Article

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Safety Assessment of Fatty Acid Amidopropyl Dimethylamines as Used in Cosmetics

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Abstract

The Cosmetic Ingredient Review Expert Panel (Panel) reviewed the safety of fatty acid amidopropyl dimethylamines, which function primarily as antistatic agents in cosmetic products. The relevant animal and human data reviewed for these ingredients indicate that they are potential dermal sensitizers that may be due in part by the sensitizing impurity, 3,3-dimethylaminopropylamine. The Panel concluded that fatty acid amidopropyl dimethylamines were safe as cosmetic ingredients when they are formulated to be nonsensitizing, which may be based on a quantitative risk assessment.

Keywords

fatty acid amidopropyl dimethylamines

Introduction

The fatty acid amidopropyl dimethylamines function primarily as antistatic agents in cosmetic products. These chemicals are sometimes referred to as "amidoamines." The full list of ingredients in this safety assessment is found in Table 1.

In December 2010, the Cosmetic Ingredient Review (CIR) Expert Panel (Panel) issued a final amended safety assessment on cocamidopropyl betaine (CAPB) and related fatty acid amidopropyl betaines.[1] The Panel concluded that these ingredients "were safe in cosmetics when they are formulated to be non-sensitizing, which may be based on a quantitative risk assessment." The Panel was aware of impurities that may exist in the amidopropyl betaines and expressed concern over their sensitizing potential. Those impurities were 3,3-dimethylaminopropylamine (DMAPA) and the fatty acid amidopropyl dimethylamines presented as ingredients in this report. A quantitative risk assessment (QRA) of DMAPA at a concentration of 0.01% in raw CAPB indicated no sensitization in finished cosmetic products; amidoamine at a concentration of 0.5% in raw CAPB may cause sensitization in certain finished cosmetic products. The Panel advised industry to continue minimizing the concentrations of the sensitizing impurities. The summaries of the studies on DMAPA and amidoamine along with a summary of the QRA on these 2 chemicals that the Panel reviewed in the CAPB safety assessment have been incorporated into this safety assessment.

Toxicological data on stearamidopropyl dimethylamine (synonym: *N*-[3-(dimethylamino)propyl] stearamide) in this safety assessment were obtained from robust summaries of data submitted to the European Chemical Agency (ECHA) by companies as part of the REACH chemical registration process. These data are available on the ECHA website.[2]

Chemistry

The definitions and CAS registry numbers, where available, and structures of the fatty acid amidopropyl dimethylamines ingredients are presented in Table 1. The available information on the physical and chemical properties of these ingredients are presented in Table 2.

The ingredients in this review each have the same core structure of a fatty acid amide, *N*-substituted with 3 propyl-*N*, *N*-dimethylamine. These ingredients are manufactured by the amidation (ie, amide-forming condensation) of fatty acids with DMAPA, most commonly under alkaline or acidic conditions (Figure 1).[3,4] The resultant ingredients have an identical

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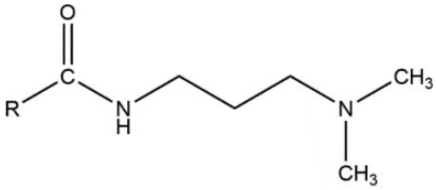
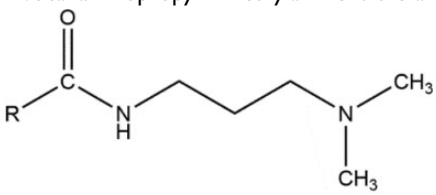
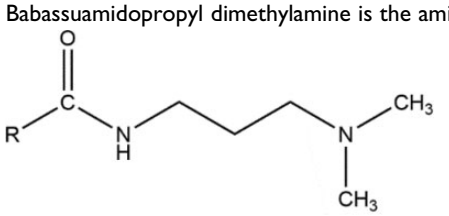
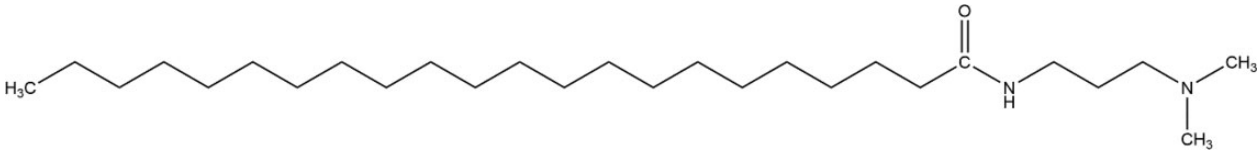
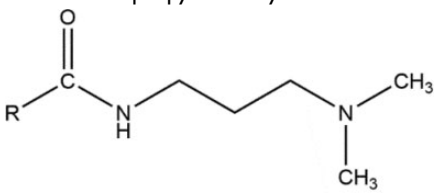
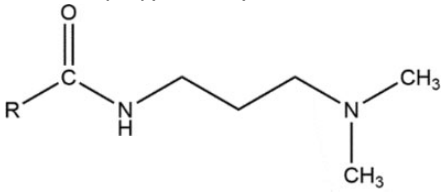
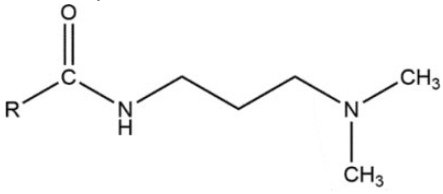
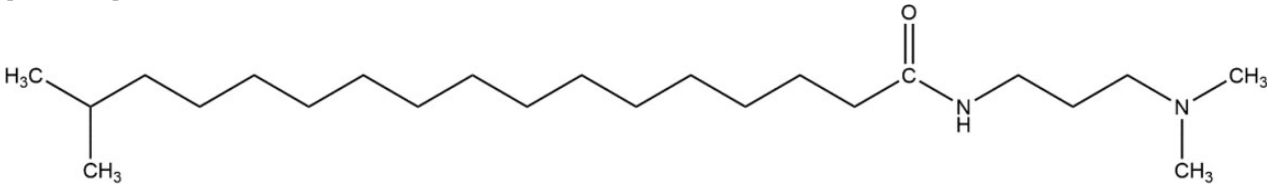
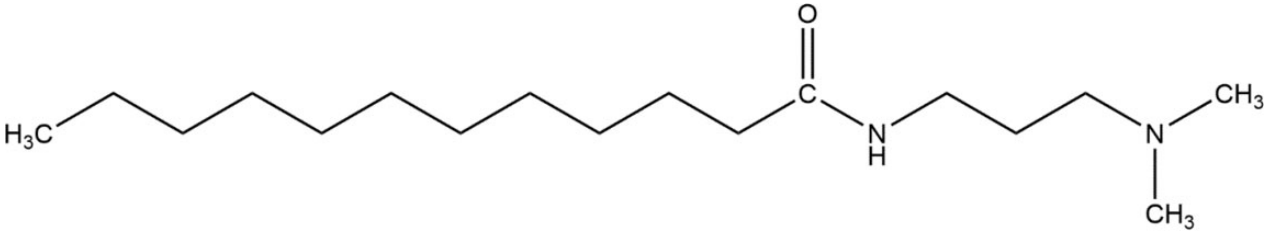
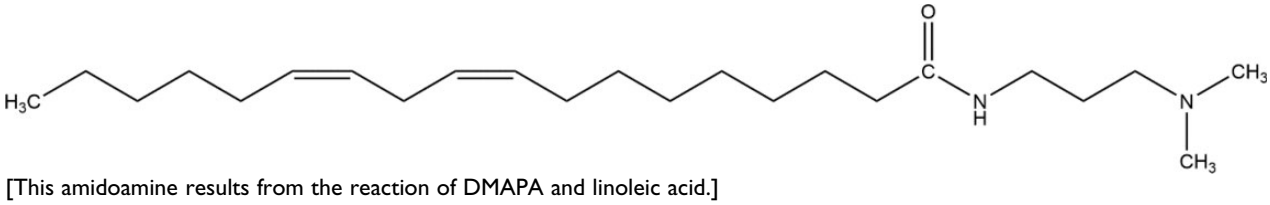
Table 1. Names, CAS Registry Numbers, and Definitions.[16] (Wherein the Italicized or Bracketed Text Has Been Added by CIR staff).

Ingredient & CAS No.	Definition
Almondamidopropyl dimethylamine	Almondamidopropyl dimethylamine is the amidoamine that conforms generally to the structure:  wherein RC(O)- represents the fatty acids derived from almond oil. [This amidoamine results from the reaction of DMAPA and the fatty acids derived from almond oil.]
Avocadamidopropyl dimethylamine	Avocadamidopropyl dimethylamine is the amidoamine that conforms generally to the structure  wherein RC(O)- represents the fatty acids derived from *Persea gratissima* (avocado) oil. [This amidoamine results from the reaction of DMAPA and the fatty acids derived from Persea gratissima (avocado) oil.]
Babassuamidopropyl dimethylamine	Babassuamidopropyl dimethylamine is the amidoamine that conforms generally to the structure  wherein RC(O)- represents the fatty acids derived from *Orbignya oleifera* (babassu) oil. [This amidoamine results from the reaction of DMAPA and the fatty acids derived from *O oleifera* (babassu) oil.]
Behenamidopropyl dimethylamine 60270-33-9 [872429-01 -1]	Behenamidopropyl dimethylamine is the amidoamine that conforms generally to the structure  [This amidoamine results from the reaction of DMAPA and behenic acid.]
Brassicamidopropyl dimethylamine	Brassicamidopropyl dimethylamine is the amidoamine that conforms generally to the structure  wherein RC(O)- represents the fatty acids derived from *Brassica campestris* (rapeseed) seed oil. [This amidoamine results from the reaction of DMAPA and the fatty acids derived from *B campestris* (rapeseed) seed oil.]

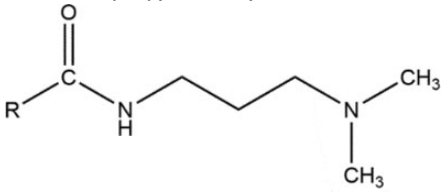
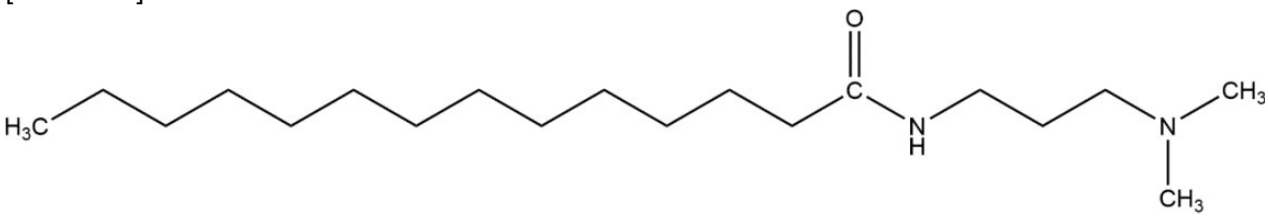
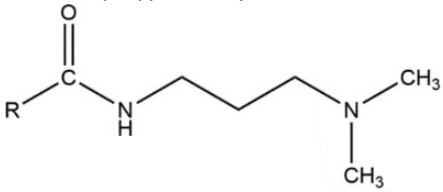
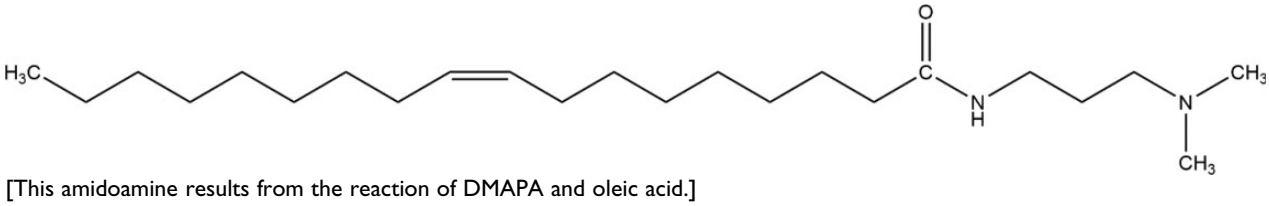
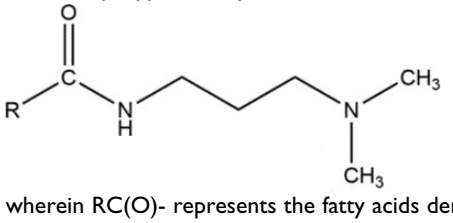
(continued)

Table 1. (continued)

Ingredient & CAS No.	Definition
Cocamidopropyl dimethylamine 68140-01-2	Cocamidopropyl dimethylamine is the amidoamine that conforms generally to the structure  wherein RC(O)- represents the fatty acids derived from coconut oil. [This amidoamine results from the reaction of DMAPA and the fatty acids derived from coconut oil.]
Dilinoleamidopropyl dimethylamine [120174-68-7]	Dilinoleamidopropyl Dimethylamine is the condensation product of dilinoleic acid and aminopropyl dimethylamine.  [wherein RC(O)- represents the variety of 36-carbon dicarboxylic acid residues, formed by the catalytic dimerization of linoleic acid.]
Isostearamidopropyl dimethylamine 67799-04-6 [3432-14-2]	Isostearamidopropyl dimethylamine is the amidoamine that conforms generally to the structure  This amidoamine results from the reaction of DMAPA and isostearic acid.
Lauramidopropyl dimethylamine 3179-80-4 [1002119-56-3] [872428-97-2]	Lauramidopropyl dimethylamine is the amidoamine that conforms generally to the structure  [This amidoamine results from the reaction of DMAPA and lauric acid.]
Linoleamidopropyl dimethylamine 81613-56-1	Linoleamidopropyl dimethylamine is the amidoamine that conforms generally to the structure  [This amidoamine results from the reaction of DMAPA and linoleic acid.]

