acid	Hair cond ag; skin cond ag—humectant; surf—foam booster; viscosity increasing ag—aq	
Lauramide MEA; 142-78-9	The ethanolamide of lauric acid	Surf—foam booster; viscosity increasing ag—aq	

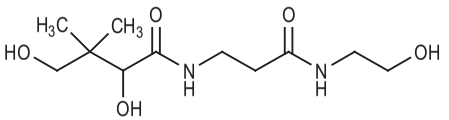
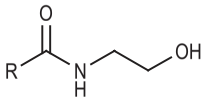
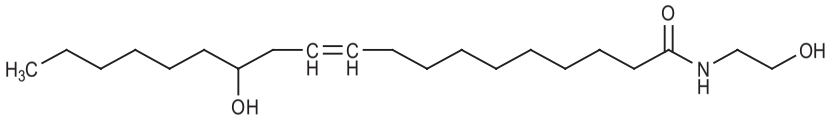
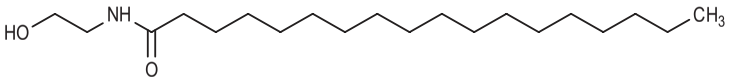
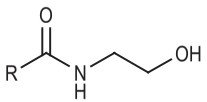
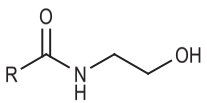
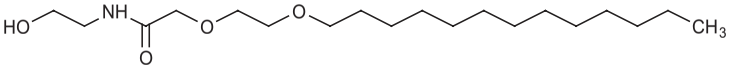
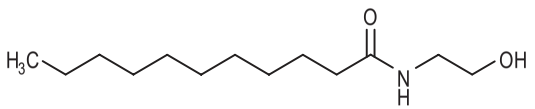
(continued)

Table 1. (continued)

Ingredient; CAS no.	Definition	Reported function[11]	Structure
Linoleamide MEA; 10015-67-5	The ethanolamide of linoleic acid	Hair cond ag; surf—foam booster; viscosity increasing ag—aq	
Myristamide MEA; 109-83-1	The ethanolamide of myristic acid	Surf—foam booster; viscosity increasing ag—aq	
Oatamide MEA	A mixture of ethanolamides of the fatty acids derived from oat kernel oil	Surf—foam booster; viscosity increasing ag—aq	 where RCO- represents the fatty acids derived from *Avena sativa* (Oat) kernel oil
Oleamide MEA; 111-58-0	The ethanolamide of oleic acid	Surf—foam booster; viscosity increasing ag—aq	
Oliveamide MEA	A mixture of ethanolamides of the fatty acids derived from olive oil	Hair cond ag; surf—foam booster; surf—solubilizing ag; viscosity increasing ag—aq	 where RCO- represents the fatty acids derived from olive oil
Palm kernelamide MEA	A mixture of ethanolamides of the fatty acids derived from *Elaeis guineensis* (palm) kernel oil	Surf—foam booster; viscosity increasing ag—aq	 where RCO- represents the fatty acids derived from palm kernel oil
Palmamide MEA	A mixture of ethanolamides of the fatty acids derived from *Elaeis guineensis* (palm) oil	Surf—foam booster; viscosity increasing ag—aq	 where RCO- represents the fatty acids derived from palm oil
Palmitamide MEA; 544-31-0	The ethanolamide of palmitic acid	Surf—foam booster; viscosity increasing ag—aq	

(continued)

Table 1. (continued)

Ingredient; CAS no.	Definition	Reported function[11]	Structure
Pantothenamide MEA	The O-monoethyleneglycol-substituted derivative pantothenamide MEA	Skin cond ag—misc	
Peanutamide MEA	A mixture of ethanolamides of the fatty acids derived from *Arachis hypogaea* (peanut) oil	Surf—foam booster; viscosity increasing ag—aq	 where RCO- represents the fatty acids derived from peanut oil
Ricinoleamide MEA; 106-16-1 75033-33-9	The ethanolamide derived from ricinoleic acid	Surf—foam booster; viscosity increasing ag—aq	
Stearamide MEA; 111-57-9	The ethanolamide of stearic acid	Surf—foam booster; viscosity increasing ag—aq	
Sunfloweramide MEA; 69227-24-3	A mixture of ethanolamides of the fatty acids derived from *Helianthus annuus* (sunflower) seed oil	Surf—cleans ag; surf—foam booster; viscosity controlling ag; viscosity increasing ag—aq	 where RCO- represents the sunflower seed oil fatty acids
Tallowamide MEA; 68440-25-5	A mixture of ethanolamides of tallow acid	surf—foam booster; viscosity increasing ag—aq	 where RCO- represents the fatty acids derived from tallow
Trideceth-2 carboxamide MEA; 107628-04-6	The ethanolamide of trideceth-2	Hair cond ag; surf—foam booster; viscosity increasing ag—aq	
Undecylenamide MEA; 20545-92-0 75046-17-2	The ethanolamide of undecylenic acid	Hair cond ag; surf—foam booster; viscosity increasing ag—aq	

Abbreviations: aq, aqueous; CAS, Chemical Abstracts Service; cond ag, conditioning agent; MEA, monoethanolamine; surf, surfactant.

Table 2. Conclusions of Previously Reviewed Ingredients and Constituents.

Ingredient	Conclusion
Previously reviewed ingredients	
Isostearamide MEA	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 17% (1995)[1]
Myristamide MEA	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 17% (1995)[1]
Stearamide MEA	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 17% (1995)[1]
Acetamide MEA	Safe as a cosmetic ingredient at concentrations not to exceed 7.5% in leave-on products; safe in the present practices of use in rinse-off products; products containing acetamide MEA should not contain nitrosating agents or significant amounts of acetamide (1993)[2]
Cocamide MEA	Safe as used in rinse-off products; safe at concentrations up to 10% in leave-on products; should not be used as an ingredient in products containing *N*-nitrosating agents, or in product formulations intended to be aerosolized (1999)[4]
Constituents	
Ethanolamine (likely an impurity)	Safe as used when formulated to be nonirritating; should not be used in cosmetic products in which *N*-nitroso compounds may be formed (2011)[32]
Arachis hypogaea (peanut) oil	Safe as used (2011)[33]
Avena sativa (oat) kernel oil	Safe as used (2011)[33]
Azelaic acid	Safe as used (2010)[34]
Cocamidopropyl betaine	Safe as used when formulated to be nonsensitizing (2010)[28]
Coconut acid	Safe as used (2008)[35]
Elaeis Guineensis (palm) kernel oil	safe as used (2011)[33]
Elaeis Guineensis (palm) oil	
Helianthus Annuus (sunflower) seed oil	Safe as used (2011)[33]
Hydroxystearic acid	Safe as used (1999)[25]
Isostearic acid	Safe as used (1983)[36]
Lactic acid	Safe for use in cosmetic products at concentrations $\leq$10%, at final formulation pH >3.5, when formulated to avoid increasing sun sensitivity or when directions for use include the daily use of sun protection. These ingredients are safe for use in salon products at concentrations $\leq$30%, at final formulation pH $\geq$3.0, in products designed for brief, discontinuous use followed by thorough rinsing from the skin, when applied by trained professionals, and when application is accompanied by directions for the daily use of sun protection (1998)[29]
Lauric acid	Safe as used (1987)[30]
Myristic acid	Safe as used (1987)[30]
Olea europaea (olive) fruit oil	Safe as used (2011)[33]
Oleic acid	Safe as used (1987)[30]
Orbignya oleifera (Babassu) oil	Safe as used (2011)[33]
Palmitic acid	Safe as used (1987)[30]
Pantothenic acid	Safe as used (1987)[37]
Ricinoleic acid	Safe as used (2007)[31]
Stearic acid	Safe as used (1987)[30]
Trideceth-2	Safe as used when formulated to be nonirritating (2010)[38]

Abbreviation: MEA, monoethanolamine.

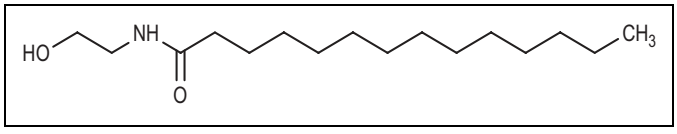


Figure 1. Myristamide MEA.

A Personal Care Products Council (Council) survey of the maximum reported use concentrations found that cocamide MEA is reported to be used at up to 18% in rinse-off formulations and at up to 5% in leave-on formulations.[13] Stearamide MEA has the highest concentration of use in leave-on formulations at up to 15%. The use information for the ethanolamides is provided in Table 4. In some cases, reports of uses were received by the VCRP, but no concentration of use data was available. For example, acetamide MEA is reported to be used in a nail formulation, but no use concentration was available. In other cases, no reported uses were received in the VCRP, but a use concentration was provided in the industry survey. For example, lauramide MEA was not reported in the VCRP to be used in baby product formulations, but the industry survey indicated that it was used in such products at 0.5%. It should be presumed that lauramide MEA is used in at least 1 baby product. Ethanolamides that are not reported to be in use, according to VCRP data and the Council survey, are listed in Table 5.

Table 3. Physical and Chemical Properties.

Property	Value	Reference
Acetamide MEA		
Molecular weight	103.12 (calculated)	39
pKa	14.56 g/cm^3 (most acidic; 25°C) −0.65 g/cm^3 (most basic; 25°C; calculated)	39
Density	1.115 g/cm^3 (25°C; calculated)	40
Melting point	63-64°C	41
Boiling point	195-196°C	40
log P	−1.336 (25°C; calculated)	39
Behenamide MEA		
Molecular weight	383.65 (calculated)	39
pKa	14.49 g/cm^3 (most acidic; 25°C) −0.67 g/cm^3 (most basic; 25°C; calculated)	39
Density	0.896 g/cm^3 (20°C; calculated)	39
log P	8.853 (25°C; calculated)	39
C16-22 acid amide MEA		
Molecular weight	117.19 (calculated)	39
pKa	14.81 g/cm^3 (most acidic; 25°C) 9.90 g/cm^3 (most basic; 25°C; calculated)	39
Density	0.875 g/cm^3 (20°C; calculated)	39
Melting point	−2°C	42
Boiling point	199°C	42
log P	0.467 (25°C; calculated)	39
Cocamide MEA		
Melting point	~72°C	21
Density	~0.894 g/cm^3 (80°C)	21
log P	3.89 (calculated)	21
Solubility	Not soluble in water	21
Hydroxystearamide MEA		
Molecular weight	343.54 (calculated)	39
pKa	14.49 g/cm^3 (most acidic; 25°C) −0.67 g/cm^3 (most basic; 25°C; calculated)	39
Density	0.954 g/cm^3 (20°C; calculated)	39
Melting point	106.5-108°C	43
Boiling point	522.4°C (calculated)	39
log P	4.753 (25°C; calculated)	39
Lauramide MEA		
Physical form	Solid	20
Molecular weight	243.39	20
pKa	14.49 g/cm^3 (most acidic; 25°C) −0.67 g/cm^3 (most basic; 25°C; calculated)	39
Density	0.925 g/cm^3 (20°C; calculated)	39
Melting point	89-91°c	44
Boiling point	410.7°C (calculated)	39
Water solubility	Miscible with water	20
log P	3.758 (25°C; calculated)	39
Linoleamide MEA		
Molecular weight	323.51 (calculated)	39
pKa	14.49 g/cm^3 (most acidic; 25°C) −0.67 g/cm^3 (most basic; 25°C; calculated)	39
Density	0.926 g/cm^3 (20°C; calculated)	39
Boiling point	499.1°C (calculated)	39
log P	6.003 (25°C; calculated)	39
Myristamide MEA		
Molecular weight	271.44 (calculated)	39
pKa	14.49 g/cm^3 (most acidic; 25°C) −0.67 g/cm^3 (most basic; 25°C; calculated)	39
Density	0.916 g/cm^3 (20°C; calculated)	39
Melting point	93-94°C	45
Boiling point	436.3°C (calculated)	39
log P	4.777 (25°C; calculated)	39
Oleamide MEA		
Molecular weight	325.53 (calculated)	39
pKa	14.49 g/cm^3 (most acidic; 25°C) −0.67 g/cm^3 (most basic; 25°C; calculated)	39
Density	0.915 g/cm^3 (20°C; calculated)	39
Melting point	63-64°C	44
Boiling point	496.4°C (calculated)	39
log P	6.406 (25°C; calculated)	39
Palmitamide MEA		
Molecular weight	299.49 (calculated)	39
pKa	14.49 g/cm^3 (most acidic; 25°C) −0.67 g/cm^3 (most basic; 25°C; calculated)	39
Density	0.910 g/cm^3 (20°C; calculated)	39
Melting point	98°C	46
Boiling point	461.5°C (calculated)	39
log P	5.796 (25°C; calculated)	39
Ricinoleamide MEA		
Molecular weight	341.53 (calculated)	39
pKa	14.49 g/cm^3 (most acidic; 25°C) −0.67 g/cm^3 (most basic; 25°C; calculated)	39
Density	0.965 g/cm^3 (20°C; calculated)	39
Melting point	58-59°C	43
Boiling point	536.2°C (calculated)	39
log P	4.592 (25°C; calculated)	39
Stearamide MEA		
Molecular weight	327.55 (calculated)	39
pKa	14.49 g/cm^3 (most acidic; 25°C) −0.67 g/cm^3 (most basic; 25°C; calculated)	39
Density	0.904 g/cm^3 (20°C; calculated)	39
Melting point	106-108°C	44
Boiling point	486.0°C (calculated)	39
log P	6.815 (25°C; calculated)	39
Undecylenamide MEA		
Molecular weight	227.34 (calculated)	39
pKa	14.49 g/cm^3 (most acidic; 25°C) −0.67 g/cm^3 (most basic; 25°C; calculated)	39
Density	0.940 g/cm^3 (20°C; calculated)	39
Melting point	56-58°C	47
Boiling point	409.4°C (calculated)	39
log P	2.841 (25°C; calculated)	39

Abbreviation: MEA, monoethanolamine.