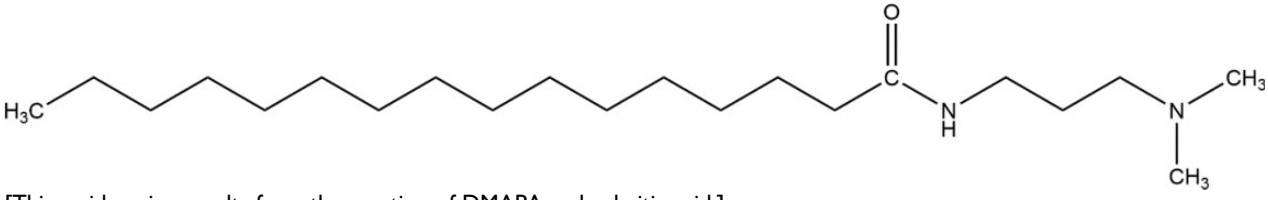
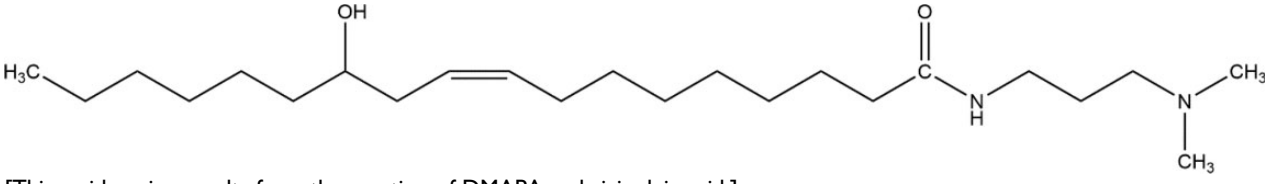
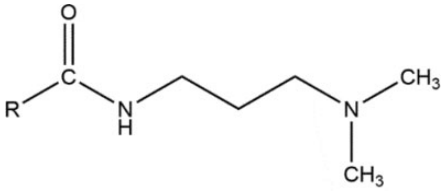
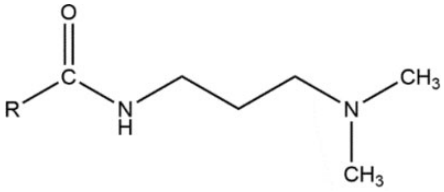
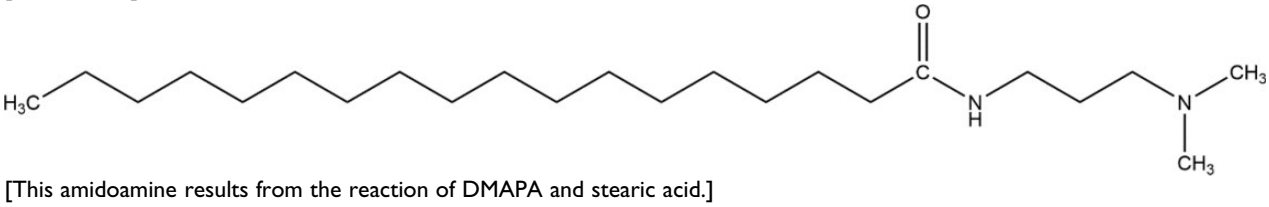
(continued)

Table 1. (continued)

Ingredient & CAS No.	Definition
Minkamidopropyl dimethylamine 68953-11-7	Minkamidopropyl dimethylamine is the amidoamine that conforms generally to the structure  wherein RC(O)- represents the fatty acids derived from mink oil. [This amidoamine results from the reaction of DMAPA and the fatty groups derived from mink oil.]
Myristamidopropyl dimethylamine 45267-19-4 [872428-98-3]	Myristamidopropyl dimethylamine is the amidoamine that conforms generally to the structure  [This amidoamine results from the reaction of DMAPA and myristic acid.]
Oatamidopropyl dimethylamine	Oatamidopropyl dimethylamine is the amidoamine that conforms generally to the structure  wherein RC(O)- represents the fatty acids derived from *Avena sativa* (oat) kernel oil. [This amidoamine results from the reaction of DMAPA and the fatty acids derived from *A sativa* (oat) kernel oil.]
Oleamidopropyl dimethylamine 109-28-4 [149879-92-5] [126150-52-5]	Oleamidopropyl dimethylamine is the amidoamine that conforms generally to the structure  [This amidoamine results from the reaction of DMAPA and oleic acid.]
Oleamidopropyl dimethylamine	Oleamidopropyl dimethylamine is the amidoamine that conforms generally to the structure  wherein RC(O)- represents the fatty acids derived from olive oil. [This amidoamine results from the reaction of DMAPA and the fatty acids derived from olive oil.]

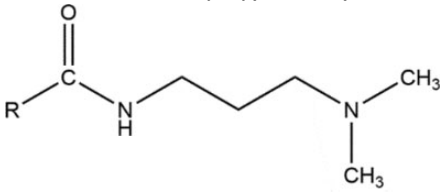
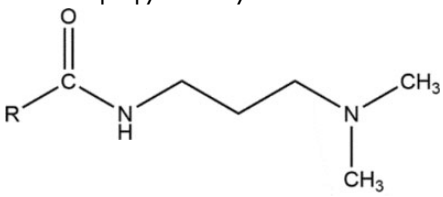
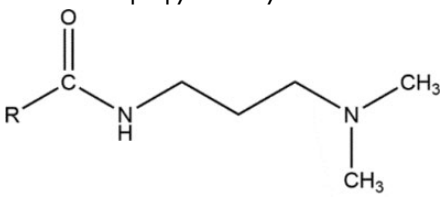
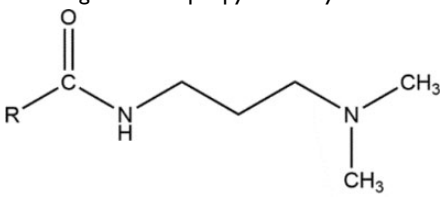
(continued)

Table 1. (continued)

Ingredient & CAS No.	Definition
Palmitamidopropyl dimethylamine 39669-97-1 [872428-99-4]	Palmitamidopropyl dimethylamine is the amidoamine that conforms generally to the structure  [This amidoamine results from the reaction of DMAPA and palmitic acid.]
Ricinoleamidopropyl dimethylamine 20457-75-4	Ricinoleamidopropyl dimethylamine is the amidoamine that conforms generally to the structure  [This amidoamine results from the reaction of DMAPA and ricinoleic acid.]
Sesamidopropyl dimethylamine	Sesamidopropyl dimethylamine is the amidoamine that conforms generally to the structure  wherein RC(O)- represents the fatty acids derived from sesame oil. [This amidoamine results from the reaction of DMAPA and the fatty acids derived from sesame oil.]
Soyamidopropyl dimethylamine 68188-30-7	Soyamidopropyl dimethylamine is the amidoamine that conforms generally to the structure  wherein RC(O)- represents the fatty acids derived from soy. [This amidoamine results from the reaction of DMAPA and the fatty acids derived from soy.]
Stearamidopropyl dimethylamine 7651-02-7 20182-63-2 [78392-15 -1]	Stearamidopropyl dimethylamine is the amidoamine that conforms generally to the structure  [This amidoamine results from the reaction of DMAPA and stearic acid.]

(continued)

Table 1. (continued)

Ingredient & CAS No.	Definition
Sunflowerseedamidopropyl dimethylamine	Sunflowerseedamidopropyl dimethylamine is the amidoamine that conforms generally to the structure  wherein RC(O)- represents the fatty acids derived from sunflower seed oil. [This amidoamine results from the reaction of DMAPA and the fatty acids derived from sunflower seed oil.]
Tallamidopropyl dimethylamine 68650-79-3	Tallamidopropyl dimethylamine is the substituted amine that conforms generally to the structure  wherein RC(O)- represents the fatty acids derived from tall oil. [This amidoamine results from the reaction of DMAPA and the fatty acids derived from tall oil.]
Tallowamidopropyl dimethylamine 68425-50-3	Tallowamidopropyl dimethylamine is the amidoamine that conforms generally to the structure  wherein RC(O)- represents the fatty acids derived from tallow. [This amidoamine results from the reaction of DMAPA and the fatty acids derived from tallow.]
Wheat germamidopropyl dimethylamine	Wheat germamidopropyl dimethylamine is the amidoamine that conforms generally to the structure  wherein RC(O)- represents the fatty acids derived from wheat germ oil. [This amidoamine results from the reaction of DMAPA and the fatty acids derived from wheat germ oil.]

Abbreviations: CIR, Cosmetic Ingredient Review; DMAPA, 3,3-dimethylaminopropylamine.

core, with 2 primary functional groups, a secondary amide and a tertiary amine, separated by a propyl chain. These ingredients differ only by the identity of the fatty acid chain(s) attached to the amide functional group of this core. The synthesis of these ingredients is a clean process with little to no by-products and typically yields products that are 98% to 99% pure fatty acid amidopropyl dimethylamines.[5] Accordingly, starting materials, such as DMAPA, represent the largest concern for impurities.

Despite the long alkyl chain substituents therein, these ingredients are readily solubilized in water, as they are easily converted to ammonium salts (ie, cationic surfactants) at even mildly acidic pH values (ie, the tertiary amines are protonated to form ammonium cations; these ingredients are alkaline materials with pK_b values in the range of 5-6).[4,5] Because of their high polarity, both as the free tertiary amines and as the ammonium salts formed in situ, these ingredients are excellent dissipators of triboelectric charges (ie, static electricity), even at low concentrations (eg, 0.1% wt/wt).[5-7] This property likely accounts for the claimed functions of these ingredients as antistatic agents and, at least in part, as conditioning agents. Although not formally claimed, these ingredients are also known to operate as functional surfactants, thickeners, and bacteriostatic agents.[5]

Table 2. Physical and Chemical Properties.

Property	Value	Reference
Behenamidopropyl dimethylamine		
Molecular weight g/mol	424.75	66
Molecular volume cm^3/mol at 20°C	487.4	66
Density/specific gravity g/cm^3 at 20°C	0.871	66
Vapor pressure, mm Hg at 25°C	6.30×10^{-12}	66
Boiling point, °C	544.8	66
Log P at 25°C	9.656	66
Cocamidopropyl dimethylamine		
Appearance	Clear liquid	8
Odor	Mild amine	8
Density/specific gravity, g/cm^3 at 25°C	0.98-1.02	8
Vapor pressure, mm Hg	< 0.01	8
Boiling point, °C at 760 mm Hg	> 100	8
Melting point, °C	< 25	8
Solubility in water	Soluble	8
pH	~ 9	8
Lauramidopropyl dimethylamine		
Molecular weight, g/mol	284.48	66
Molecular volume, cm^3/mol at 20°C	322.3	66
Density/specific gravity, g/cm^3 at 20°C	0.882	66
Vapor pressure, mm Hg at 25	3.17×10^{-7}	66
Boiling Point, °C	418.9	66
Melting Point, °C	28.5-30.0	5
Log P at 25°C	4.561	66
Linoleamidopropyl dimethylamine		
Molecular weight, g/mol	364.61	66
Molecular volume, cm^3/mol at 20°C	408.6	66
Density/specific gravity, g/cm^3 at 20°C	0.892	66
Vapor pressure, mm Hg at 25°C	2.69×10^{-10}	66
Boiling point, °C	504.3	66
Log P at 25°C	6.805	66
Myristamidopropyl dimethylamine		
Molecular weight, g/mol	312.53	66
Molecular volume, cm^3/mol at 20°C	355.3	66
Density/specific gravity, g/cm^3 at 20°C	0.879	66
Vapor pressure, mm Hg at 25°C	3.84×10^{-8}	66
Boiling point, °C	445.8	66
Log P at 25°C	5.580	66
Oleamidopropyl dimethylamine		
Physical form	Liquid	11
Color	Amber	11
Molecular weight, g/mol	366.62	66
Molecular volume, cm^3/mol at 20°C	414.9	66
Density/specific gravity, g/cm^3 at 20°C	0.883	66
Vapor pressure, mm Hg at 25°C	2.57×10^{-10}	66
Boiling Point, °C	504.8	66
Solubility	Slightly in water, readily when neutralized with acid	11
Log P at 25°C	7.209	66
pH at 25°C	9.0-10.0	11
Palmitamidopropyl dimethylamine		
Molecular weight, g/mol	340.59	66
Molecular volume, cm^3/mol at 20°C	388.3	66
Density/specific gravity g/cm^3 at 20°C	0.876	66
Vapor pressure, mm Hg at 25°C	4.52×10^{-9}	66
Boiling point, °C	471.8	66
Log P at 25°C	6.599	66
Ricinoleamidopropyl dimethylamine		
Molecular weight, g/mol	382.62	66
Molecular volume, cm^3/mol at 20°C	412.8	66
Density/specific gravity, g/cm^3 at 20°C	0.926	66
Vapor pressure, mm Hg at 25°C	8.20×10^{-14}	66
Boiling point, °C	537.9	66
Log P at 25°C	5.395	66
Stearamidopropyl dimethylamine		
Physical form	Waxy flake	13
Molecular weight, g/mol	368.64	66
Molecular volume, cm^3/mol at 20°C	421.7	66
Density/specific gravity, g/cm^3 at 20°C	0.874	66
Vapor pressure, mm Hg at 25°C	5.19×10^{-10}-9.03×10^{10}	66
Boiling point, °C	490.6-496.9	66
Melting point, °C	58.5-59.5; 65-70	5,13
Log P at 25°C	7.618-7.629	66

Method of Manufacturing

Cocamidopropyl Dimethylamine

According to a supplier, cocamidopropyl dimethylamine is made by mixing together refined coconut oil with DMAPA and heating the mixture to >75°C and <175°C.[8] The progress of

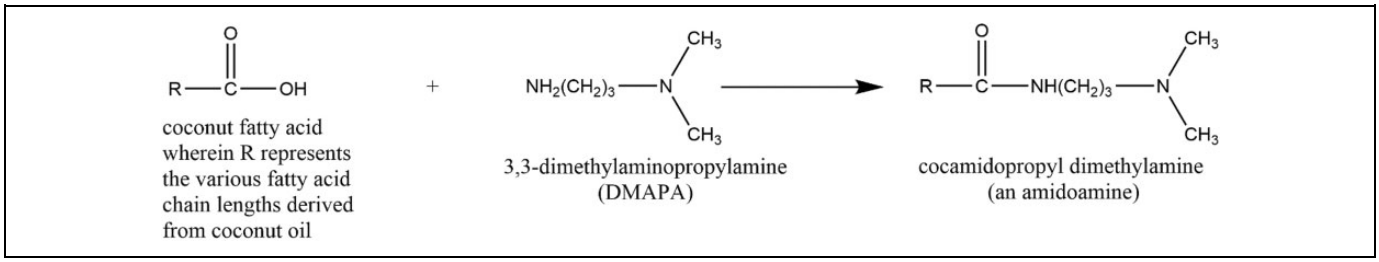


Figure 1. Synthesis of cocamidopropyl dimethylamine.

the reaction is followed using standard analytical tests until specifications are met. The product is then filtered and stored in lined steel drums.

N-Nitrosation and Safety Issues

Although nitrosamine content has not been reported, fatty acid amidopropyl dimethylamines are composed of secondary amides and tertiary amines and potentially can be nitrosated. Of the approximately 209 nitrosamines tested, 85% have been shown to produce cancer in laboratory animals.[9] Nitrosation can occur under physiologic conditions.[3] Depending on the nitrosating agent and the substrate, nitrosation can occur under acidic, neutral, or alkaline conditions. Atmospheric NO_2 may also participate in the nitrosation of amines in aqueous solution.[4] Accordingly, fatty acid amidopropyl dimethylamines should be formulated to avoid the formation of nitrosamines.

Impurities

Behenamidopropyl Dimethylamine

A supplier has indicated that the maximum level of DMAPA in behenamidopropyl dimethylamine is 115 ppm.[10] The supplier stated that the typical use level of this material in hair conditioners is 2.3%, which results in a maximum DMAPA level of 2.65 ppm in the finished product.

Cocamidopropyl Dimethylamine

A supplier reported the final composition of the product cocamidopropyl dimethylamine to be 83% to 90% cocamidopropyl dimethylamine, 8.9% to 9.4% glycerin, 1.0% (max) DMAPA, and 5.0% (max) glyceryl esters.[8]

Oleamidopropyl Dimethylamine

A product description sheet indicates that oleamidopropyl dimethylamine is at minimum 88% pure and has a maximum concentration of 0.60% DMAPA.[11]

Stearamidopropyl Dimethylamine

The maximum level of DMAPA in stearamidopropyl dimethylamine has been reported to be 30 ppm.[12] The supplier stated that, in the typical use concentration of 2.14% stearamidopropyl dimethylamine in hair conditioners, the DMAPA level in the finished product is a maximum of 0.65 ppm. Another supplier indicated that the free DMAPA in stearamidopropyl dimethylamine is less than 0.2%.[13]

In another sample of stearamidopropyl dimethylamine, the chemical composition was at minimum 97% of the active matter and contained at maximum 0.002% free DMAPA and 3.0% free fatty acid.[14] The C-chain distribution for this sample of stearamidopropyl dimethylamine was reported as the following: $< C16 < 1\%$; $C16 < 5\%$; $C18 > 93\%$; and $> C18 < 1\%$. Finally, a sample of stearamidopropyl dimethylamine was determined to have < 20 ppm residual DMAPA, < 1 ppm secondary amines, and < 50 ppb nitrosamines.[15]

Use

Cosmetic

All but 1 of the 24 fatty acid amidopropyl dimethylamines included in this safety assessment function as antistatic agents in cosmetic formulations.[16] Brassicamidopropyl dimethylamine is reported to function as a hair- and skin-conditioning agent. In addition to being an antistatic agent, stearamidopropyl dimethylamine is reported to function as a hair conditioning agent.

Table 3 presents the frequency and maximum use concentration ranges for fatty acid amidopropyl dimethylamines. According to information supplied to the Food and Drug Administration by industry as part of the Voluntary Cosmetic Registration Program (VCRP), stearamidopropyl dimethylamine has the most reported uses in cosmetic and personal care products, with a total of 427; 355 of those uses are in rinse-off formulations.[17] Most of the rinse-off uses are in hair conditioners. Behenamidopropyl dimethylamine has the second greatest number of overall uses reported, with a total of 35; of those, 32 uses are in rinse-off formulations. Again, most of the rinse-off uses are in hair conditioners. A few uses were reported each for brassicamidopropyl dimethylamine (1), cocamidopropyl dimethylamine (6), isostearamidopropyl dimethylamine (13), lauramidopropyl dimethylamine (1), minkamidopropyl dimethylamine (1), oleamidopropyl dimethylamine (12), and palmitamidopropyl dimethylamine (1). No uses were reported to the VCRP for the remaining fatty acid amidopropyl dimethylamines.

Table 3a. Frequency (2014) and Concentration of use (2012) According to Duration and Type of Exposure for Fatty Acid Amidopropyl Dimethylamine Ingredients.[17,18]

	# of uses	Max conc of use, %	# of uses	Max conc of use, %	# of uses	Max conc of use, %	# of uses	Max conc of use, %	# of uses	Max conc of use, %	# of uses	Max conc of use, %	# of uses	Max conc of use, %	# of uses	Max conc of use, %	# of uses	Max conc of use, %
	Behenamidopropyl dimethylamine		Brassicamidopropyl dimethylamine		Cocamidopropyl dimethylamine		Isostearamidopropyl dimethylamine		Lauramidopropyl dimethylamine		Minkamidopropyl dimethylamine		Oleamidopropyl dimethylamine		Palmitamidopropyl dimethylamine		Stearamidopropyl dimethylamine	
Totals[a]	53	0.3-3	5	0.2-4	17	0.003-6.5	10	0.04-0.38	2	NR	1	NR	13	0.0015-1	1	NR	551	**0.01-5**
Duration of use																		
Leave-on	2	1	NR	0.2	6	0.03	1	0.04	NR	NR	NR	NR	4	0.0015-1	NR	NR	84	0.02-3
Rinse off	51	0.3-3	5	4	11	0.003-6.5	9	0.38	2	NR	1	NR	9	0.8	1	NR	467	0.01-5
Diluted for (bath) use	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Exposure type																		
Eye area	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	1.5 -1.8
Incidental ingestion	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	1.7
Incidental inhalation-spray	NR	1[b]	NR	NR	3[b]; 2[c]	NR	1[c]	NR	NR	NR	NR	NR	4[b]	0.0015[b]; 1[c]; 0.15[d]	NR	NR	64[b]	1.8; 2-3[b]
Incidental inhalation-powder	NR	NR	NR	NR	2[c]	NR	1[c]	NR	NR	NR	NR	NR	NR	1[c]	NR	NR	NR	1.7
Dermal contact	5	NR	NR	0.2	15	0.03-6.5	1	0.04	1	NR	NR	NR	NR	1	NR	NR	26	0.01-2
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Hair—noncoloring	48	0.3-3	5	4	2	0.003	9	0.38	1	NR	1	NR	13	0.0015-0.8	1	NR	431	0.05-5
Hair coloring	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	94	0.3-2
Nail	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Mucous membrane	5	NR	NR	NR	5	1.3-5	NR	NR	1	NR	NR	NR	NR	NR	NR	NR	NR	1.7 -1.8
Baby products	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	1	NR

Abbreviation: NR, not reported.

[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]It is possible these products may be sprays, but it is not specified whether the reported uses are sprays.

[c]Not specified whether a powder or a spray, so this information is captured for both categories of incidental inhalation.

[d]0.15% in a hair tonic, dressing, or other hair grooming aid pump spray.

Table 3b. Ingredients Not Reported in Use.

Almondamidopropyl dimethylamine
Avocadamidopropyl dimethylamine
Babassuamidopropyl dimethylamine
Dilinoleamidopropyl dimethylamine
Linoleamidopropyl dimethylamine
Myristamidopropyl dimethylamine
Oatamidopropyl dimethylamine
Oleamidopropyl dimethylamine
Ricinoleamidopropyl dimethylamine
Sesamidopropyl dimethylamine
Soyamidopropyl dimethylamine
Sunflowerseedamidopropyl dimethylamine
Tallamidopropyl dimethylamine
Tallowamidopropyl dimethylamine
Wheat germamidopropyl dimethylamine

In a survey of use concentrations conducted by the Personal Care Products Council, stearamidopropyl dimethylamine is reported to be used at a range of maximum concentrations of 0.01% to 5%, with 5% reported in noncoloring hair conditioners.[18] In behenamidopropyl dimethylamine, the range of maximum concentrations was reported to be 0.3% to 3%, with 3% reported in noncoloring hair conditioners. A range of maximum concentrations for cocamidopropyl dimethylamine was reported to be 0.003% to 6.5%, with 6.5% reported in skin cleansing products. No use concentrations were reported for almondamidopropyl dimethylamine, avocadoamidopropyl dimethylamine, babassuamidopropyl dimethylamine, minkamidopropyl dimethylamine, oatamidopropyl dimethylamine, oleamidopropyl dimethylamine, sesamidopropyl dimethylamine, and tallamidopropyl dimethylamine.[19]

Oleamidopropyl dimethylamine is used in cosmetic sprays, including hair tonics and dressings. Oleamidopropyl dimethylamine and stearamidopropyl dimethylamine may also be used in colognes and indoor tanning products. When used in cosmetic sprays, these ingredients could possibly be inhaled. The maximum concentration of these ingredients reported to be used in a spray product is 0.15% (oleamidopropyl dimethylamine) in a hair tonic, dressing, or other hair-grooming pump spray product. 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 to pump sprays.[20,21] 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.[22,23] The amidoamine ingredients in this safety assessment currently are not restricted from use in any way under the rules governing cosmetic products in the European Union.[24]

Noncosmetic

Myristamidopropyl dimethylamine is used as a biocide in contact lens disinfecting solution (concentration reported to be ~0.0005%) and may have uses as a broad-spectrum therapeutic antimicrobial for keratitis and for surgical prophylaxis.[25-30]

Toxicokinetics

Absorption, Distribution, Metabolism, and Excretion

In an IH Skin Perm quantitative structure–activity relationship (QSAR) model, the dermal absorption of stearamidopropyl dimethylamine has been estimated to be 0.04 mg and 0.12 mg after 8 and 24 hours, respectively.[2] The maximum dermal absorption rate was calculated to be 2.40×10^{-6} mg/cm^2/h. The calculations were based on an instantaneous deposition dose of 9257 mg and a skin area of 2000 cm^2. No other studies were found on the absorption, distribution, metabolism, and excretion of fatty acid amidopropyl dimethylamines.

Toxicological Studies

Acute Toxicity

Oral—Nonhuman

Stearamidopropyl dimethylamine. The acute oral toxicity of 10% (wt/wt) stearamidopropyl dimethylamine in propylene glycol was tested in 6 female Wistar rats.[2] The rats received 2 dosages of 1,000 mg/kg body weight of the test material within 24 hours. The rats were observed daily for clinical signs of toxicity for 14 days. Two of the 6 animals died on day 2 and day 3, respectively. Clinical signs observed of both the animals found dead, and the surviving animals included hunched posture, lethargy, uncoordinated movements, piloerection, diarrhea, chromodacryorrhea, pallor, and/or ptosis. Recovery from these symptoms in the surviving animals occurred between days 7 and 10. The 2 animals that died during observation had either slight weight gain or weight loss. Three of the 4 surviving animals had body weight loss between days 1 and 8 but gained body weight between day 8 and the end of the observation period. In 1 dead animal, necropsy showed watery-turbid fluid in the stomach and watery-clear, yellowish fluid in the small intestine. The other dead animal had a spleen of reduced size. In the surviving animals, 1 rat had pelvic dilation of the kidneys. No other abnormalities were observed in the remaining animals. The oral lethal dose 50 (LD_{50}) for stearamidopropyl dimethylamine in this study was determined to be greater than 2,000 mg/kg body weight.

In another oral toxicity study, 40% (wt/wt) stearamidopropyl dimethylamine in deionized water was tested in 20 male and 20 female Sprague-Dawley rats.[2] Dose levels were 420, 1,990, 3,910, and 5,470 mg/kg body weight and were delivered in dose volumes of 1.67, 2.21, 4.44, and 6.22 mL/kg body weight, respectively. Posttreatment, animals were observed for clinical signs and mortality at 1/2, 2, and 4 hours and then daily up to 14 days. No mortalities were observed in the 420 and 1,990 mg/kg dose groups. Two males and 4 females in the 3,910 mg/kg dose group, and all rats in the 5,470 mg/kg dose group died during the observation period and within 8 days of

administration of the test material. Clinical signs observed included diarrhea, soft stool, brown-stained abdomen, anal or urogenital region, hypoactivity, hypersensitivity to touch, red-stained nose and mouth, hair loss on abdomen and hindquarters, ataxia, emaciation, bloated abdomen, red stain around eyes, piloerection, lacrimation, high carriage, dyspnea, and hypothermia to touch. At necropsy of the animals that died during the observation period, reddened mucosa (organs not described) was observed in 3 animals from 3,910 mg/kg dose group and 1 animal from 5,470 mg/kg dose group. No other treatment-related changes were reported for any animals in this study. The oral LD_{50} for stearamidopropyl dimethylamine in this study was determined to be 1,396 mg/kg body weight.

Repeated Dose Toxicity

Oral—Nonhuman

Stearamidopropyl dimethylamine. In an oral 14-day, dose range–finding study performed in accordance to Organization for Economic Cooperation and Development (OECD) guideline 407, stearamidopropyl dimethylamine in propylene glycol (concentration not reported) was administered to 3 Crl: WI(Han) rats/sex/dose via gavage at doses of 0, 50, 200, and 500 mg/kg body weight per day.[2] No mortalities were observed during the treatment period in the low- and mid-dose groups. All animals in the 200 mg/kg/d dose group were observed with piloerection on 2 days during the second week only. No clinical signs of toxicity were observed in the low-dose group. Body weights, body weight gains, and feed consumption were comparable to controls. Hematological changes in the low- and mid-dose groups consisted of slightly lower red blood cell and higher reticulocyte counts in males. No dose-related trend was noted with these changes. Clinical biochemistry changes consisted of higher alanine aminotransferase activity in 2 males in the low-dose group and 2 males and 1 female in the mid-dose group, higher alkaline phosphatase activity in 1 female in the mid-dose group, and higher potassium levels in males in the low- and mid-dose groups. No abnormalities or histopathological changes were noted at necropsy of the low- and mid-dose groups. Slight increases in spleen and thymus weights of the mid-dose group females were comparable to those in control animals.

All animals in the high-dose group were killed for humane reasons between days 6 and 8. From day 4 of treatment and after, these animals were observed with lethargy, hunched posture, labored respiration, abdominal swelling, piloerection, chromodacryorrhea, a lean appearance, and/or ptosis. All animals showed weight loss or reduced body weight gain and reduced food consumption during the treatment period. Necropsy of the high-dose animals found gelatinous contents in the gastrointestinal tract or parts thereof and emaciation. The researchers determined the main cause for moribundity in the high-dose group was fore stomach ulceration and/or hyperplasia of the squamous epithelium of the fore stomach. Other histopathological changes noted at this dose level included lymphoid atrophy of the thymus, correlating with reduced size of the thymus at necropsy; hyperplasia and inflammation of the fore stomach; hyperplasia of the villi in the duodenum and jejunum; foamy macrophages and sinusoidal dilation and congestion/erythrophagocytosis in the mesenteric lymph node; and absence of spermiation and degeneration of spermatids in the testes, oligospermia and seminiferous cell debris in the epididymides, and reduced contents in the prostate and seminal vesicles, which corresponded to a reduced size of seminal vesicles, prostate, and epididymides at necropsy. (Full details on which organs were examined microscopically were not provided in the ECHA summary.) The results of this study were used to determine the doses for a reproduction/developmental toxicity test.[2]

Dermal—Nonhuman

Stearamidopropyl dimethylamine. A dermal 90-day repeated dose toxicity study of stearamidopropyl dimethylamine was performed in accordance with OECD Guideline 411 in groups of 5 male and 5 female New Zealand White rabbits.[2] Test solutions were prepared fresh weekly in 30%/70% ethanol/water for each group. The test material was applied at doses of 0%, 0.25%, or 10% wt/vol (equivalent to 0, 5, and 200 mg/kg/d, respectively) in a dose volume of 2 mL/kg/d to intact rabbit skin once daily, 5 d/wk for 13 consecutive weeks. Test sites were not occluded. The animals were collared to prevent oral ingestion of the test material. Clinical signs of toxicity were observed daily, and necropsy and histological examinations were performed at the end of the treatment period.

No mortality was observed during the study. Slight conjunctivitis was observed in 1 control animal and 2 animals in the 0.25% dose group, which was not related to the test material. Animals that received 0.25% test material had moderate or slight erythema, slight edema, slight desquamation, and slight fissuring. Animals that received 10% test material were observed with moderate erythema, slight edema, slight desquamation, and slight fissuring. No treatment-related changes in body weight and body-weight gain were observed during the study. No test-related biologically significant changes were noted in the absolute and relative liver, kidney, and adrenal weight determinations. Statistically significant increases in white blood cell values were noted in the 10% dose group. In addition, there was an increase in platelet values from baseline to necropsy of the 0.25% dose group. The changes in white blood cells of the 10% dose group were attributed to the chronic stress of collaring and not considered to be related to the test material. The significant increase in platelet values of the 0.25% dose group was a result of low baseline values. At necropsy, the treated skin in both the 0.25% and the 10% dose groups had a dry hair coat with an accumulation of test material on the surface. Histopathological examinations revealed minimal acanthosis and hyperkeratosis at the treatment sites of all treated groups. The incidence and severity were similar in both groups. Incidental nontreatment-related histopathological changes were noted in several other tissues such as brain, liver,

kidney, prostate, and pancreas. The researchers in this study determined the systemic no observed adverse effect level (NOAEL) of stearamidopropyl dimethylamine was greater than 10% wt/vol in 30%/70% ethanol/water (equivalent to 200 mg/kg body weight per day).[2]

Reproductive and Developmental Toxicity

Stearamidopropyl Dimethylamine

The effects of stearamidopropyl dimethylamine (100% active ingredient) on reproduction and development were studied in 10 Wistar rats/sex/dose by oral gavage in accordance with OECD guideline 421.[2] Dose levels tested were 0, 20, 70, and 200 mg/kg body weight per day at a dose volume of 5 mL/kg body weight. Parental males were exposed to the test material 2 weeks prior to mating, during mating, and up to study termination. Parental females were exposed 2 weeks prior to mating, during mating, during gestation, and during at least 4 days of lactation. In the 200 mg/kg males, a weight loss of up to 15% of day 1 weight was observed during the first 2 weeks of treatment, but this effect seemed to recover during the treatment period. The mean body weight and body weight gain of the 200 mg/kg males remained statistically significantly lower throughout treatment. Females of the same dose group had statistically significant reduced body weight gain during the first 2 weeks of treatment as well as during gestation. Food intake was reduced during the entire premating period for males and during the first week of the premating period for the females. Additionally, the feed consumption of the females remained slightly lower throughout pregnancy and lactation. No other treatment-related changes were observed in the parental animals.