Table 4. Frequency and Concentration of Use According to the Duration and Type of Exposure.

	# of uses[12]	Max conc of use, %[13]	# of uses[12]	Max conc of use, %[13]	# of uses[12]	Max conc of use, %[13]
	Acetamide MEA		Cocamide MEA		Cocamide methyl MEA	
Totals[a]	148	0.03-8	1122	0.2-18	NR	5
Duration of use						
Leave-on	64	0.03-8	33	0.5-5	NR	NR
Rinse-off	84	0.06-5	1008	0.2-18	NR	5
Diluted for (bath) use	NR	NR	81	2-6	NR	NR
Exposure type						
Eye area	1	0.5	NR	NR	NR	NR
Incidental ingestion	NR	NR	NR	NR	NR	NR
Incidental inhalation—spray	14	0.1-0.4	3[b]	0.7[b]; 1	NR	NR
Incidental inhalation—powder	NR	NR	NR	NR	NR	NR
Dermal contact	25	0.03-8	579	0.2-10	NR	NR
Deodorant (underarm)	9[c]	2[c]	NR	NR	NR	NR
Hair—noncoloring	121	0.06-5	367	1-15	NR	5
Hair—coloring	1	NR	173	3-18	NR	NR
Nail	1	NR	2	NR	NR	NR
Mucous membrane	3	3-4	521	1-10	NR	NR
Baby products	NR	NR	4	2	NR	NR
	# of uses[12]	Max conc of use, %[13]	# of uses[12]	Max conc of use, %[13]	# of uses[12]	Max conc of use, %[13]
	Cocamidopropyl betainamide MEA Chloride		Lactamide MEA		Lauramide MEA	
Totals[a]	21	1-3	27	0.02-3	87	0.3-4
Duration of use						
Leave-on	NR	NR	21	0.02-2	3	0.5-4
Rinse-off	21	1-3	6	0.2-3	80	0.3-3
Diluted for (bath) use	NR	NR	NR	2	4	2
Exposure type						
Eye area	NR	NR	1	NR	NR	NR
Incidental ingestion	NR	NR	NR	NR	NR	NR
Incidental inhalation—spray	NR	NR	4	0.02-0.2	1	1
Incidental inhalation—powder	NR	NR	NR	NR	NR	NR
Dermal contact	21	1-3	9	2-3	35	0.3-4
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair—noncoloring	NR	NR	17	0.02-3	9	1-3
Hair—coloring	NR	NR	NR	NR	43	3
Nail	NR	NR	1	NR	NR	1
Mucous membrane	18	1-3	1	2-3	28	1-3
Baby products	NR	NR	NR	NR	NR	0.5
	# of uses[12]	Max conc of use, %[13]	# of uses[12]	Max conc of use, %[13]	# of uses[12]	Max conc of use, %[13]
	Myristamide MEA		Peanutamide MEA		Ricinoleamide MEA	
Totals[a]	1	0.3-4	NR	0.3	NR	0.02
Duration of use						
Leave-on	NR	4	NR	NR	NR	NR
Rinse-off	1	0.3	NR	0.3	NR	0.02
Diluted for (bath) use	NR	NR	NR	NR	NR	NR
Exposure type						
Eye area	NR	NR	NR	NR	NR	NR
Incidental ingestion	NR	NR	NR	NR	NR	NR
Incidental inhalation—spray	NR	NR	NR	NR	NR	NR
Incidental inhalation—powder	NR	NR	NR	NR	NR	NR
Dermal contact	1	0.3-4	NR	0.3	NR	0.02
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair—noncoloring	NR	NR	NR	NR	NR	NR
Hair—coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous membrane	1	NR	NR	NR	NR	NR
Baby products	NR	NR	NR	NR	NR	NR

(continued)

Table 4. (continued)

	# of uses[12]	Max conc of use, %[13]	# of uses[12]	Max conc of use, %[13]	# of uses[12]	Max conc of use, %[13]
	Stearamide MEA		Trideceth-2 Carboxamide MEA		Undecylenamide MEA	
Totals	10	0.07-17	189	2-14	3	NR
Duration of use						
Leave-on	2	2-15	NR	2	2	NR
Rinse-off	8	0.07-6	189	2-14	1	NR
Diluted for (bath) use	NR	17	NR	NR	NR	NR
Exposure type						
Eye area	NR	6-7	NR	NR	NR	NR
Incidental ingestion	NR	NR	NR	NR	NR	NR
Incidental inhalation—spray	NR	NR	NR	NR	1	NR
Incidental inhalation—powder	NR	NR	NR	NR	NR	NR
Dermal contact	3	0.2-15	1	NR	2	NR
Deodorant (underarm)	2[c]	15[c]	NR	NR	1[c]	NR
Hair—noncoloring	NR	0.07	5	2	NR	NR
Hair—coloring	7	2-6	183	4-14	1	NR
Nail	NR	2	NR	NR	NR	NR
Mucous membrane	NR	17 (diluted prior to use)	1	NR	NR	NR
Baby products	NR	NR	NR	NR	NR	NR

Abbreviations: max conc; maximum concentration; MEA, monoethanolamine; NR, no reported uses.
[a]Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.
[b]Includes suntan products, in that it is not known whether or not the reported product is a spray.
[c]It is not known whether or not the product is a spray.

A few of the ethanolamides may be used in products applied to baby skin or used near the eye area or mucous membranes. Additionally, some of the ethanolamides are used in cosmetic sprays, with reported maximum use concentrations of 0.4% acetamide MEA in aerosol hair sprays and 1% cocamide MEA and lauramide MEA in foot sprays.[13] These products could possibly be inhaled. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 μm, with propellant sprays yielding a greater fraction of droplets/particles below 10 μm compared with pump sprays.[14-17] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (ie, they would not enter the lungs) to any appreciable amount.[14,16]

Acetamide MEA, stearamide MEA, and undecylenamide MEA are reported to be used in deodorants, and stearamide MEA has the highest reported concentration of use in deodorants at 15%. It is not known whether or not these products are sprayed. There is some evidence indicating that, generally, deodorant spray products, compared with hair sprays, can release substantially larger fractions of particulates having aerodynamic equivalent diameters in the range considered to be respirable.[14] However, the information is not sufficient to determine whether significantly greater lung exposures result from the use of deodorant sprays, compared to other cosmetic sprays.

Monoalkylamines, monoalkanolamines, and their salts are listed by the European Commission in Annex III Part 1: the list of substances which cosmetic products must not contain, except subject to the restrictions and conditions laid down.[18] These ingredients are allowed a maximum secondary amine content of 0.5% in finished product, are not to be used with nitrosating agents, and must have a minimum purity of 99%. The maximum secondary amine content of 0.5% is allowed for raw materials, maximum nitrosamine content allowed is 50 μg/kg, and the chemicals must be kept in nitrite-free containers. Acetamide MEA and babassuamide MEA, 2 ethanolamides included in this safety assessment, are listed in this category. All the other ethanolamides are listed in the European Union inventory.