The nonstatistically significant decrease in the mean number of corpora lutea was observed in the 70 and 200 mg/kg dose groups when compared to the control animal; however, a statistically significant lower number of implantation sites were noted in the 200 mg/kg dose group females. A statistically significant lower number of live pups was noted in the 70 and 200 mg/kg dose groups. No other treatment-related changes were noted in any of the remaining reproductive parameters investigated in this study (ie, mating, fertility and conception indices and precoital time, testes and epididymides weights, spermatogenic staging profiles). Based on the results of this study on stearamidopropyl dimethylamine, the researchers determined the paternal NOAEL to be 70 mg/kg body weight per day, the maternal NOAEL to be 70 mg/kg body weight per day, and the developmental NOAEL to be 200 mg/kg body weight per day.[2]

In the dermal 90-day repeated dose toxicity study in rabbits described earlier, no treatment-related findings concerning the reproductive organs were observed.[2] The dermal developmental toxicity potential of stearamidopropyl dimethylamine was studied in 80 artificially inseminated New Zealand White rabbits.[2] Groups of 20 rabbits received the test material at 0, 5, 100, or 200 mg/kg body weight per day at a dose volume of 2 mL/kg body weight during days 7 through 18 of gestation. The test material was applied to the clipped backs of the rabbits as a solution in 30% isopropanol and 70% reverse osmosis, membrane-processed deionized water. The test sites were not occluded and were rinsed with water 2 hours after each application. The rabbits were collared to prevent oral ingestion of the test material. The rabbits were observed daily during and after the dosage periods for clinical signs of toxicity, skin irritation, mortality, abortion, delivery, body weight, and feed consumption. All rabbits were killed on day 29, and complete gross necropsy was performed. Reproductive organs that were examined included the prostate, seminal vesicles, testis, epididymis in males and the ovaries, uterus, and vagina in females. The uteri were examined for pregnancy, number of implantations, live and dead fetuses, and early and late resorptions. Corpora lutea were counted. Each fetus was weighed and subsequently examined for gross external variations and gender, prior to examination for soft tissue and skeletal variations.

No mortalities were observed during the course of the study. Clinical signs attributed to administration of the test material included alopecia (5, 100, and 200 mg/kg/d doses), excess lacrimation (100 and 200 mg/kg/d dosages), ungroomed coat and green-colored matted fur around mouth and rump (200 mg/kg/d dosage). Statistically significant ($P \leq 0.05$ to $P \leq 0.01$) increases in the incidences of rabbits with these signs occurred only in the mid- and high-dose groups when compared to the controls. Dose-dependent skin reactions including atonia, desquamation, and fissuring were observed in mid- and high-dose groups. One high-dose group rabbit had eschar present, attributed to the treatment. Two low-dose group rabbits aborted on day 21 of gestation and 1 rabbit in the high-dose group delivered prematurely; however, these events were not test material–related. Body weight gains were significantly decreased in the mid-dose ($P \leq 0.05$) and high-dose ($P \leq 0.01$) group animals. High-dose group animals had a significant decrease ($P \leq 0.01$) in average body weight during treatment and continued to have lower average body weights than control rabbits during the post-dosage period. Body weights and body weight gain of low-dose group rabbits were comparable to control values. When compared to the control values, maternal feed consumption was affected in the mid- and high-dose groups, with the average daily feed consumption of the high-dose group rabbits significantly decreased ($P \leq 0.05$ to $P \leq 0.01$) from day 15 through day 21 of gestation.

Slightly impaired implantation was observed, along with slightly decreased litter sizes, in the 200 mg/kg dose when compared to the control group, but this effect was not statistically significant ($P > 0.05$). All of the values were within expected historical control values. The test material did not adversely affect pregnancy incidence or average numbers of corpora lutea or resorptions. Viable fetuses were present in 20, 14, 17, and 14 litters from control, low-, middle-, and high-dosage groups, respectively. One rabbit each from low- and high-dose group had all implantations resorbed. No treatment-related fetal variations at gross external, soft tissue, or skeletal examination were observed.

The researchers concluded that dermal application of stearamidopropyl dimethylamine in rabbits during gestation days 7 through 18 did not produce evidence for developmental toxicity. The maternal no observed effect level (NOEL) was determined to be 5 mg/kg body weight per day, the maternal NOAEL was determined to be100 mg/kg body weight per day based on variations in body weight and feed-consumption data, and the developmental NOAEL was determined to be 200 mg/kg body weight per day in this study.[2]

Genotoxicity

Stearamidopropyl Dimethylamine

The mutagenic potential of 85% stearamidopropyl dimethylamine was studied in reverse mutation assay using *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537 and *Escherichia coli* strain WP2 uvrA, with and without S9 metabolic activation.[31] The test concentrations ranged from 5 to 5,000 μg/plate. The positive controls were 2-nitrofluorene, 9-aminoacridine, sodium azide, methyl methane sulfonate, and 2-aminoanthracene. The test material was cytotoxic at >50 μg/plate in *S typhimurium* and >500 μg/plate in *E coli*. No biologically relevant increases in revertant colony numbers were observed in any test strain at any dose level, with or without metabolic activation. Controls yielded expected results. It was concluded that stearamidopropyl dimethylamine was not mutagenic in this assay.

The mutagenic potential of 100% pure stearamidopropyl dimethylamine in ethanol was studied for cell mutation in mouse lymphoma L5178Y TK+/− cells in accordance with OECD guideline 467 in 2 independent experiments.[2] Concentrations tested were 0.003 to 60 μg/mL, and the experiments were performed with and without 8% or 12% S9 metabolic activation. No statistically significant positive effects with or without S9 activation were observed in either experiment. Positive controls yielded the expected results. It was concluded that stearamidopropyl dimethylamine was not mutagenic in this assay.

The genotoxic potential of stearamidopropyl dimethylamine in ethanol was studied in a chromosome aberration study using human peripheral blood lymphocytes in accordance with OECD guideline 473.[2] In experiment 1 of this 2-part study, the test material was tested up to 10 μg/mL, without and with S9 metabolic activation. In experiment 2, the test material was tested up to 25 and 10 μg/mL, without and with S9, respectively. Incubation for cells in the first experiment was 3 hours, and in the second experiment, incubation was 3 hours and 24 hours or 48 hours. In both experiments, no statistically or biologically significant increased number of cells with chromosomal aberrations were observed both with and without metabolic activation. Solvent and positive controls yielded expected results. Under the conditions of this study, stearamidopropyl dimethylamine was not considered clastogenic.

Carcinogenicity

No studies were found on the carcinogenicity potential of fatty acid amidopropyl dimethylamines.

Irritation and Sensitization

The North American Contact Dermatitis Group (NACDG) evaluated 25,813 patients for allergic contact dermatitis with patch tests from 1998 to 2007.[32] "Amidoamine" produced relevant allergic reactions in 0.5% of the seniors (20/4, 215; ages >65), 0.7% of the adults (136/20, 162; ages 19 to <64), and 0.7% of the children (10/1436; ages <18) tested.

Ocular irritation studies are summarized in Table 4.[2,33-38] No minimal irritation was observed in ocular irritation assays of behenamidopropyl dimethylamine and dilinoleamidopropyl dimethylamine. All but 1 ocular irritation study of stearamidopropyl dimethylamine report no minimal irritation; the exception found severe ocular irritation when tested at 100% in rabbit eyes.

Dermal irritation studies are summarized in Table 5.[2,39-42] Stearamidopropyl dimethylamine was considered not irritating in nonhuman studies when tested at 100%. Behenamidopropyl dimethylamine (up to 3%), 0.1% oleamidopropyl dimethylamine, and 0.045% stearamidopropyl dimethylamine in personal care products were not irritating in several in-use studies.

Dermal sensitization studies are summarized in Table 6.[43-57] Behenamidopropyl dimethylamine at 0.3% diluted to 1%, 4% brassicamidopropyl dimethylamine, and stearamidopropyl dimethylamine up to 2% in hair conditioners were not contact sensitizers. However, irritation reactions were observed.

The sensitization studies of DMAPA and amidoamine that the Panel reviewed in the safety assessment of cocamidopropyl betaine (CAPB) have been summarized in Table 7.[1] In the tables, amidoamine refers to cocamidopropyl dimethylamine.

Clinical Use

Case Reports

The case reports of DMAPA and amidoamine that the Panel reviewed in the safety assessment of cocamidopropyl betaine (CAPB) have been summarized in Table 8.[1] In the tables, amidoamine refers to cocamidopropyl dimethylamine.

Oleamidopropyl dimethylamine. In the Netherlands, 13 female patients were reported to have allergic contact dermatitis to a baby lotion that contained 0.3% oleamidopropyl dimethylamine.[58,59] Reactions were especially prevalent when the baby lotion was applied to damaged skin and/or the periorbital area. To investigate the possibility of cross-reactions, these patients were patch tested with oleamidopropyl dimethylamine (0.4%), ricinoleamidopropyl dimethylamine lactate (0.5%), stearamidopropyl dimethylamine lactate (0.5%), behenamidopropyl dimethylamine (0.5%), isostearamidopropyl dimethylamine (0.3%), tallowamidopropyl dimethylamine (0.3%), lauramidopropyl dimethylamine (0.2%), myristamidopropyl

Table 4. Nonhuman Ocular Irritation Studies.

Ingredient	Concentration	Method	Results	Reference
In vitro				
Behenamidopropyl dimethylamine	0.3% in a shampoo, diluted with deionized water to a 10% solution	EpiOcular irritation study	No/minimal irritation	33,36
Behenamidopropyl dimethylamine	0.3% in a shampoo, diluted with deionized water to a 10% solution	EpiOcular irritation study	No/minimal irritation	34,36
Stearamidopropyl dimethylamine	0.045% in a pre-shave scrub, diluted to 10% solution	EpiOcular irritation study	No/minimal irritation	37
Stearamidopropyl dimethylamine	2% in a hair conditioner, diluted to 10% solution	EpiOcular irritation study	No/minimal irritation	35
Stearamidopropyl dimethylamine	100% in pellet form	Bovine corneal opacity and permeability (BCOP) test method performed according to OECD Guideline 437; test material was washed at least 3 times after 4-hour incubation with test substance; GLP compliant	Mean in vitro irritancy score was 29 (threshold for corrosive/severe irritant is >55.1); not severely irritating/not corrosive	2
In vivo				
Dilinoleamidopropyl dimethylamine	In a 2% dilution with corn oil	Eye irritation study in a single male rabbit (strain not described)	No irritation	38
Stearamidopropyl dimethylamine	100% in pellet form	Eye irritation study in a single male New Zealand White rabbit performed according to OECD Guideline 405; ~0.1 mL test material instilled into conjunctival sac of 1 eye; eye was not rinsed after application; GLP compliant	Severe irreversible effects on the eye consisting of injury to the cornea (opacity maximum grade 2), iridial irritation (grade 1), ad severe effect on the conjunctivae; fluorescein examination not performed due to bloody discharge	2

Abbreviations: GLP, good laboratory practice; OECD, Organization for Economic Cooperation and Development.

dimethylamine (0.05%), cocamidopropyl dimethylamine (0.1%), minkamidopropyl dimethylamine (0.1%), and palmitamidopropyl dimethylamine (0.025%). The test solutions were prepared by adding water to the raw material, unless the material was insoluble, then phosphoric acid was added until a clear solution formed. All 13 patients reacted to the oleamidopropyl dimethylamine. One patient had no reactions to any of the other substances, but 12 patients had reactions to at least 4 of the related substances: ricinoleamidopropyl dimethylamine lactate and tallowamidopropyl dimethylamine (11 patients, 85%), lauramidopropyl dimethylamine (9 patients of 12 tested, 75%), and myristamidopropyl dimethylamine (6 patients, 46%). Five patients reacted to isostearamidopropyl dimethylamine, minkamidopropyl dimethylamine, and cocamidopropyl dimethylamine (12 patients tested). The remaining substances elicited a response in only 1 or 2 patients. The author of this study could not rule out that some of these reactions may have been irritant reactions.

In another Dutch report, one medical practitioner reported 3 cases of allergic contact dermatitis in patients who had used a body lotion.[60] In the first case, a 32-year-old female had itchy swelling of the eyelids. Both the upper and the lower lids were edematous, red, and scaly. The symptoms disappeared a few days following use of corticosteroid ointment and avoidance of cosmetics. Patch tests showed the patient was allergic to balsam of Peru and a body lotion that the patient had used around the eyes for several years. When tested with the lotion's ingredients, the patient had a positive reaction to oleamidopropyl dimethylamine.

In the second case, a 21-year-old was reported to have itchy dermatosis around the eyes and diffuse itching of the body. Upon examination, only mild desquamation was observed on the upper eyelids. The symptoms disappeared within a week of avoiding her cosmetics. Patch tests showed the patient was allergic to nickel cobalt and a body lotion that she had been using. The patient had positive reactions to oleamidopropyl dimethylamine and quaternium-15 when tested with the lotion's ingredients.

The third case, a 29-year-old female with a history of atopic dermatitis and no active dermatitis, reported dry and itchy skin. Scratch tests were positive for several inhalant allergens. Patch tests showed a positive reaction to a body lotion she had been using. Doubtful reactions were noted for hydroxycitronellal and quaternium-15. Further tests showed a positive reaction

Table 5. Dermal Irritation Studies.

Ingredient	Concentration	Method	Results	Reference
Nonhuman				
Stearamidopropyl dimethylamine	100% in pellets	In vitro skin irritation study (EpiSkin model) according to OECD Guideline 439; exposure to test tissue 15 min; GLP compliant	Not irritating	2
Stearamidopropyl dimethylamine	100% active material tested as 0.5 g in 0.7 mL water	In vivo skin irritation study in 3 New Zealand White rabbits according to OECD Guideline 404; semi-occluded patches (6 cm^2) on clipped skin; 1 animal exposed for 3 minutes, 1 hour, and 4 hours; remaining 2 animals exposed for 4 hours; GLP compliant	No skin reactions following the 3 minutes and 1 hour applications; very slight edema observed 1 hour after patch removal in all 3 animals; very slight erythema observed 1 hour after patch removal in 2 animals; very slight to slight erythema and very slight to slight edema were noted in all 3 animals 24, 48, and 72 hours after patch removal; reactions were fully reversible in 1 animal within 7 days and in the remaining 2 within 15 days; study classified this material as not irritating to rabbit skin	2
Human				
Behenamidopropyl dimethylamine	3% in a hair conditioner	Two-week daily use study in 28 female subjects	No dermal irritation or other adverse events	39
Behenamidopropyl dimethylamine	0.3% in a shampoo	Two-week daily use study in 28 female subjects	No dermal irritation or other adverse events	40
Oleamidopropyl dimethylamine	0.1% in an aqueous solution	48-hour patch test in 102 subjects; semi-occluded 2 cm^2 Webril patch	No dermal irritation or other adverse events	42
Stearamidopropyl dimethylamine	0.045% in a pre-shave scrub	Two-week daily use study in 30 male subjects	No dermal irritation	41

Abbreviations: GLP, good laboratory practice; OECD, Organization for Economic Cooperation and Development.

to oleamidopropyl dimethylamine. The itching improved after the patient discontinued using the body lotion.[60]

Oleamidopropyl Dimethylamine and Cocamidopropyl Dimethylamine

A 10-year retrospective study of patients with allergic eyelid dermatitis investigated the possible allergens.[61] Patch testing was performed in these patients with the NACDG's standard screening tray and other likely allergen trays. Of 46 patients with confirmed allergic eyelid dermatitis, 5 (10.9%) had relevant reactions to oleamidopropyl dimethylamine, and 2 (4.3%) had relevant reactions to cocamidopropyl dimethylamine.

Quantitative Risk Assessment

3,3-Dimethylaminopropylamine and Cocamidopropyl Dimethylamine ("Amidoamine") in CAPB

The Council's Task Force on Sensitization Risk from CAPB Impurities (Task Force) conducted a QRA of DMAPA and cocamidopropyl dimethylamine ("amidoamine") in support of the CIR safety assessment of CAPB.[1,62-64] Both of these substances are reactants used in the synthesis of CAPB and are, thus, present as impurities in CAPB used as ingredients in cosmetic formulations. 3,3-dimethylaminopropylamine is present in CAPB ingredients, as supplied ("raw"; typically 30% CAPB) to cosmetics manufacturers at 0.00025% to 0.01%, and "amidoamine" is present at 0.05% to 5.0% (0.5% was "typical" and 1.5% was the suggested maximum concentration). The Task Force derived conservative weight-of-evidence no expected sensitization induction levels (WoE NESILs) of 425 μg/cm^2 for DMAPA, based on data from 8 local lymph node assay (LLNAs) performed with a variety of vehicles, and 180 μg/cm^2 for "amidoamine," based on data from an human repeated insult patch test (HRIPT) and an LLNA. The NESILs were then used to calculate margins of safety (MOSs) for the potential for sensitization from dermal exposure to these impurities in cosmetic ingredients, assuming 0.01% DMAPA and 0.5% "amidoamine" in "raw" CAPB and default safety assessment factors. Cocamidopropyl betaine ingredients, as supplied, are used at concentrations up to 11% in cosmetic products.[1] The MOSs calculated for DMAPA were acceptable for all 35 product categories addressed in the QRA and for "amidoamine" were acceptable for 30 of the 35 categories.[62] The Task Force recommended refining the QRA for "amidoamine" in the remaining 5 product categories and that "raw" CAPB users should set the CAPB concentrations in finished products based on QRAs for these impurities.

Table 6. Dermal Sensitization Studies.[a]

Ingredient	Concentration	Method	Results	Reference
Nonhuman				
Stearamidopropyl dimethylamine	2.5% for intradermal induction, 1% for dermal induction, 2% in challenge; vehicle was paraffin oil	Guinea pig maximization using 10 Dunkin Hartley female guinea pigs for the test material	Nonsensitizing; however, mild and moderate skin reactions and necrosis were observed after both sets of inductions	44
Stearamidopropyl dimethylamine	NA	QSAR modeling for sensitization using TOPKAT	Not sensitizing—no compounds sufficiently similar to the query structure were found	43
Human				
Behenamidopropyl dimethylamine	0.3% in a shampoo, prepared as a 1% vol/vol aq. solution	HRIPT; occlusive with 0.2 mL sample; 106 subjects completed	No dermal sensitization or other adverse events	47
Behenamidopropyl dimethylamine	0.3% in a shampoo, prepared as a 1% vol/vol aq. solution	HRIPT; occlusive with 0.2 mL sample; 103 subjects completed	No dermal sensitization or other adverse events	46
Brassicamidopropyl dimethylamine	4% in a hair masque, tested neat	HRIPT; semi-occlusive with 0.2 mL sample; 102 subjects completed	No skin reactivity observed	49
Stearamidopropyl dimethylamine	2% in a hair conditioner, diluted to a 1% aq. solution	HRIPT; occlusive; 104 subjects completed	No significant potential for eliciting dermal irritation or sensitization	50
Stearamidopropyl dimethylamine	0.045% in a body lotion	HRIPT; occlusive with 0.2 mL sample; 102 subjects completed	No adverse events	45
Stearamidopropyl dimethylamine	0.045% in a pre-shave scrub, 1% dilution in deionized water	HRIPT; occlusive with 0.2 mL sample on a 2-cm^2 patch; 104 subjects completed	43/104 subjects had barely perceptible (+) to mild (1) irritant responses, which were not considered clinically meaningful. No induced contact allergy	51
Stearamidopropyl dimethylamine	0.75% in a rinse-off hair conditioner, 2% dilution in deionized water	HRIPT; occlusive with a 0.2 mL sample on a 2-cm^2 patch; 106 subjects completed	1 subject had (++) erythema and edema on sixth induction patch, which was determined to be possible contact dermatitis. Overall, study concluded no sensitization	48
Stearamidopropyl dimethylamine	0.5% in a leave-on hair conditioner	HRIPT; semi-occlusive with a 0.02 mL sample on a 1-cm^2 patch; 55 subjects completed	No irritation or sensitization	52
Stearamidopropyl dimethylamine	0.5% in a leave-on hair conditioner	HRIPT; semi-occlusive with a 0.02 mL sample on a 1-cm diameter patch; 56 subjects completed	No irritation or sensitization	53
Stearamidopropyl dimethylamine	0.05% in a face and neck product	HRIPT; occlusive with a 25-38 mg/cm^2 sample on a patch; 50 subjects completed	No irritation or sensitization	54
Stearamidopropyl dimethylamine	2% in a hair conditioner	HRIPT; semi-occlusive with a 0.2-g sample on a 4-cm^2 patch; 104 subjects completed; estimated dose/unit area = 1000 $\mu g/cm^2$	Not a dermal sensitizer	45
Stearamidopropyl dimethylamine	Diluted with distilled water to 0.6% in a hair conditioner	HRIPT; occlusive with a 0.3 mL sample on a 4-cm^2; 100 subjects completed; estimated dose/unit area = 300 $\mu g/cm^2$	Not a dermal sensitizer	55
Stearamidopropyl dimethylamine	Diluted with distilled water to 0.6% in a hair conditioner	HRIPT; occlusive with a 0.15 mL sample on a 4-cm^2 patch; 122 subjects completed; estimated dose/unit area = 300 $\mu g/cm^2$	Mild erythema observed in several subjects on 1 or more days in induction phase. In challenge phase, 10 subjects exhibited mild erythema. Test material determined to be an irritant; no evidence of delayed contact hypersensitivity	56

(continued)

Table 6. (continued)

Ingredient	Concentration	Method	Results	Reference
Stearamidopropyl dimethylamine	Diluted with distilled water to 0.6% in a hair conditioner	HRIPT; occlusive with a 0.2 mL sample on a 4-cm^2 patch; 107 subjects completed; estimated dose/unit area = 300 $\mu g/cm^2$	In induction phase, 2 subjects exhibited mild erythema; a third had mild erythema with edema and papules. In challenge phase, 3 subjects observed with mild erythema. Test material was a primary irritant, no evidence of delayed contact hypersensitivity	57

Abbreviations: HRIPT, human repeated insult patch test; NA, not applicable; QSAR, quantitative structure–activity relationship.
[a]Estimated dose/unit area = concentration × amount × density × unit conversion × area.

Stearamidopropyl Dimethylamine

The Council's CIR Science and Support Committee (SSC) performed a QRA of potential dermal sensitization for stearamidopropyl dimethylamine in accordance with the procedure described above for DMAPA and "amidoamine" in CAPB.[1,65] Table 9 presents the QRA calculations from the CIR SCC. The CIR SSC derived a conservative WoE NESIL of 1000 $\mu g/cm^2$ based on data from 11 HRIPTs, a guinea pig maximization test, a Buehler guinea pig test, and an LLNA. Greater weight was given to the HRIPT data than the animal data, and the 1000 $\mu g/cm^2$ NESIL reflects the highest dose tested in the HRIPTs. The MOSs calculated for stearamidopropyl dimethylamine were acceptable for 9 of the 22 product categories addressed, assuming the highest maximum use concentration reported for each category.[62] This includes use at 5% in hair conditioners but not at 1.5% in eye make-up removers, for example. The CIR SSC concluded that further justification is needed for current use levels of this ingredient in the remaining 13 product categories.

Summary

The fatty acid amidopropyl dimethylamines, referred to as "amidoamines," function primarily as antistatic agents in cosmetic products. The CIR Panel has expressed concern about these chemicals in a safety assessment of fatty acid amidopropyl betaines, in which fatty acid amidopropyl dimethylamines were noted as impurities with sensitizing potential.

Fatty acid amidopropyl dimethylamines have the core structure of a fatty acid amide, *N*-substituted with 3 propyl-*N'*, *N'*-dimethylamine. These ingredients are manufactured by the amidization (ie, amide forming condensation) of fatty acids with DMAPA, most commonly under alkaline or acidic conditions. Fatty acid amidopropyl dimethylamines are composed of secondary amides and tertiary amines and potentially can be nitrosated. Therefore, fatty acid amidopropyl dimethylamine should be formulated to avoid the formation of nitrosamines.

Of the ingredients in this safety assessment, stearamidopropyl dimethylamine has the most reported uses in cosmetic and personal care products, with a total of 427; of those uses, 355 are in rinse-off formulations. Behenamidopropyl dimethylamine has the second greatest number of overall uses reported, with a total of 35; of those uses, 32 are in rinse-off formulations. For both ingredients, most of the rinse-off uses are in hair conditioners. A few uses were reported each for brassicamidopropyl dimethylamine, cocamidopropyl dimethylamine, isostearamidopropyl dimethylamine, lauramidopropyl dimethylamine, minkamidopropyl dimethylamine, oleamidopropyl dimethylamine, and palmitamidopropyl dimethylamine. No uses were reported to the VCRP for the remaining fatty acid amidopropyl dimethylamines.

In a survey of use concentrations conducted by the Personal Care Products Council, stearamidopropyl dimethylamine is reported to be used at a range of maximum concentrations of 0.01% to 5%, with 5% reported in noncoloring hair conditioners. In behenamidopropyl dimethylamine, the range of maximum concentrations was reported to be 0.3% to 3%, with 3% reported in noncoloring hair conditioners. A range of maximum concentrations for cocamidopropyl dimethylamine was reported to be 0.03% to 6.5%, with 6.5% reported in skin-cleansing products.

No use concentrations were reported for almondamidopropyl dimethylamine, avocadoamidopropyl dimethylamine, babassuamidopropyl dimethylamine, minkamidopropyl dimethylamine, oatamidopropyl dimethylamine, oleamidopropyl dimethylamine, sesamidopropyl dimethylamine, and tallamidopropyl dimethylamine. The amidoamine ingredients in this safety assessment are not restricted from use in any way under the rules governing cosmetic products in the European Union. Myristamidopropyl dimethylamine has reported uses as a biocide in contact lens disinfecting solution.

In a QSAR model, the dermal absorption of stearamidopropyl dimethylamine has been estimated to be 0.04 mg and 0.12 mg after 8 and 24 hours, respectively. The maximum dermal absorption rate was calculated to be 2.40×10^{-6} $mg/cm^2/h$. The LD_{50} values in 2 acute oral toxicity studies of stearamidopropyl dimethylamine in rats were > 2,000 mg/kg body weight and 1396 mg/kg body weight, respectively.

Systemic toxicity was observed in an oral 14-day dose range-finding rat study of stearamidopropyl dimethylamine at a dose of 500 mg/kg body weight per day. In rabbits, the systemic NOAEL of stearamidopropyl dimethylamine in a dermal repeated dose study was greater than 10% wt/vol in 30%/70% ethanol water (equivalent to 200 mg/kg body weight per day).

Table 7. Sensitization Studies of DMAPA and Amidoamine Previously Reviewed by the CIR Expert Panel.[1]

Substances	Concentrations	Method	Results	Reference
Sensitization studies: Nonhuman				
Stearamidopropyl dimethylamine	Induction with 1.0% wt/vol test material in 80% ethanol/20% distilled water; challenge with 0.25% w/v test material in acetone; rechallenge with 0.25%, 0.125%, and 0.0625% wt/vol	Delayed contact hypersensitivity study in 20 Hartley outbred guinea pigs with 25-mm diameter occluded Hill Top chambers on clipped, intact skin; induction applied for 6 h/wk for total of 3 exposures at a dose volume of 0.3 mL (estimated dose/unit area = 6.1 × 102 μg/cm^2); exposure sites were rinsed after removal of chambers; control group of 10 guinea pigs received the vehicle alone; primary challenge patches on naïve skin after 2 week rest (estimated dose/unit area = 1.5 × 102 μg/cm$^{2)}$	One guinea pig had delayed contact hypersensitivity to the test material; control animals had no reactions. A rechallenge was conducted in 6 guinea pigs 13 days after the primary challenge; an additional 5 animals were used as controls. One guinea pig had a positive response to the test material at 0.25%. No other reactions were observed	67
Palmityl/stearylamidopropyl dimethylamine	25% active material in 8.95% phosphoric acid and 66.05% water; rechallenge with 0.25% and 0.5% active material	Delayed contact hypersensitivity in 10 male and 10 female albino Dunkin/Hartley guinea pigs with 4 cm^2 occluded patches on clipped skin; induction applied 6 h/wk for a total of 3 exposures at a dose volume of 0.4 mL (estimated dose/unit area = 2.5 × 10^4 μg/cm^2); control group was 10 untreated animals; primary challenge patches on naive skin after 2-week rest	All but 3 of the 20 guinea pigs had patchy to severe erythema at the 24 and 48 hours observation periods; 4 control animals had slight to moderate patchy erythema during the observation periods. A rechallenge was conducted; no sensitization was observed with the 0.25% active material, but 0.5% active material elicited reactions in sensitized animals	68
Cocamidopropyl dimethylamine	0.1% test material in DOBS/saline vehicle and Freund's complete adjuvant (50/50 ratio) for intradermal injections; 5% test material in acetone/PEG400 for the induction patch; 0.5% test material in acetone/PEG 400 for challenge patch	Maximization study in 10 albino Dunkin/Hartley guinea pigs (6 females and 4 males); a single occlusive 48-hour induction patch (2 × 4 cm^2) of 0.2-0.3 mL a week following intradermal injections; control group was 4 male animals that received intradermal injections and induction patches using only the vehicle mixture; single occlusive 24-hour challenge patch (8 mm diameter in a Finn chamber) after a 2-week rest; 2 more challenges were made 1 and 2 weeks after the first challenge; reactions were scored on a scale of 0 (no reaction) to 3 (severe erythema and edema)	At the first challenge, 7 animals had a reaction score ≥ 0.5 at 24 hours after the removal of the patch. After 48 hours, 6 animals had a reaction score ≥ 0.5. Three of 10 animals had a reaction score of 2. At the second challenge, 7 guinea pigs had a score ≥ 0.5 twenty-four-hour after patch removal. These scores were consistent at the 48-hour reading. Five of 10 animals had a reaction score of 2. At the third challenge, all 10 guinea pigs had a score ≥ 1 24 hours after patch removal. These scores remained largely consistent at the 48-h reading. Eight of the 10 animals had a reaction score of 2	69
Cocamidopropyl dimethylamine	0.025% test material for intradermal injections; 1% test material for topical induction; 0.5% test material in acetone/PEG 400 for challenge patch	Guinea pig maximization study conducted in the same manner as above except 4 female guinea pigs were used as controls and only 2 challenges were made	At the first challenge, 3 animals had a reaction score ≥ 1 at both the 24- and 48-hour readings, with one of the animals scoring a 2. At the second challenge, 3 animals had a reaction score ≥ 1 at 24- and 48-hour readings, although 1 animal had no reaction at 48 hours that had one at 24 hours while another that had no reaction at 24 hours had one at 48 hours	69
DMAPA (99.0+% pure), plus 3 other recognized human contact allergens	0.5%, 1.0%, 2.5%, 5.0%, or 10.0% of the test material in 8 different vehicles: acetone, olive oil (4:1), dimethyl sulfoxide, methyl ethyl ketone, dimethyl formamide, propylene glycol, and 50:50 and 90:10 mixtures of ethanol and water	LLNA study in groups of 4 female CBA/Ca mice	At 10.0% DMAPA, the stimulation indices (SIs) ranged from 2.2 in propylene glycol to 15.7 in dimethyl formamide. The estimated concentrations for an SI of 3 (EC_3) ranged from 1.7% (in dimethyl formamide) to > 10% (in propylene glycol).	70
Stearamidopropyl Dimethylamine (TEGO AMID S 18) with a DMAPA concentration ≤ 20 ppm, amine concentration 150.8 mg KOH/g (limit	0.1%, 0.5%, 1%, 2.5%, or 5% (wt/vol) of the test material in ethanol/water (7/3, vol/vol); control was vehicle only; positive	LLNA study in groups of 4 CBA/Ca female mice	No deaths occurred during the treatment period in any dose group, and no clinical signs of toxicity were observed during treatment in the control group or in the 0.1% and 0.5% dose groups. Slight to moderate	71,72

(continued)

Table 7. (continued)