Toxicokinetics

No published toxicokinetic data were discovered, and no unpublished data were submitted.

Toxicological Studies

Acute (Single) Dose Toxicity

Dermal

Acetamide MEA. No deaths occurred when rabbits were dosed dermally with 20 mL/kg acetamide MEA.[2]

Cocamide MEA. The dermal median lethal dose (LD_{50}) of cocamide MEA was evaluated by applying 2 g/kg to the abraded and intact skin of rabbit under occlusive patches.[19,20] The dermal LD_{50} in rabbits was >2 g/kg.

Oral

Cocamide MEA. The acute oral toxicity of cocamide MEA (purity not specified) was evaluated in a number of studies

Table 5. Not Reported to be in Use.

Azelamide MEA
Babassuamide MEA
Behenamide MEA
C16-22 acid amide MEA
Hydroxystearamide MEA
Isostearamide MEA
Linoleamide MEA
Oatamide MEA
Oleamide MEA
Oliveamide MEA
Palm kernelamide MEA
Palmamide MEA
Palmitamide MEA
Pantothenamide MEA
Sunfloweramide MEA
Tallowamide MEA

Abbreviation: MEA, monoethanolamine.

using rats.[19-21] In most studies, the highest dose administered was 5 g/kg or 5 mL/kg; the LD_{50} was greater than this dose. In a study in which doses of 1 to 32 g/kg were used, the LD_{50} was reported to be 7.4 g/kg in rats.[19,20] In 2 other rat studies, the oral LD_{50} of cocamide MEA was identified as 3.3 g/kg and >3.125 g/kg, respectively.[21] In studies in mice, the oral LD_{50} of cocamide MEA was >10 g/kg in most studies. However, a value of 3.125 g/kg was reported in 1 study using mice. (Details were not provided.)

Acetamide MEA. The oral LD_{50} of acetamide MEA has been reported as 26.95 and as 27.66 g/kg in rats. The acute LD_{50} of 2 hair products containing 1.3% acetamide MEA was >16.9 g/kg for 1 product and >25 mL/kg for the other; these were the highest doses tested.[2]

Lauramide MEA. The oral LD_{50} of lauramide MEA was >2 g/kg in rats.[22]

Repeated Dose Toxicity

Dermal

Acetamide MEA. In a 13-week study, a hair product containing 1.3% acetamide MEA, applied as an aqueous (aq) solution that was diluted to 50% (w/v), was not toxic to rabbits. Slight-to-moderate erythema was observed sporadically at the application site from days 44 to 84 of the study.[2]

Cocamide MEA. Cocamide MEA, 25% in olive oil, was applied to mice twice a day for 1 week and the application site was not covered.[21] No dermal reactions were observed. Additional details were not provided.

Stearamide MEA. The dermal toxicity of a formulation containing 17.0% stearamide MEA was evaluated in a 4-week study in rabbits; 2 g/kg of a 10% aq solution of the formulation was applied to intact and abraded skin; no gross or microscopic lesions were observed. In a 13-week dermal study, a formulation containing 5.27% stearamide MEA was not toxic in rats.[1]

Oral

Cocamide MEA. Groups of 10 male and 10 female Wistar rats were dosed by gavage with 0, 70, 250, or 750 mg/kg body weight (bw)/d cocamide MEA in olive oil; the high dose was increased to 1500 mg/kg bw after 14 days.[19] The animals were dosed once daily, 5×/wk, for 4 weeks. Recovery groups of 5 male and 5 female rats per dose level were included. None of the animals died, and no significant test article-related gross or microscopic lesions were observed. The no observed adverse effect level (NOAEL) was >750 mg/kg bw/d.

Reproductive and Developmental Toxicity

Data on the reproductive and developmental toxicity of the ethanolamides were not found. Since ethanolamine may be present as an impurity in the ethanolamides, and since amidases in the skin could possibly convert some of the ethanolamide to ethanolamine and the corresponding carboxylic acid, a summary of available data from the reports on ethanolamine and the constituents of these ethanolamides is provided subsequently.

MEA: In a dietary study, 0 to 7800 ppm of a composite hair dye and base containing 22% ethanolamine was fed to 60 gravid female rats on days 6 to 15 of gestation, and the rats were killed on day 19 of gestation. No developmental effects were observed. In another dietary study, 30 male rats were fed 0 to 7800 ppm of the hair dye for 8 weeks prior to mating with female rats that were being fed a basal diet, while a group of 60 female rats were fed 0 to 7800 ppm of the test substance for 8 weeks prior to mating with male rats being fed a basal diet. No effects on reproduction or fertility were observed. In rabbits, no developmental effects were observed when pregnant females were dosed by gavage on days 6 to 18 of gestation with 0 to 19.5 mL/kg/d of the hair dye containing 22% ethanolamine.[23]

Arachis hypogaea (peanut) oil: Peanut oil was used as the vehicle in a fertility study in rats. It was administered orally for 28 days prior to mating and for 6 days during mating. No unusual findings were noted in the vehicle group. No unusual findings were observed in a teratogenicity study in which rats were injected with a test article, and peanut oil was used as the vehicle. Treatment-related changes were not observed in a study in which rabbits were dosed intramuscularly with 21% peanut oil on day 8 of gestation. However, in a study of the effects of oil vehicles on early embryonic lethality in mice, it was stated that plant oils proved to be unsuitable carriers of test mutagens in female dominant-lethal studies where the route of administration is via the peritoneal cavity.[24]

Hydroxystearic acid: The dermal teratogenicity of 2 formulations containing 7% hydroxystearic acid was evaluated using female rats. No teratogenic effects were observed. (However, dermal irritation was reported.)[25]

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 as determined by measuring estradiol, prolactin, and luteinizing hormone.[26]

Palm kernel oil: In the second generation resulting from the mating of adult *Mongolian gerbils* fed 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 group.[26]

Genotoxicity

In Vitro

Acetamide MEA. Acetamide MEA, ≤5000 μg/plate, was not mutagenic in the presence or absence of metabolic activation in an Ames test, and ≤5000 μg/mL acetamide MEA did not induce unscheduled DNA synthesis in primary rat hepatocytes.[2]

Cocamide MEA. In an Ames test, 50 μg/plate cocamide MEA was mutagenic in *Salmonella typhimurium* TA100 with metabolic activation; it was not mutagenic with *S typhimurium* TA98, TA1535, TA1537, or TA1538, with or without metabolic activation or in TA100 without metabolic activation. Cocamide MEA was not mutagenic in a plate incorporation assay.[4]

The mutagenic potential of cocamide MEA was evaluated in an Ames test using *S typhimurium* TA1535, TA1537, TA1538, TA98, and TA100, with and without metabolic activation.[19,20] Cocamide MEA, evaluated at doses of 4 to 2500 μg/plate, was not mutagenic. (No data for controls were provided.)

Lauramide MEA. The mutagenic potential of lauramide MEA was evaluated in an Ames test with *S typhimurium* TA98, TA100, TA1535, TA1537, and TA1538 at doses of 33 to 3333 μg/plate, with and without metabolic activation.[27] Doses of 3.3 and 10 μg/plate were tested with TA1537 without metabolic activation, and a dose of 10 μg/plate was tested in strains TA100 without metabolic activation. Negative controls were used and gave expected results. Lauramide MEA was not mutagenic in this assay.