Substances	Concentrations	Method	Results	Reference
range = 148.0-152.0 mg KOH/g), and melting point 68.0°C (limit range 66.0°C-69.0°C)	control was α-hexylcinnamaldehyde in acetone: olive oil (4:1, vol/vol)		ear erythema was observed after the second or third application at both dosing sites in all mice in the 1%, 2.5%, and the 5% dose groups that persisted for 2 days in the 1% dose group and until treatment end in the 2.5% and 5% dose groups. Body weight was not affected in any of the animals. The SI were 1.4, 2.1, 2.1, 5.8, and 3.9 for the 0.1%, 0.5%, 1%, 2.5%, and 5% dose groups, respectively. The EC_3 was calculated as 1.4%. The positive control group had the expected results	
Cocamidopropyl dimethylamine (~99% C12-C18)	0%, 0.1%, 0.5%, 1%, 2.5%, or 5% of the test material in ethanol/water, 7:3 (vol/vol) neutralized to pH 6.0 with citric acid monohydrate; positive control was 35% hexylcinnamaldehyde	LLNA in groups of 5 mice	Very slight erythema was observed on day 3 and very slight erythema and edema were observed on days 4 to 6 of the 2.5% dose group; in the 5% dose group, 4 of the 5 mice treated had very slight erythema and very slight edema on day 2. On days 3 to 6, mice in this dose group had well defined erythema and slight edema. The SI were 1.8, 1.0, 3.1, 24.5, and 60.6 for the 0.1%, 0.5%, 1%, 2.5%, or 5% dose groups, respectively. The EC_3 was calculated as 0.98%. The positive control group had the expected results	73
Predictive sensitization studies: Human				
Stearamidopropyl dimethylamine	0.25% wt/vol in undiluted mineral oil	HRIPT with 112 subjects; 0.3 mL sample on Webril patches	Frequent incidences of slight to moderate irritation, including erythema, some edema, papules, glazing, and cracking observed during induction period but considered transient. Five subjects had a reaction of grade 1 or greater during challenge phase. Responses to test material were considered indicative of primary irritation rather than contact sensitization	74
Stearyl/palmitylamidopropyl dimethylamine	4% aqueous liquid fabric softener formulation containing 0.5% of the test material	HRIPT with 77 subjects; 0.5-mL sample on a ¾-inch square Webril pad (estimated dose/unit area = 6.9×10^2 μg/cm^2)	The test material caused some irritation in most volunteers during induction. Eight subjects reacted at challenge, and 7 of the 8 submitted to rechallenge with 4% and 0.4% aqueous formulations. No reactions indicative of sensitization occurred at rechallenge	75
Oleamidopropyl dimethylamine along with CAPB (1% aq.) and DMAPA (1% aq.)	0.5% aq.	HRIPT with a supplemented European standard series in 285 consecutive dermatitis patients	Twenty-three patients (8%) had allergic responses to DMAPA, 14 patients (4.9%) had allergic responses to DMAPA and oleamidopropyl dimethylamine, and 8 patients (2.8%) had allergic responses to all three of the supplemental chemicals. Analyses by TLC of the oleamidopropyl dimethyl amine sample revealed contamination with DMAPA (6 ppm or 0.12% of the sample) and indicated that the allergic responses to the 3 test substances in the last group were not attributable to cross-reactivity. (From study documentation, it was not possible to determine whether the administered CAPB concentration was 1% active or 1% aqueous, which would equate to 0.3% active)	76

(continued)

Table 7. (continued)

Substances	Concentrations	Method	Results	Reference
CAPB and DMAPA as well as positive patients' personal cosmetics diluted in water at 1:10, 1:100, and 1:1,000	Up to 1% for CAPB in water; up to 1% for DMAPA in petrolatum	2-year study of 1,190 eczema patients using standard technique and grading according to the European Contact Dermatitis Group (ECDG)	17 patients were diagnosed with allergic contact dermatitis to CAPB. Relevance established with an additional positive patch test score of 2+ or more to at least one personal care product containing CAPB used by the patients. Fifteen patients were further tested with 12 patients tested with their personal cosmetics, of which 9 had positive reactions to at least 1 dilution and 5 had irritant reactions. All except 3 patients, who were not tested, had 2 or 3+ reaction to DMAPA at concentrations as low as 0.05%. One patient had a positive reaction to CAPB. The presence of DMAPA was investigated via thin-layer chromatography in the personal cosmetics of 4 of the patients that had positive reactions. The positive reactions to DMAPA suggest that the positive reaction to CAPB-containing products was likely attributable to DMAPA present as an impurity. DMAPA was measured in the products at 50 to 150 ppm. The concentration of DMAPA was also measured in the 2 CAPB types: one had a concentration of DMAPA at 200 ppm and DMAPA was below the detection limit (detection limit value not reported) in the other type. (From the study documentation, it was not possible to determine whether the administered CAPB concentration was 1% active or 1% aqueous, which would equate to 0.3% active)	77
CAPB (30% active ingredient), amidoamine, DMAPA, monochloroacetic acid, and Tego 103 G	Up to 1% aq. CAPB, DMAPA, and Tego 103 G, respectively, and up to 0.05% amidoamine	1,200 consecutive patients with dermatitis of various types were patch tested with European standard series supplemented with CAPB; patients that subsequently had allergic or irritant reactions to CAPB were then patch tested with the chemicals that were intermediates or reactants in the synthesis of CAPB (amidoamine, DMAPA, and monochloroacetic acid) along with a sample of CAPB of greater purity and Tego 103 G 1% aq	Positive allergic reactions to CAPB observed in 46 subjects (3.8%), while irritant reactions were recorded in 15 subjects (1.25%). Of the 46 subjects, 30 had positive reactions to DMAPA 1% aq. In these 30 subjects, 3 and 16 were positive to purer grade of CAPB 0.5% aq. and CAPB 1% aq., respectively. Patients with irritant reactions had negative reactions to synthesis materials and purer grade of CAPB. No allergic or irritant reactions to DMAPA were observed in 50 healthy controls. No positive reactions to amidoamine 0.05% were observed. (From the study documentation, it was not possible to determine whether the administered CAPB concentrations were 0.5% active and 1% active or 0.5% aqueous and 1% aqueous, which would equate to 0.15% active and 0.3% active, respectively)	78
CAPB and sodium chloride and N, N-dimethyl-propylene-diamino triacetic acid blend	1% aq, respectively	30 patients with a history of contact allergy to 1% aq. CAPB and 1% DMAPA were patch tested with pure CAPB and an impurity that was isolated from a sample of CAPB (Tego Betaine F 30% solution) by thin-layer chromatography and infrared spectrum analysis	None of the subjects reacted to any of the chemicals. (From the study documentation, it was not possible to determine whether the administered CAPB concentration was 1% active or 1% aqueous, which would equate to 0.3% active)	79

(continued)

Table 7. (continued)

Substances	Concentrations	Method	Results	Reference
DMAPA in various vehicles including water, SLES 2% aq. solution, and polysorbate-20 2% aq. solution, as well as to CAPB and 10 substances chemically related to DMAPA	0.00005% to 0.1% for DMAPA	34 subjects with confirmed contact allergy to 1% aq. DMAPA were patch tested to the various DMAPA solutions, CAPB, and the DMAPA-related substances; and a series of 10 substance; test sites were occluded for 2 days and the sites were scored for reactions on days 2, 3, 4, and 7	18 subjects had positive reactions to DMAPA in water at 0.1%, no positive reactions were noted for DMAPA in water at 0.01% to 0.00005%. Positive reactions were observed with DMAPA in SLES, with 27 subjects positive at the highest concentration, 10 subjects positive at 0.01%, 5 subjects positive at 0.005%, and 1 subject positive at 0.0001%. Positive reactions were also observed with DMAPA in polysorbate-20 in 21 subjects at 0.1% and 4 subjects at 0.01%. Patch tests for the chemically related structures were positive in 28 subjects for N, N-dimethyl-2-ethylenediamine 1% aq., 12 subjects for cocamidopropylamine oxide 1% aq. (35% active material), and 18 subjects for CAPB 1% aq. (30% active material). No other reactions occurred	80
DMAPA in surfactant solutions (1% or 2% wt/wt surfactants) that included purified CAPB (DMAPA $<$ 1 ppm), SLES, polysorbate20 (Tween20), lauryl polyglucoside (APG), SLES/CAPB 3:1 (wt/wt), and APG/CAPB 3:2 (wt/wt)	Serial dilutions of DMAPA up to 100 ppm	20 patients with confirmed nonoccupational contact allergy to DMAPA (1% aq.) and CAPB (1% aq.) and an intolerance to detergents and shampoos	Positive reactions observed with DMAPA at 1 ppm and higher in 1% CAPB (1 reaction each to 1 ppm and 5 ppm DMAPA, 3 reactions to 10 ppm DMAPA, and 4 reactions to 50 ppm DMAPA). Similar positive observations were made with DMAPA in 1% SLES/CAPB 3:1. No positive reactions were observed when DMAPA (100 ppm) was tested in water, but 7 positive reactions were recorded when the material was tested in 2% CAPB. A greater number of reactions were observed when 100-ppm DMAPA was mixed with 2% SLES/CAPB (5 reactions) than when mixed with 2% APG/CAPB (2 reactions). The authors noted that CAPB and SLES/CAPB 3:1 act as carriers for DMAPA when applied under occlusion at 1%, and that surface activity in more concentrated surfactant solutions may be responsible for allergic reactions to DMAPA. (From the study documentation, it was not possible to determine whether the administered CAPB concentrations were 1% active and 2% active or 1% aqueous and 2% aqueous, which would equate to 0.3% active and 0.6%, respectively)	81
DMAPA and CAPB	1% pet. and 1% aq. for DMAPA and 1% aq. CAPB with a maximum residual DMAPA $<$ 15 ppm	80 subjects (mainly hairdressers) with dermatitis from 1996 to 1999 patch tested with the hairdresser's series supplemented with DMAPA	Of the 80 subjects, 6 had + to +++ reactions to CAPB; none of these 6 had reactions to DMAPA. A housewife with scalp and neck dermatitis had a + reaction to DMAPA 1% aq. and a +? reaction to DMAPA 1% pet. This subject had no positive reaction to CAPB. (From the study documentation, it was not possible to determine whether the administered CAPB concentration was 1% active or 1% aqueous, which would equate to 0.3% active)	82
Partially purified CAPB, cocamidopropylamine, DMAPA, and 1.0% pure CAPB	1% aq. CAPB containing $<$ 0.5% cocamidopropylamine, 0.1% and 0.01% cocamidopropylamine, 0 to 10,000 ppm	4/7 subjects that had relevant dermatitis to CAPB following use of liquid soaps, and in one case, an eye make-up remover, patch tested with partially purified	One subject tested with the partially purified CAPB had a positive reaction that appeared only to cocamidopropylamine, while another had a reaction	83

(continued)

Table 7. (continued)

Substances	Concentrations	Method	Results	Reference
	DMAPA, 0.2% aq. DMAPA in SLS, 1.0% CAPB containing <0.3% cocamidopropylamine and <10 ppm DMAPA	CAPB; 6/7 subjects patched tested with DMAPA, DMAPA in SLS, and 1.0% CAPB, on normal and tape stripped skin	only to CAPB; however, irritancy could not be ruled out because the subject's patch sites were read only on 1 day. The other 2 patients had positive reactions to cocamidopropylamine and CAPB. Control subjects had negative patch results. 1 of the 6 subjects tested with DMAPA reacted to DMAPA on normal and tape-stripped skin at concentrations >1000 ppm. Three of the 6 subjects reacted to DMAPA in 0.2% SLS (one at 10,000 ppm, one at 1000 to 10 000 ppm, and one at 100 to 10 000 ppm). None of the subjects reacted to the 1.0% pure CAPB. (From the study documentation, it was not possible to determine whether the administered CAPB concentration was 1% active or 1% aqueous, which would equate to 0.3% active)	
DMAPA, amidoamine, and CAPB	1% aq. CAPB (from 2 different suppliers), 1% aq. DMAPA, 0.1%-0.5% purified amidoamine	10 subjects with known CAPB allergy patch tested with CAPB, DMAPA, and amidoamine	All the subjects had ++ reactions to DMAPA at 1% and purified amidoamine at 0.5%. Most subjects also had ++ reactions to purified amidoamine at 0.25% and the remaining had + reactions to this concentration. 4 patients had positive reactions (++) to the purified amidoamine at 0.1%. No reactions were observed with 1 of the supplied CAPB, which was suggested to have a higher purity by the authors. Control patches in 20 volunteers were negative for amidoamine. (From the study documentation, it was not possible to determine whether the administered CAPB concentration was 1% active or 1% aqueous, which would equate to 0.3% active)	84
CAPB and amidoamine	1.0% aq. CAPB, 1.0% amidoamine	Retrospective study of 957 patients in 2001 that had positive patch test results to 1.0% aq. CAPB and/or 1.0% amidoamine	49 patients had positive reactions to CAPB, amidoamine, or both. A follow-up evaluation in 35 patients was performed to establish the relevance of reactions to CAPB and amidoamine to the use of products containing these chemicals. Fifteen patients (42.9%) reacted to CAPB, 12 patients (34.3%) reacted to amidoamine, and 8 (22.8%) patients reacted to both. Of the 35 patients, 29 (83%) could identify products containing CAPB at home. (From the study documentation, it was not possible to determine whether the administered CAPB concentration was 1% active or 1% aqueous, which would equate to 0.3% active)	85
CAPB and amidoamine	1.0% CAPB, 0.1% amidoamine	Retrospective study of 975 patients in 2001 with CAPB and/or amidoamine contact allergy	15 patients had positive patch test reactions to CAPB only, 25 had positive patch test reactions to amidoamine only, and 18 had positive reactions to both (58 patients total). Definite and probable relevance (known exposure to CAPB) was determined in 16 patients that tested positive for amidoamine and in 16 that tested positive for CAPB. (From the study documentation, it was not possible to determine whether the administered CAPB concentration was 1% active or 1% aqueous, which would equate to 0.3% active)	86

(continued)

Table 7. (continued)

Substances	Concentrations	Method	Results	Reference
CAPB and amidoamine	1% aq. CAPB. 0.1% aq. Amidoamine	4,913 patients patch tested for allergic contact dermatitis with an extended screening series of 65 allergens that included CAPB and amidoamine from January 1, 2001, to December 31, 2002	Positive results for CAPB observed in 2.8% of the patients while 2.3% were positive for amidoamine. Relevance of the CAPB and amidoamine reactions (present and past) was 90.9% and 85%, respectively. (From the study documentation, it was not possible to determine whether the administered CAPB concentration was 1% active or 1% aqueous, which would equate to 0.3% active)	87
CAPB and DMAPA	1% aq. purified CAPB, 1% aq. DMAPA	429 Chinese patients with suspected contact allergy were patch tested with the European standard series supplemented with CAPB and DMAPA	9 patients had irritant reactions, 12 had questionable reactions, and 42 had + reactions to CAPB. No reactions to CAPB greater than ++ were observed. Also, of the 429 patients, 76 were diagnosed with cosmetic allergic contact dermatitis. Twentu-seven of the 76 diagnosed with cosmetic allergic contact dermatitis and 15 (out of 353) of the noncosmetic allergic contact dermatitis subjects had positive reactions to CAPB ($P < 0.05$). Only 25 of the former and none of the latter had relevant reactions. Ten of the 429 patients had positive reactions to DMAPA, 8 of which were considered relevant. Six of the 10 patients also had positive reactions to CAPB. (From the study documentation, it was not possible to determine whether the administered CAPB concentration was 1% active or 1% aqueous, which would equate to 0.3% active)	88
Provocative sensitization studies: Human CAPB, DMAPA, amidoamine, and other potential allergens	CAPB-F grade (active level of CAPB in shampoo was 5.0%; active level in hand soap and body wash was 5.2%), CAPB grades F and S (both 1% aq.), DMAPA (0.1% pet), amidoamine (0.1% aq.), sodium monochloroacetate (0.1% aq.)	Provocative use study of products containing CAPB in 10 subjects that had positive reactions to CAPB in routine patch testing. Ten control subjects were also enrolled. Study divided into 3 phases with 3 different test products: Phase I was a forearm wash test with the shampoo diluted to 10% in tap water. If no allergic reaction occurred in phase I, subjects then entered phase II of the study: ie, daily use of shampoo as hair cleanser. Subjects proceeded to phase III of the study if no allergic reactions to the shampoo occurred. In phase III, the subjects used the shampoo, body wash, and hand soap for 3 weeks. At least 2 months after the product use tests, the subjects were patch tested with CAPB DMAPA, amidoamine, sodium monochloroacetate, a proprietary mixture of preservatives for CAPB, and other potential allergens (perfumes and preservatives) that were in the test product formulations. Control subjects were patched with 1% CAPB	-Three subjects completed the product use phases without experiencing an allergic reaction. Seven subjects had erythema, scaling, and pruritus on the arms, face, and/or neck in either phase I or II of the study. One subject that experienced a positive reaction in the first phase was asked to repeat the forearm use test with the CAPB-containing shampoo on the left arm and with a CAPB-absent shampoo on the right arm. The subject experienced a positive reaction on both arms, which was likely caused by the preservatives in the shampoo products (as shown through patch testing). In phase III, 3 subjects had scalp, face, and/or neck and body dermatitis. -Patch testing was performed in 9 of the 10 subjects, with 6 subjects reacting to amidoamine. Five of these 6 subjects had positive reactions during the product use phases. Two subjects had reactions to the CAPB-F grade with preservative, 3 had reactions to CAPB-F grade without preservative, 1 reacted to the CAPB-S grade, and 1 reacted to the proprietary preservative mixture. 2 subjects had questionable reactions to DMAPA. No other adverse reactions were noted in the subjects. (From the study documentation, it was not possible to determine whether the administered CAPB concentration was 1% active or 1% aqueous, which would equate to 0.3% active)	89