Carcinogenicity

Data on the carcinogenicity of the ethanolamides included in this report were not found in the published literature, and no unpublished data were provided. Since ethanolamine may be present as an impurity in the ethanolamides, and since amidases in the skin could possibly convert some of the ethanolamide to ethanolamine and the corresponding carboxylic acid, a summary of available data from the reports on constituents of these ethanolamides is provided.

Cocamidopropyl betaine: The carcinogenic potential of a nonoxidative hair dye formulation containing 0.09% active cocamidopropyl betaine was determined in Swiss Webster mice. A dose of 0.05 mL per mouse was applied 3 times weekly for 20 months to interscapular skin that was clipped free of hair. Dermal changes were noted, but the incidence of neoplasms in treated animals did not differ significantly from control groups.[28]

Hydroxystearic acid: In an 18-month subcutaneous carcinogenicity study in female Swiss-Webster mice, hydroxystearic acid was injected subcutaneously twice weekly for a total dose of 4 or 80 mg delivered in a total of 8 mL tricaprylin. Hydroxystearic acid was classified as tentatively carcinogenic in Swiss-Webster mice. Subcutaneous sarcomas were observed at the site of injection in 9 of the 28 mice (14 per dose group) that were alive at 6 months. All of the sarcomas were observed in the low-dose group. In a second study in which 9 A/He male mice received a total intraperitoneal dose of 60 mg hydroxystearic acid over a period of 4 weeks, the frequency of lung tumors was within the spontaneous occurrence.[25]

Lactic acid: Female rabbits were dosed by gavage with 0.1 to 0.2 g/kg lactic acid in 100 to 150 mL water twice daily for 5 months, and 5 female rabbits were dosed orally with 0.1 to 0.7 g/kg lactic acid in 50 to 100 mL water twice daily for 16 months. No tumors were reported.[29]

Lauric acid: Treatment of mice with repeated subcutaneous injections of 25 and 50 mg lauric acid was not carcinogenic.[30]

Oleic acid: Intestinal and gastric tumors were found in mice receiving dietary oleic acid at daily concentrations of up to 200 mg/mouse. No malignant tumors were induced by repeated subcutaneous injections of 1 to 16.5 mg oleic acid in 2 species of mice.[30]

Palmitic acid: Feeding of 50 g/kg/d palmitic acid to rats resulted in lipogranulomas observed in fat associated with the testis or ovary; this lesion was reversible upon diet substitution and attributed to dietary imbalance. Low incidences of carcinomas, sarcomas, and lymphomas were observed in mice receiving single or repeated subcutaneous injections of 25 and 50 mg palmitic acid.[30]

Ricinoleic acid: None of 20 mice injected intravaginally with 2% ricinoleic acid (in gum tragacanth) had neoplasms or hyperplastic lesions of the corpus uteri, cervix uteri, vagina, or perineal skin. However, benign lung adenomas were observed in 10 of the 13 mice dosed with ricinoleic acid and in 6 of the 24 vehicle control mice that were killed after the 14th month of dosing.[31]

Stearic acid: Feeding of up to 50 g/kg/d dietary stearic acid to mice was not carcinogenic. Low incidences of carcinomas, sarcomas, and lymphomas were observed in mice receiving single or repeated subcutaneous injections of $\leq$82 mg stearic acid.[30]

Irritation and Sensitization

Irritation

Dermal

Nonhuman. Acetamide MEA

Acetamide MEA, applied neat, was a mild skin irritant in an open-patch Draize test in 12 rabbits. In another study, acetamide MEA (70% active, minimum) was not a primary irritant when applied to the intact and abraded skin of rabbits using a 24-hour occlusive patch.[2]

Cocamide MEA

The irritancy potential of 50% cocamide MEA in petrolatum was evaluated in a 24-hour patch test in guinea pigs, rabbits, and hairless mice. Cocamide MEA was slightly irritating to rabbits but was not irritating to guinea pigs and hairless mice.[4]

The irritation potential of cocamide MEA was evaluated in rabbits.[21] Cocamide MEA, 25%, was not irritating to rabbits when applied under an occlusive patch for 24 hours. (Additional details were not provided.)

Lauramide MEA

In a Draize study, lauramide MEA was not irritating to rabbit skin.[22] No details were provided.

Stearamide MEA

The primary irritation index of a formulation containing 17.0% stearamide MEA was 1.00/8 in a group of 3 rabbits.[1]

Human. Irritation data were available from earlier CIR safety assessments indicate that acetamide MEA and cocamide MEA were not irritating; however, a 1% aq solution of a formulation containing 17% stearamide MEA produced questionable to mild reactions in 10 of the 19 subjects in the study.[1,2,4] In a 21-day, 14-subject, cumulative irritation study in which 0.2 mL of a formulation containing 5.0% stearamide MEA was applied using occlusive patches, slight irritation was observed, with a composite total score of 156/882.

Sensitization

Nonhuman

Acetamide MEA. Acetamide MEA was not a sensitizer in a maximization study using 10 guinea pigs. Induction included an intradermal injection of 5.0% acetamide MEA in propylene glycol and in Freund's complete adjuvant and a topical application of 10% acetamide MEA.[2]

Cocamide MEA. Cocamide MEA was not a sensitizer in a guinea pig maximization study. Details were not provided.[21]

Human

Acetamide MEA. In earlier CIR safety assessments that support the safety of ethanolamides, aq solution of 7.5% acetamide MEA did not cause primary irritation or sensitization in a 50-subject study, however, a repeated insult patch test (RIPT) of a hair product containing 1.3% acetamide MEA showed mild reactions during induction and challenge. However, the researchers concluded that a hair product containing 1.3% acetamide MEA was not a sensitizer.[2]

Stearamide MEA. In an RIPT using 100 subjects in which 0.1 mL of formulation containing 5.27% stearamide MEA was applied using occlusive patches, the formulation did not produce sensitization.[1]

Ocular Irritation

Nonhuman. Irritation data from earlier CIR safety assessments show that 1.3% acetamide MEA and 5.27% stearamide MEA were not irritating to rabbit eyes however 70% minimal activity of acetamide MEA was practically nonirritating and 17% stearamide MEA was reported to be minimally to moderately irritating.[1,2]

Lauramide MEA. In a Draize ocular irritation study, Lauramide MEA was highly irritating to rabbit eyes.[22] Details were not provided.

Summary

This report assesses the safety of 28 ethanolamides. This safety assessment originated as a rereview of isostearamide MEA, myristamide MEA, and stearamide MEA and was expanded to include 25 additional related ingredients. Some of these ingredients have been previously reviewed by the CIR and are included because they fit scientifically and conceptually within this family of ingredients.