(continued)

Table 7. (continued)

Substances	Concentrations	Method	Results	Reference
Purified CAPB containing only 1 ppm amidoamine, CAPB grade F containing approximately 3,000 ppm amidoamine, and amidoamine	Concentrations of CAPB not reported, 0.01% and 0.1% amidoamine	Follow-up patch test with 7 of the subjects from the above provocative test	Two subjects had questionable reactions to the purified CAPB, while there were 3 positive reactions to the CAPB-F grade, 4 positive reactions to the higher concentration of amidoamine, and 2 positive reactions to the lower concentration of amidoamine	89,90
CAPB and DMAPA	CAPB (25% dilution; DMAPA below 1 ppm); 0.1%, 0.3%, and 1.0% dilutions of CAPB (CKKB); and 0.1%, 0.3%, and 1.0% dilutions of DMAPA	Provocative use test in 10 subjects that had positive reactions to CAPB. Twenty volunteers served as controls for the study. Study divided into 3 phases with 3 different test products: Phase I, a 0.1-ml test sample of shower gel containing was applied, lathered for 1 minute, and rinsed on the subjects' forearms twice daily for 7 days; phase II of the study consisted of patch testing to differentiate irritant reactions from allergic reactions and to reconfirm sensitivity to CAPB and DMAPA. The subjects were patch tested with CAPB (CKKB) and DMAPA; subjects that had no allergic reactions in phase I participated in phase III. In phase III, the subjects used the shower gel or 4 weeks as they would normally	No skin irritation was observed in phase I of the study. One subject with a history of atopic dermatitis was removed from the study due to a flare. Another subject had an immediate "wheal-like reaction" on days 3 and 6 that cleared within minutes. This subject continued the forearm test an extra week and had no further effect. In phase II, one control had an irritating reaction to 1% CAPB. In the study group, 5 of the 10 subjects had a positive reaction to 1% CAPB and another 3 had marginal allergic and/or irritant reactions. One subject had a positive reaction to DMAPA but had no clear reaction to CAPB. Another subject that had a positive reaction to CAPB had a doubtful reaction to 1% DMAPA. Eight subjects did not react to DMAPA. Only 7 subjects participated in phase III of the study (the other 2 were not available), and no adverse reactions were observed in these subjects. (From the study documentation, it was not possible to determine whether the administered CAPB concentration was 1% active or 1% aqueous, which would equate to 0.3% active)	91

Abbreviations: CAPB, cocamidopropyl betaine; CIR, Cosmetic Ingredient Review; DMAPA, 3,3-dimethylaminopropylamine; HRIPT, human repeated insult patch test; LLNA, Local lymph node assay; SLS, sodium lauryl sulfate;TLC, thin-layer chromatography.

Table 8. Case Reports of DMAPA and Amidoamine Previously Reviewed by the CIR Expert Panel.[1]

Mode of contact	Patient(s)	Indication	Reference
Occupational exposures in chemical factory workers to DMPAPA and CAPB	50-year-old man who worked in a chemical factory which produced amines and a 54-year-old man who worked with DMAPA and CAPB	-First patient a developed a red itchy face that cleared after treatment with topical corticosteroids and a week away from work. The patient had 4 more episodes over 6 months with swelling and spreading to the neck, shoulders, arms, and hands. Patching testing with the European series yielded a + reaction only to ethylenediamine. Further patch testing with other amines, including DMAPA, produced a positive reaction (++) to DMAPA. Patch testing with serial dilutions of DMAPA revealed a ++ reaction at 1%, a?+ reaction at 0.1%, and negative reactions at 0.01% and 0.001%. Twenty controls had negative reactions when patch tested with 0.1% and 1% DMAPA. DMAPA was being utilized at the factory where the patient worked to make CAPB. The dermatitis signs improved but did not completely clear when the patient was moved to another part of the plant to work. -In the second patient, an itchy red scaly face and right palm was observed that cleared over 2 weeks. The patient had 6 more episodes over the next year. The dermatitis was resolved after the patient avoided contact with DMAPA. Patch testing with the chemicals used at the chemical factory yielded a ++ reaction only to DMAPA (1% pet.) on day 3 of site scoring	92
Occupational exposures to shampoos and hand cleansers that may have contained DMAPA	34-year-old woman employed as an assistant nurse without earlier skin symptoms	Patient reported dermatitis that would clear during periods of leave from work but would reappear as soon as the patient resumed work. The patient was patch tested with the standard series, an antimicrobial series, and a cosmetics series. This testing only yielded a positive reaction to nickel. Initially, the hand dermatitis was considered to be occupational irritant contact dermatitis. The patient was forced to leave her career because of the condition and experienced occasional relapses afterward. Four years later, the patient was patched tested with the European standard series (minus nickel sulfate), an antimicrobial series, and a cosmetics series which included CAPB, oleamidopropyl dimethylamine, DMAPA, and coconut diethanolamide. Only DMAPA (>99% purity, 1% pet.) elicited a positive reaction with + readings on days 2 and 3 and a ++ reading on day 4	93
Baby shampoo containing CAPB	37-year-old woman with no history of atopic or seborrheic dermatitis	Patient reported to have a 5-month history of eyelid dermatitis. A family physician had instructed the patient to apply baby shampoo to the eyelids daily to treat an infection of the eyelids. Patch testing revealed a + reaction to CAPB and a ++ reaction to amidoamine (concentrations tested not reported). The dermatitis cleared after discontinuing use of the product	94
Dermatitis of face and eyelids from unknown substance, possibly facial cream, that worsened with patient's hair touched her face	39-year-old woman with personal history of eczema and asthma	Patient reported with a 6-month history of persistent dermatitis of the face and eyelids. The patient complained of a burning sensation, pruritus, erythema, and occasional swelling of the eyelids. Patch testing using the NACDG standard series; the preservatives, vehicles, and cosmetics series; and the patient's facial creams was conducted. Concentrations of the materials tested were not reported. On day 4, the patient reacted positively to nickel sulfate (++), gold sodium thiosulfate (++), cobalt chloride (+), tosylamide formaldehyde resin (+), CAPB (+), amidoamine (+), DMAPA (+), and oleamidopropyl dimethylamine (+). The patient did not have a positive reaction to cocamide diethanolamide	95
Allergic contact dermatitis from unknown substance, possibly personal care products containing DMAPA	58-year-old housewife, a 36-year-old male office worker, and a 24-year-old hairdresser	Patients with allergic contact dermatitis underwent patch testing with several test types including the standard series, the cosmetics series, the hairdresser's series, and with their own personal care products. All 3 patients tested positive to DMAPA (reactions ranged from + to ++ on day 7) but were negative for CAPB. After the initial patch testing, the patients were further tested with serial dilutions of 1% aq. DMAPA and 1% aq. CAPB (concentrations tested were 0.1%, 0.2%, 0.5%, and 1% for each). The first patient had a ± reaction to 1% CAPB only. The other patients had no reactions to CAPB at any concentration. Allergic responses were noted in all 3 patients to DMAPA at concentrations of 0.2% and higher (± to + at 0.2%, +/- to ++ at 0.5%, and + to +++ to 1%). (From the study documentation, it was not possible to determine whether the administered CAPB concentration was 1% active or 1% aqueous, which would equate to 0.3% active)	96
Eyelid dermatitis to an unknown substance	42-year-old female	Patient reported with a 4-month history of severe recalcitrant eyelid dermatitis. The patient's condition did not improve after use of all eye makeup was discontinued. The patient presented with bilateral periorbital and postauricular erythema, and a biopsy found spongiotic dermatitis. Patch testing using a modified NACDG standard series and a comprehensive cosmetic series was conducted. On day 4, the patient had + reaction to 1% aqueous DMAPA, a + reaction to neomycin, and a +++ reaction to bacitracin. There were no reactions to CAPB or amidoamine	97

Abbreviations: CAPB, cocamidopropyl betaine; DMAPA, 3,3-dimethylaminopropylamine; NACDG, SLS, sodium lauryl sulfate; SLES, sodium lauryl ether sulfate; The North American Contact Dermatitis Group.

Table 9. Quantitative Risk Assessment of Stearamidopropyl Dimethylamine in Cosmetic Products.[65,a]

Product category	Max Use concentration, %	Product exposure, μg/cm^2	CEL, μg/cm^2	NESIL, μg/cm^2	SAF	AEL	AEL/CEL
Eye lotion	1.8	2,170	39.06	1,000.00	300.00	3.33	0.09
Eye makeup remover	1.5	900	13.50	1,000.00	100.00	10.00	0.74
Cologne and toilet waters	1.8	17,700	318.60	1,000.00	100.00	10.00	0.03
Hair conditioners	5	200	10.00	1,000.00	30.00	10.00	1.00
Rinses (noncoloring)	1	170	1.70	1,000.00	100.00	10.00	5.88
Shampoos (noncoloring)	2	170	3.40	1,000.00	100.00	33.33	9.80
Tonics, dressings and other hair grooming aids	3	990	29.70	1,000.00	100.00	10.00	0.34
Other hair preparations (noncoloring) rinse-off	0.5	200	1.00	1,000.00	100.00	10.00	10.00
[b]Hair dyes and colors	2	1,000	20.00	1,000.00	100.00	10.00	0.50
Face powders	1.7	1,000	17.00	1,000.00	100.00	10.00	0.59
Foundations	0.25	3,170	7.93	1,000.00	100.00	10.00	1.26
Lipsticks	1.7	11,460	194.82	1,000.00	300.00	3.33	0.02
Makeup bases	1.6	4,200	67.20	1,000.00	100.00	10.00	0.15
Bath soaps and detergents	1.8	10	0.18	1,000.00	100.00	10.00	55.56
Aftershave lotions	2	2,210	44.20	1,000.00	100.00	10.00	0.23
Pre-shave lotions (all types)	0.05	2,200	1.10	1,000.00	100.00	10.00	9.09
Skin cleansing (cold creams, cleansing lotions, liquids, and pads)	0.07	900	0.63	1,000.00	100.00	10.00	15.87
Face and neck creams, lotions, and powders	1.2	2,700	32.40	1,000.00	100.00	10.00	0.31
Body and hand creams, lotions, and powders	1.5	1,120	16.80	1,000.00	300.00	3.33	0.20
Moisturizers	1	2,700	27.00	1,000.00	100.00	10.00	0.37
Other skin care products	0.1	2,200	2.20	1,000.00	100.00	10.00	4.55
Indoor tanning preparations	2	2,200	44.00	1,000.00	100.00	10.00	0.23

Abbreviations: AEL, acceptble exposure level; CEL, consumer exporsure level; CIR, Cosmetic Ingredient Review; NESIL, no expected sensitization induction levels; SAF, safety assessment factor.
[a]Shaded rows indicate the ratio of AEL $\times$ CEL^{-1} is <1.
[b]Note that this product category may be diluted prior to application.

In an oral reproduction and developmental toxicity study of stearamidopropyl dimethylamine tested up to 200 mg/kg body weight per day in rats, the researchers determined the paternal NOAEL to be 70 mg/kg body weight per day, the maternal NOAEL to be 70 mg/kg body weight per day, and the developmental NOAEL to be 200 mg/kg body weight per day. The dermal application of stearamidopropyl dimethylamine tested up to 200 mg/kg body weight per day in rabbits during gestation days 7 through 18 produced no evidence of developmental toxicity. The maternal NOEL was determined to be 5 mg/kg body weight per day, the maternal NOAEL was determined to be100 mg/kg body weight per day based on variations in body weight and food consumption data, and the developmental NOAEL was determined to be 200 mg/kg body weight per day in this study.

No studies were found on the carcinogenicity of fatty acid amidopropyl dimethylamines. Stearamidopropyl dimethylamine was not genotoxic in a reverse mutation assay, a cell mutation assay in mouse lymphoma, or a chromosome aberration study in human peripheral blood lymphocytes.

No to minimal irritation was observed in ocular irritation assays of behenamidopropyl dimethylamine and dilinoleamidopropyl dimethylamine. All but 1 ocular irritation study of stearamidopropyl dimethylamine report no to minimal irritation; the exception found severe ocular irritation when tested at 100% in rabbit eyes.

In an NACDG retrospective analysis, "amidoamine" produced relevant allergic reactions in 0.5% to 0.7% of seniors, adults, and children tested, respectively.

Behenamidopropyl dimethylamine at concentrations up to 3% and 0.045% stearamidopropyl dimethylamine in personal care products were not irritation in several in-use studies. Behenamidopropyl dimethylamine at 0.3% diluted to 1%, 4% brassicamidopropyl dimethylamine, and stearamidopropyl dimethylamine at 2% neat or diluted to 30% were not contact sensitizers. However, irritation reactions were observed.

Possible cross-reactions to several fatty acid amidopropyl dimethylamines were observed in patients who were reported to have allergic contact dermatitis to a baby lotion that contained 0.3% oleamidopropyl dimethylamine.

A 10-year retrospective study found that of 46 patients with confirmed allergic eyelid dermatitis, 10.9% had relevant reactions to oleamidopropyl dimethylamine and 4.3% had relevant reactions to cocamidopropyl dimethylamine. Several cases of allergic contact dermatitis were reported in patients from the Netherlands that had used a particular type of body lotion that contained oleamidopropyl dimethylamine.

Researchers have included the CAPB impurities, DMAPA and amidoamine, in the scope of sensitization and case studies and have found that one or both of the impurities may be the responsible agent for contact allergy to CAPB. Quantitative

risk assessments of these ingredients may be performed to ensure acceptable levels of risk in consumers.

Discussion

The CIR Panel expressed concern in the previous Cocamidopropyl Betaine and Related Fatty Acid Amidopropyl Betaines safety assessment about impurities that have sensitizing potential. These impurities of CAPB include the ingredients discussed in this safety assessment. In addition, the Panel recognizes that there are increasing concerns about the contact sensitization potential of oleamidopropyl dimethylamine, which was recently added to the NACDG's test panel. The Panel noted that, although a safe conclusion was reached for fatty acid amidopropyl dimethylamines, DMAPA in oleamidopropyl dimethylamine appeared to be present at concentrations greater than those reported for the other amidopropyl dimethylamines. Based on the data submitted, DMAPA in oleamidopropyl dimethylamine could exceed the limit recommended by the Panel in the CAPB safety assessment (ie, 0.01% DMAPA in "raw" CAPB used at the highest reported maximum use concentration of 11% in the product category "other shaving preparations"). The Panel requested that industry provide additional information on DMAPA in oleamidopropyl dimethylamine.