Amidases, such as FAAH, which is known to be present in human skin, could potentially convert the ethanolamides to ethanolamine and the corresponding fatty acids. The yield of ethanolamine from metabolism of ethanolamides in human skin is unknown. Also, secondary amides do tend to react with nitrosating agents to form nitrosamides. Impurity data were available for acetamide, myristamide, and stearamide MEA: acetamide MEA contained up to 0.0029% ethanolamine, 0.0030% acetamide, and no *N*-nitrosodiethanolamine; myristamide contained a maximum of 1.5% ethanolamine; and stearamide MEA contained up to 2.0% free amine (as ethanolamine).

Most of the ethanolamides are reported to function in cosmetics as hair-conditioning agents, skin-conditioning agents, and surfactant—foam boosters; a few are reported to have other uses. In 2011, stearamide MEA was reported to have only 10 uses, myristamide MEA had 1, and isostearamide had none.

Cocamide MEA has the highest frequency of use, with 1122 reported uses; only 33 of those are in leave-on products. Cocamide MEA is reported to be used at up to 18% in rinse-off formulations and at up to 5% in leave-on formulations. Stearamide MEA has the highest concentration of use in leave-on formulations at up to 15%. In Europe, monoalkylamines, monoalkanolamines, and their salts are on the list of substances that must not form part of the composition of cosmetic products, except subject to restrictions and conditions laid down. Acetamide MEA and babassuamide MEA are included in this list. These restrictions include a maximum secondary amines contaminant content of 0.5% in finished products, a maximum secondary amines content of 0.5% in raw materials, and a maximum nitrosamine content of 50 μg/kg.

In an acute dermal study in rabbits, the LD_{50} for cocamide MEA was >2 g/kg and for acetamide MEA, it was >20 mL/kg. In oral studies, the LD_{50} of cocamide MEA was >5 g/kg in rats and >10 g/kg in mice. The oral LD_{50} values in rats for acetamide and lauramide MEA were 27 and >2 g/kg, respectively. In repeated dose dermal studies, acetamide MEA (50%; 13 weeks in rabbits), cocamide MEA (25%; 1 week in mice), and stearamide MEA (10% solution of a formulation containing 17% in rabbits, applied for 4 weeks; 5.27% in rats, applied for 13 weeks) were not toxic. In a 14-day oral study, the NOAEL of cocamide MEA in rats was >750 mg/kg/d, the highest dose tested.

No data on the reproductive and developmental toxicity or carcinogenicity of the ethanolamides included in this report were found. Available data from previous CIR reports on ethanolamine and some of the constituents were summarized, and no relevant toxic effects were noted.

Acetamide MEA (≤5000 μg/plate), cocamide MEA (≤2500 μg/plate), and lauramide MEA (≤3333 μg/plate) were not mutagenic in Ames tests with or without metabolic activation. Acetamide MEA did not induce unscheduled DNA synthesis in primary rat hepatocytes.

Acetamide MEA was a mild skin irritant in rabbits and in humans, and a formulation containing 0.5% acetamide MEA was not an irritant. Cocamide MEA was slightly irritating to rabbit skin and was not irritating to guinea pigs and hairless mice. In clinical testing, 50% cocamide MEA in petrolatum was not irritating. A formulation containing 17% stearamide MEA had a primary irritation score of 1/8 in rabbits, and in a clinical single-insult occlusive patch test, a 1% aq solution of this formulation produced questionable reactions in 7 and mild reactions in 3 of 19 subjects; in a clinical cumulative irritation study, 5% stearamide MEA produced slight irritation. Acetamide MEA and cocamide MEA were not sensitizers in guinea pigs. In clinical testing, a solution of 7.5% acetamide MEA, a formulation containing 1.3% acetamide MEA, and a formulation containing 5.27% stearamide MEA were not sensitizers.

Acetamide MEA (70% minimum activity) was practically nonirritating to rabbit eyes, and formulations containing 1.3% acetamide MEA and 5.27% stearamide MEA were not irritating to rabbit eyes. A formulation containing 17% stearamide MEA was a moderate ocular irritant, and lauramide MEA was highly irritating to rabbit eyes.

Discussion

Isostearamide MEA, myristamide MEA, and stearamide MEA, along with acetamide MEA and cocamide MEA, have been reviewed previously by the CIR Expert Panel. This amended safety assessment includes those 5 ingredients and 23 additional ethanolamides that are also secondary carboxamides comprising the amidation products of alkyl carboxylic acids and ethanolamine. This amended safety assessment was originated as a rereview of isostearamide MEA, myristamide MEA, and stearamide MEA and was expanded to include the additional ethanolamides, the safety of which was supported by the data available in the original safety assessment and by other published and unpublished studies.

The Panel noted gaps in the available safety data for other end points for many of the ethanolamides included in this group. Because these ingredients are secondary amides, whereby one of the nitrogen substituents is ethanol and the second is a carbonyl attached substituent, their chemical structures are similar, their structure–activity relationships are expected to be similar, and their functions in cosmetics are similar, supporting the use of the available data to support the safety of all the ethanolamides included in this safety assessment.

Published toxicokinetics data are lacking, as are reproductive and developmental toxicity and carcinogenicity data. However, the Panel was of the opinion that dermal penetration would be limited based on the size and the lipophilicity of these ethanolamides. Based on the totality of the data set, the Panel did not think these ingredients would have reproductive or carcinogenic effects.

Also, while it is a metabolic possibility that amidases present in human skin could potentially convert the ethanolamides to ethanolamine and the corresponding acid, such potential amidase activity would at most cleave a small fraction of the applied ethanolamides. If these ethanolamides were cleaved into ethanolamine and the respective acids, the substantial data available on ethanolamine and other constituents indicate that these components do not have reproductive or carcinogenic effects.

Because it could be possible that DEA may exist as an impurity, the Panel reiterated its discussion regarding the positive findings reported in a dermal carcinogenicity study of DEA. The hepatocarcinogenicity that was reported in mice was considered to have little relevance to the safety of DEA in personal care products. Additionally, renal lesions reported in mice could have been the result of DEA-induced choline deficiency, a mechanism that has little relevance in humans. If DEA-induced choline deficiency was not the cause of the renal lesions, it was thought there was still no carcinogenic risk to humans because DEA does not appear to penetrate human skin to any significant extent at concentrations relevant to human exposures from the use of personal care products.

The ethanolamides consist of covalent, secondary amides. The Panel was concerned that secondary amides tend to react with nitrosating agents to form nitrosamides. Because of the

potential for this process to occur, ethanolamides should not be used in cosmetic products in which *N*-nitroso compounds may be formed.

The potential exists for dermal irritation with the use of products formulated using ethanolamides. The Panel specified that products containing ethanolamides must be formulated to be nonirritating. Test data indicate that these ingredients are not sensitizers.

Because the ethanolamides can be used in products that may be aerosolized, including aerosol hair sprays and foot sprays, the Panel discussed the issue of incidental inhalation exposure. In the absence of inhalation data, the Panel noted that there was lack of systemic toxicity in dermal and oral single and repeated dose toxicity studies, negative results for genotoxicity in Ames tests and an unscheduled DNA synthesis assay, and little to no irritation potential and no sensitization potential. Further, this ingredient is reportedly used at concentrations of $\leq 1\%$ in cosmetic products that may be aerosolized. The Panel noted that 95% to 99% of droplets/particles produced in cosmetic aerosols would not be respirable to any appreciable amount. However, the potential for inhalation toxicity is not limited to respirable droplets/particles deposited in the lungs. Inhaled droplets/particles deposited in the nasopharyngeal and bronchial regions of the respiratory tract may cause toxic effects depending on their chemical and other properties. Nevertheless, coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects.

Conclusion

The CIR Expert Panel concluded that the ethanolamides listed subsequently are safe in the present practices of use and concentration described in this safety assessment when formulated to be nonirritating. The Expert Panel cautioned that these ingredients should not be used in cosmetic products in which *N*-nitroso compounds may be formed.

acetamide MEA,
azelamide MEA*,
babassuamide MEA*,
behenamide MEA*,
C16-22 acid amide MEA*,
cocamide MEA,
cocamide methyl MEA,
cocamidopropyl betainamide MEA chloride,
hydroxystearamide MEA*,
isostearamide MEA*,
lactamide MEA,
lauramide MEA,
linoleamide MEA*,
myristamide MEA,
oatamide MEA*,
oleamide MEA*,
oliveamide MEA*,
palm kernelamide MEA*,
palmamide MEA*,
palmitamide MEA*,
pantothenamide MEA*,
peanutamide MEA,
ricinoleamide MEA,
stearamide MEA,
sunfloweramide MEA*,
tallowamide MEA*,
trideceth-2 carboxamide MEA, and
undecylenamide MEA,

Were the ingredients not in current use (as indicated by *) to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in this group.

Authors' Note

Unpublished sources cited in this report are available from the Director, Cosmetic Ingredient Review, 1620 L Street, NW, Suite 1200, Washington, DC 20036, USA.

Author Contributions

M. M. Fiume contributed to conception and design; acquisition, analysis, and interpretation; and drafted the article. B. A. Heldreth contributed to conception and design; acquisition, analysis, and interpretation; drafted the article; and critically revised the article. Gill, L., W. F. Bergfeld, D. V. Belsito, R. A. Hill, C. D. Klaassen, D. C. Liebler, J. G. Marks, T. J. Slaga, and P. W. Snyder contributed to conception and design, analysis and interpretation, and critically revised the article. R. C. Shank contributed to conception and design and analysis and interpretation. Former CIR Director F. Alan Anderson contributed to conception and design, analysis, and interpretation and critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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References

1. Pang S. Isostearamide DEA & MEA, Myristamide DEA & MEA, Stearmide DEA & MEA; 1995. Available from the CIR, 1101 17th Street, NW, Ste 412, Washington, DC 20036. Web site. http://cir-safety.org.
2. Andersen FA (ed). Final report on the safety assessment of acetamide MEA. *J Am Coll Toxicol*. 1993;12(3):225-236.

3. Andersen FA (ed). Annual Review of Cosmetic Ingredient Safety Assessments: 2007-2010. *Int J Toxicol*. 2011;30(suppl 2): 73S-127S.
4. Andersen FA (ed). Final report on the safety assessment of cocamide MEA. *Int J Toxicol*. 1999;18(suppl 2):9-16.
5. Bíró T, Tóth BI, Haskó G, Paus R, Pacher P. The endocannabinoid system of the skin in health and disease: novel perspectives and therapeutic opportunities. *Trends Pharmacol Sci*. 2009;30(8): 411-420.
6. Bisogno T, De Petrocellis L, Di Marzo V. Fatty acid hydrolase, an enzyme with many bioactive substrates. Possible therapeutic implications. *Curr Pharm Des*. 2002;8(7):125-133.
7. Gray GM, Tabiowo A, Trotter MD. Studies on the soluble membrane-bound amino acid 2-naphthylamidases in pig and human epidermis. *Biochem J*. 1977;161(3):667-675.
8. Knaak JB, Leung HW, Stott WT, Busch J, Bilsky J. Toxicology of mono-, di-, and triethanolamine. *Rev Environ Contam Toxicol*. 1997;149:1-86.
9. Fernandez-Perez M, Otero C. Enzymatic synthesis of amide surfactants from ethanolamine. *Enzyme Microb Technol*. 2001;28(6): 527-536.
10. Abdul Rahman MB, Yap CL, Dzulkefly K, Abdul Rahman RNZ, Salleh AB, Basri M. Synthesis of palm kernel oil alkanolamide using lipase. *J Oleo Sci*. 2003;52(2):65-72.
11. Gottschalck TE, Breslawec HP. *International Cosmetic Ingredient Dictionary and Handbook*. 14th ed. Washington, DC: Personal Care Products Council; 2012.
12. Food and Drug Administration. *Frequency of Use of Cosmetic Ingredients. FDA Database*. Washington, DC: FDA; 2011.
13. Personal Care Products Council. Concentration of Use by FDA Product Category: Ethanolamine and Ethanolamine Containing Ingredients. Unpublished data submitted by Personal Care Products Council; 2011:9.
14. Bremmer HJ, Prud'homme de Lodder LCH, Engelen JGM. Cosmetics Fact Sheet: to assess the risks for the consumer; Updated version for ConsExpo 4. Report No. RIVM 320104001/2006, 1-77; 2006.
15. Johnsen MA. The influence of particle size. *Spray Technol Mark*. 2004;November:24-27.
16. Rothe H, Fautz R, Gerber E, et al. Special aspects of cosmetic spray safety evaluations: principles on inhalation risk assessment. *Toxicol Lett*. 2011;205(2):97-104.
17. Rothe H. Special Aspects of Cosmetic Spray Evalulation. Unpublished data presented at the 26 September CIR Expert Panel meeting. Washington, DC; 2011.
18. European Commission. European Commission Enterprise and Industry. Cosmetics—Cosing. Annex III/Part 1, 61—monoalkylamines, nomoalkanolamines and their salts; 2010. Web site. http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.details&id=33796. Accessed date 10-5-2010.
19. Environmental Protection Agency. Appendix 1. Robust summaries. ACC FND Amides Category I—FND Amides; 2004. Web site. http://www.epa.gov/hpv/pubs/summaries/fantdrad/c13319rr.pdf. Summaries of unpublished data.
20. Environmental Protection Agency. Screening-level hazard characterization, fatty nitrogen derived (FND) amides category; 2010. Web site. http://www.epa.gov/chemrtk/hpvis/hazchar/Category_FND%20Amides_September_2010.pdf. Summaries of unpublished data.
21. European Commission—European Chemicals Bureau. IUCLID dataset. Amides, coco, N-(Hydroxyethyl); 2000. Web site. http://esis.jrc.ec.europa.eu/doc/existing-chemicals/IUCLID/data_sheets/68140001.pdf. Accessed August 4, 2011.
22. European Commission—European Chemicals Bureau. IUCLID Dataset. N-(2-hydroxyethyl)dodecanamide; 2000. Web site. http://esis.jrc.ec.europa.eu/doc/existing-chemicals/IUCLID/data_sheets/142789.pdf.
23. Elder RE (ed). Final report on the safety assessment of triethanolamine, diethanolamine, and monoethanolamine. *J Am Coll Toxicol*. 1983;2(7):183-235.
24. Andersen FA (ed). Final report on the safety assessment of peanut (*Arachis hypogaea*) oil, hydrogenated peanut oil, peanut acid, peanut glycerides, and penaut (*Arachis hypogaea*) flour. *Int J Toxicol*. 2001;20(suppl 2):65-77.
25. Andersen FA (ed). Amended final report on the safety assessment of hydroxystearic acid. *Int J Toxicol*. 1999;18(suppl 1):1-10.
26. Andersen FA (ed). Final report on the safety assessment of elaeis guineensis (palm) oil, elaeis guineensis (palm) kernel oil, hydrogenated palm oil and hydrogenated palm kernel oil. *Int J Toxicol*. 2000;19(suppl 2):7-28.
27. Zeiger E, Andersen B, Haworth S, Lawlor T, Mortelmans K, Speck W. *Salmonella* mutagencitiy tests: III. Results from the testing of 25 chemicals. *Environ Mutagen*. 1987;9(suppl 9): 1-110.
28. Burnett CL, Bergfeld WF, Belsito DV, et al. Final report of the safety assessment of cocamidopropyl betaine. *Int J Toxicol*. 2012; 31(Suppl 4):77S-111S. Available from the CIR, 1101 17th Street, NW, Ste 412, Washington DC 20036. Web site. http://cir-safety.org.
29. Andersen FA (ed). Final report on the safety assessment of glycolic acid, ammonium, calcium, potassium, and sodium glycolates, methyl, ethyl, propyl, and butyl glycolates, and lactic acid, ammonium, calcium, potassium, sodium, and TEA-lactates, methyl, ethyl, isoprpyl, and butyl lactates, and lauryl, myristyl, and cetyl lactates. *Int J Toxicol*. 1998;17(suppl 1):1-241.
30. Elder RL (ed). Final report on the safety assessment of oleic acid, lauric acid, palmitic acid, myristic acid, and stearic acid. *J Am Coll Toxicol*. 1987;6(3):321-401.
31. Andersen FA (ed). Final report on the safety assessment of *Ricinus communis* (castor) seed oil, hydrogenated castor oil, glyceryl ricinoleate, glyceryl ricinoleate se, ricinoleic acid, potassium ricinoleate, sodium ricinoleate, zinc ricinoleate, cetyl ricinoleate, ethyl ricinoleate, glycol ricinoleate, isopropyl ricinoleate, methyl ricinoleate, and octyldodecyl ricinoleate. *Int J Toxicol*. 2007; 26(suppl 3):31-77.
32. Fiume MM, Bergfeld WF, Belsito DV, et al. Tentative amended safety assessment of ethanolamine and ethanolamine salts as used in cosmetics; 2011. Available from the Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 412, Washington, DC 20036. Web site. www.cir-safety.org.
33. Burnett CL, Fiume MM, Bergfeld WF, et al. Final report of the CIR Expert Panel on the safety of plant-derived fatty acid oils and

used in cosmetics; 2011. Available from the CIR, 1101 17th Street, NW, Ste 412, Washington DC 20036. Web site. http://cir-safety.org.

34. Fiume MM, Heldreth BA, Bergfeld WF, et al. Final report of the safety assessment on dicarboxlic acids and their salts and esters of dicarboxylic acids as used in cosmetics. *Int J Toxicol*. 2012; 31(Suppl 4):5S-76S. Available from the CIR, 1101 17th Street, NW, Ste 412, Washington DC 20036. Web site. http://cir-safety.org.
35. Burnett C, Bergfeld WF, Belsito DV, et al. Amended safety assessment of *Cocos nucifera* (coconut) oil, coconut acid, hydrogenated coconut acid, hydrogenated coconut oil, ammonium cocomonoglyceride sulfate, butylene glycol cocoate, caprylic/capric/coco glycerides, cocoglycerides, coconut alcohol, coconut oil decyl esters, decyl cocoate, ethylhexyl cocoate, hydrogenated coco-glycerides, isodecyl cocoate, lauryl cocoate, magnesium cocoate, methyl cocoate, octyldodecyl cocoate, pentaerythrityl cocoate, potassium cocoate, potassium hydrogenated cocoate, sodium cocoate, sodium cocomonoglyceride sulfate, sodium hydrogenated cocoate, and tridecyl cocoate. *Int J Toxicol*. 2011;30(Suppl 3):5S-16S. Available from the CIR, 1101 17th Street, NW, Ste 412, Washington DC 20036. Web site. http://cir-safety.org.
36. Elder RL (ed). Final report on the safety assessment of isostearic acid. *J Am Coll Toxicol*. 1983;2(7):61-74.
37. Elder RL (ed). Final report on the safety assessment of panthenol and pantothenic acid. *J Am Coll Toxicol*. 1987;6(1):139-162.
38. Fiume MM, Heldreth BA, Bergfeld WF, et al. CIR Expert Panel final amended report on alkyl PEG ethers as used in cosmetics. *Int J Toxicol*. 2012;31(Suppl 5):169S-244S. Available from the CIR, 1101 17th Street, NW, Ste 412, Washington DC 20036. Web site. http://cir-safety.org.
39. ACD/Labs. *Advanced Chemistry Development (ACD/Labs) Software*. Version 9.02. Canada: ACD/Labs; 2011.
40. Wenker H. Synthesis of 2-oxazolines and 2-thiazolines from N-acyl-2-aminoethanols. *J Am Chem Soc*. 1935;57(6):1079-1080.
41. Effenberger F, Bessey E. Transacylations with acyl derivatives of 4-pyridone. *Chemische Berichte*. 1980;113(6):2100-2109.
42. Syracuse Research Corporation. *PhysProp data*. Syracuse, NY: Syracuse Research Corporation; 1997.
43. Rowe RG, Flower G Jr. Antistatic plastics. US 2,773,852. December 11, 1956.
44. Morales-Sanfrutos J, Megia-Fernandez A, Hernandez-Mateo F, Giron-Gonzalez MD, Salto-Gonzalez R, Santoyo-Gonzalez F. Alkyl sulfonyl derivatized PAMAM-G2 dendrimers as nonviral gene delivery vectors with improved transfection efficiencies. *Org Biomol Chem*. 2011;9(3):851-864.
45. Kimura C, Kashiwaya K, Murai K, Suzuki S. Preparation and surface active properties of sodium 2-(N-alkanoylamino)ethyl sulfates. *Yukagaku*. 1983;32(11):692-694.
46. Roe ET, Miles TD, Swern D. Fatty acid amides. V. Preparation of N-(2-acetoxyethyl) amides of aliphatic acid. *J Am Chem Soc*. 1952;74(13):3442-3443.
47. Guan LP, Zhao DH, Xiu JH, Sui X, Piao HR, Quan ZS. Synthesis and anticonvulsant activity of N-(2-hydroxyethyl)amide derivatives. *Archiv der Pharmazie*. 2009;342(1):34-40.