The Panel also noted that, for stearamidopropyl dimethylamine, the highest reported maximum use concentration in leave-on products may result in DMAPA concentrations that exceed the limit for this impurity recommended by the Panel for CAPB. Eleven HRIPT studies of normal human participants indicated that no sensitization was induced by stearamidopropyl dimethylamine applied to the skin at concentrations of use; 2 guinea pig sensitization studies were also negative. However, an LLNA yielded an EC_3 of 1.4% (350 μg/cm^2), indicating that stearamidopropyl dimethylamine is a potential sensitizer. A QRA based on the HRIPTs and rodent studies yielded a conservative, WoE NESIL of 1,000 μg/cm^2 for stearamidopropyl dimethylamine and confirmed that this ingredient has the potential to cause sensitization at reported use concentrations in many categories of finished cosmetic products.

Additionally, the Panel acknowledged the QRAs for the CAPB impurities DMAPA and cocamidopropyl dimethylamine ("amidoamine"), which were originally submitted to support the CIR safety assessment of CAPB. WoE NESILs derived for DMAPA and cocamidopropyl dimethylamine were 425 μg/cm^2 and 180 μg/cm^2, respectively.

The Panel concluded that nonsensitizing concentrations of fatty acid amidopropyl dimethylamine ingredients in finished products can be determined by formulators based on the QRAs for cocamidopropyl dimethylamine (for the ingredients with fatty acid chain lengths $<$ C18), for stearamidopropyl dimethylamine (for the ingredients with fatty acid chain lengths $\geq$ C18), and for DMAPA (for all of the ingredients), using appropriate NESILs for these substances. The Panel advised industry to continue minimizing the concentrations of the sensitizing impurity DMAPA.

The Panel expressed concern about the possible ability of amidopropyl dimethylamines with fatty-acid chain lengths $<$C18 to be absorbed through the skin and into the systemic circulation. However, the high NOAELs in toxicity tests of amidopropyl dimethylamines with longer fatty acids alleviated this concern. The Panel felt that the overall toxicological data and low expected exposures supported the safety of the amidopropyl dimethylamines ingredients.

In past ingredient safety assessments, the CIR Panel had expressed concern over *N*-nitrosation reactions in ingredients containing amine groups. Fatty acid amidopropyl dimethylamines contain secondary amides and tertiary amines that may be *N*-nitrosated. Additionally, these ingredients may contain secondary amine impurities which may serve as substrates for *N*-nitrosation. Therefore, the Panel recommended that these ingredients should not be included in cosmetic formulations containing *N*-nitrosating agents.

The Panel also expressed concern about pesticide residues and heavy metals that may be present in botanical-derived ingredients. They stressed that the cosmetics industry should continue to use current good manufacturing practices to limit impurities.

The Panel discussed the issue of incidental inhalation exposure from cologne, indoor tanning products, and other propellant and pump spray products. No inhalation toxicology data were identified in the published literature or provided by industry. These ingredients reportedly are used at concentrations up to 0.15% in cosmetic products that may be aerosolized. The Panel noted that 95% to 99% of droplets/particles would not be respirable to any appreciable amount. 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 toxic effects upon exposure by incidental inhalation. The Panel considered other data available to characterize the potential of fatty acid amidopropyl dimethylamines to cause systemic toxicity, irritation, sensitization, or other effects. They noted no safety concerns for these substances from the results of acute and repeated dose toxicity studies and genotoxicity studies. Additionally, little or no irritation was observed at use concentrations in multiple tests of dermal and ocular exposure. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at http://www.cir-safety.org/cir-findings.

Conclusion

The CIR Panel concluded that the 24 fatty acid amidopropyl dimethylamines ingredients listed below are safe in cosmetics when they are formulated to be nonsensitizing, which may be based on a QRA.

almondamidopropyl dimethylamine*
avocadamidopropyl dimethylamine*

babassuamidopropyl dimethylamine*
behenamidopropyl dimethylamine
brassicamidopropyl dimethylamine
cocamidopropyl dimethylamine
dilinoleamidopropyl dimethylamine*
isostearamidopropyl dimethylamine
lauramidopropyl dimethylamine
linoleamidopropyl dimethylamine*
minkamidopropyl dimethylamine
myristamidopropyl dimethylamine*
oatamidopropyl dimethylamine*
oleamidopropyl dimethylamine
oleamidopropyl dimethylamine*
palmitamidopropyl dimethylamine
ricinoleamidopropyl dimethylamine*
sesamidopropyl dimethylamine*
soyamidopropyl dimethylamine*
stearamidopropyl dimethylamine
sunflowerseedamidopropyl dimethylamine*
tallamidopropyl dimethylamine*
tallowamidopropyl dimethylamine*
wheat germamidopropyl dimethylamine*

*Not in current use. Were ingredients in this group not in current use 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 Executive Director, Cosmetic, Ingredient Review, 1620 L Street, NW, Suite 1200, Washington, DC 20036, USA.

Author Contribution

Burnett, C. contributed to conception and design; contributed to acquisition, analysis, and interpretation; drafted manuscript; and critically revised manuscript. Boyer, I. contributed to analysis and interpretation. Bergfeld, W., Belsito, D., Hill, R., Klaassen, C., Liebler, D., Marks, J., Shank, R., Slaga, T., Snyder, P., and Gill, L. contributed to conception and design, contributed to analysis and interpretation, and critically revised manuscript. Heldreth, B. contributed to design, contributed to analysis and interpretation, and critically revised 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. Burnett CL, Bergfeld WF, Belsito DV, et al. Final report of the cosmetic ingredient review expert panel on the safety assessment of cocamidopropyl betaine (CAPB). *Int J Toxicol*. 2012;31(Suppl 1):77-111.
2. European Chemicals Agency. N-[3-(dimethylamino)propyl]stearamide. http://echa.europa.eu/. Accessed January 23, 2014.
3. Zamora D, Alcala M, Blanco M. Determination of trace impurities in cosmetic intermediates by ion mobility spectrometry. *Anal Chim Acta*. 2011;708(1-2):69-74.
4. Minguet M, Subirats N, Castan P, Sakai T. Behenamidopropyl dimethylamine: unique behaviour in solution and in hair care formulations. *Int J Cosmetic Sci*. 2010;32(4):246-257.
5. Muzyczko TM, Shore S, Loboda JA. Fatty amidoamine derivatives: N, N-Diemthyl-N-(3-alkylamidopropyl)amiens and their salts. *J Am Oil Chem Soc*. 1968;45(11):720-725.
6. Jachowicz J, Wis-Surel G, Garcia ML. Relationship between triboelectric charging and surface modifacations of human hair. *J Soc Cosmet Chem*. 1985;36:189-212.
7. La Torre C, Bhushan B, Yang JZ, Torgerson PM. Nanotribological effects of silicone type, silicone deposition level, and surfactant type on human hair using atomic force microscopy. *J Cosmet Sci*. 2006;57(1):37-56.
8. Personal Care Products Council. Information on cocamidopropyl dimethylamine. Unpublished data submitted by the Personal Care Products Council. February 14, 2012: 1
9. Shank RC, Magee PN. Toxicity and carcinogenicity of N-nitroso compounds. Chapter: 1. In: Shank RC, ed. *Mycotoxins and N-Nitroso Compounds: Environmental Risks*. Boca Raton, FL: CRC Press; 1981:185-217.
10. Personal Care Products Council. DMAPA levels in behenamidopropyl dimethylamine. Unpublished data submitted by the Personal Care Products Council on March 28, 2012:1
11. Rhodia Inc. Product description: Makine® 501 V (INCI Name: Oleamidopropyl Dimethylamine). Unpublished data submitted by Personal Care Products Council. 2011:4.
12. Personal Care Products Council. HRIPTs of hair conditioners containing stearamidopropyl dimethylamine. Unpublished data submitted by Personal Care Products Council. March 30, 2012:93.
13. Rhodia Inc. Product description: Makine® 301 (INCI Name: Stearamidopropyl Dimethylamine). Unpublished data submitted by Personal Care Products Council. 2010: 4.
14. Evonik Industries. Information on the production and specifications of Stearamidopropyl Dimethylamine. Unpublished data submitted by Personal Care Products Council. 2012.
15. Personal Care Products Council. Studies of products containing stearamidopropyl dimethylamine. Unpublished data submitted by Personal Care Products Council. May 9, 2012.
16. Gottschalck TE, Breslawec HP. International Cosmetic Ingredient Dictionary and Handbook. 14th ed. Washington, DC: Personal Care Products Council; 2012.
17. Food and Drug Administration (FDA). Frequency of use of cosmetic ingredients. *FDA Database*. Washington, DC: Author; 2014. Data received February 25, 2014 in response to a Freedom of Information Act request.

18. Personal Care Products Council. Updated Concentration of Use by FDA product category: fatty acid amidopropyl dimethylamines. Unpublished data submitted by Personal Care Products Council. July 3, 2012: 4.
19. Personal Care Products Council. Comments on the scientific literature review of the fatty acid amidopropyl dimethylamine ingredients as used in cosmetics. Unpublished data submitted by Personal Care Products Council. March 30, 2012: 1.
20. Rothe H. Special aspects of cosmetic spray evalulation. Unpublished data presented at the 26 September CIR Expert Panel meeting. Washington, DC. September 26, 2011.
21. Johnsen MA. The influence of particle size. *Spray Technology and Marketing*. 2004;14(11):24-27.
22. 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.
23. Bremmer HJ, Prud'homme de Lodder LCH, Engelen JGM. Cosmetics fact sheet: to assess the risks for the consumer; Updated version for ConsExpo 4. 2006. Report No. RIVM 320104001/ 2006. pp. 1-77.
24. European Union. 1976, Council Directive 1976/768/EEC of 27 July 1976 on the approximation of the laws of the member states relating to cosmetic products, as amended through commission directive 2008/42/EC. 2008. http://eur-lex.europa.eu/LexUriServ/ LexUriServ.do?uri=CONSLEG:1976L0768:20080424: en: PDF. Accessed March 24, 2010.
25. Codling CE, Maillard JY, Russell AD. Aspects of the antimicrobial mechanisms of action of a polyquaternium and an amidoamine. *J Antimicrob Chemoth*. 2003;51(5):1153-1158.
26. Hughes R, Dart J, Kilvington S. Activity of the amidoamine myristamidopropyl dimethylamine against keratitis pathogens. *J Antimicrob Chemoth*. 2003;51(6):1415-1418.
27. Zhu H, Ding A, Bandara M, Wilcox MDP, Stapleton F. Broad spectrum of antibacterial activity of a new multipurpose disinfecting solution. *Eye Contact Lens*. 2007;33(6):278-283.
28. Dutot M, Warnet JM, Baudouin C, Rat P. Cytotoxicity of contact lens multipurpose solutions: role of oxidative stress, mitochondrial activity and P2X7 cell death receptor activation. *Eur J Pharm Sci*. 2008;33(2):138-145.
29. Paugh JR, Nguyen AL, Hall JQ, et al. A preliminary study of silicone hydrogel lens material and care colution bioincompatibilities. *Cornea*. 2011;30(7):772-779.
30. Lipener C. A randomized clinical comparison of OPTI-FREE EXPRESS and ReNu MultiPLUS multipurpose lens care solutions. *Adv Ther*. 2009;26(4):435-446.
31. Evonik Industries. Summary: Evaluation of a test article (Stearamidopropyl Dimethylamine) in the *Salmonella typhimurium/ Escherichia coli* plate incorporation/ preincubation mutation assay in the presence and absence of Aroclor-induced rat liver S-9 with a confirmation study. Unpublished data submitted by Personal Care Products Council. 1995.
32. Warshaw EM, Raju SI, Fowler JF, et al. Positive patch test reactions in older individuals: retrospective analysis from the north american contact dermatitis group, 1994-2008. *J Am Acad Dermatol*. 2012;66(2):229-240.
33. Institute for In Vitro Sciences Inc. Topical application occular irritation screening assay using the EpioCular™ human cell construct (shampoo containing 0.3% Behenamidopropyl Dimethylamine) Study Number 09AE62, 01AH56.015001. Unpublished data submitted by Personal Care Products Council. 2009.
34. Institute for In Vitro Sciences Inc. Topical application occular irritation screening assay using the EpioCular™ human cell construct (shampoo containing 0.3% Behenamidopropyl Dimethylamine) Study Number 11AD72, 10AO41.015001. Unpublished data submitted by Personal Care Products Council. 2011.
35. Institute for In Vitro Sciences Inc. Topical application ocular irritation screening assay using the EpioCular™ human cell construct (hair conditioner containing 2% Stearamidopropyl Dimethylamine). Study Number 06AC91, 02AC84.015001. Unpublished data submitted by Personal Care Products Council. 2006.
36. MatTek Corporation. Ocular irritation protocol: dilution method. For use with EpiOcular TIssue Model (OCL-200). Received from MatTek Corporation on May 30, 2012.
37. BioScience Laboratorie0s Inc. In-vitro evaluation of the ocular irritation potential of various test products (preshave scrub containing 0.045% Stearamidopropyl Dimethylamine) Study number: 050609-250. Unpublished data submitted by Personal Care Products Council. 2007.
38. Wells Laboratories. Report on eye irritation test in rabbits in dilinoleamidopropyl dimethylamine. Laboratory No.: K-5671. Unpublished data submitted by the Personal Care Products Council. 1984: 2.
39. Clinical Research Laboratories Inc. Safety and consumer evaluation of a hair care product (hair conditioner containing 3% Behenamidopropyl Dimethylamine) CRL Study Number: CRL49009. Unpublished data submitted by Personal Care Products Council. 2009.
40. Clinical Research Laboratories Inc. Safety and consumer evaluation of a hair care product (shampoo containing 0.3% Behenamidopropyl Dimethylamine). CRL Study Number CRL48909. Unpublished data submitted by Personal Care Products Council. 2009.
41. Clinical Research Laboratories Inc. An in-use safety evaluation to determine the dermal irritation potential of a personal care product (pre-shave scrub containing 0.045% Stearamidopropyl Dimethylamine) CRL Study Number CRL27037. Unpublished data submitted by Personal Care Products Council. 2007.
42. Product Investigations Inc. Single patch test summary: oleamidopropyl dimethylamine 1% Oil. Report No. 17227. Unpublished data submitted by Personal Care Products Council. 2003: 9.
43. Evonik Industries. Summary of QSAR modeling (TOPKAT) of the sensitization potential of Stearamidopropyl Dimethylamine. Unpublished data submitted by Personal Care Products Council. 2007.
44. Evonik Industries. Summary of a guinea pig maximization test of Stearamidopropyl Dimethylamine. Unpublished data submitted by Personal Care Products Council. 2009.
45. TKL Research Inc. Repeated insult patch test of a hair conditioner containing 2% Stearamidopropyl Dimethylamine (product test

undiluted). Unpublished data submitted by Personal Care Products Council. 2002: 93.
46. TKL Research Inc. Summary report: Repeated insult patch test of a shampoo containing 0.3% Behenamidopropyl Dimethylamine. TKL Study No: DS102411 -1. Unpublished data submitted by Personal Care Products Council. 2011.
47. TKL Research Inc. Summary report: repeated insult patch test of a shampoo containing 0.3% Behenamidopropyl Dimethylamine. TKL Study No.: DS103909-5. Unpublished data submitted by Personal Care Products Council. 2009.
48. TKL Research Inc. Repeat insult patch test of a rinse-off hair conditioner containing 0.75% Stearamidopropyl Dimethylamine. TKL Study No. DS106003 -1. Unpublished data submitted by Personal Care Products Council. 2003.
49. Clinical Research Laboratories Inc. Summary of HRIPT of a hair masque containing 4% Brassicamidopropyl Dimethylamine. Unpublished data submitted by Personal Care Products Council. 2010: 1.
50. Clinical Research Laboratories Inc. Repeated insult patch test of a hair conditioner containing 2% Stearamidopropyl Dimethylamine. CRL Study Number CRL62406-2. Unpublished data submitted by Personal Care Products Council. 2006.
51. RCTS Inc. Clinical safety evaluation: human repeated insult patch test (HRIPT) of a preshave scrub containing 0.045% Stearamidopropyl Dimethylamine. RCTS Study No 2186. Unpublished data submitted by Personal Care Products Council. 2007.
52. Medcin Instituto da Pele S/C Ltda. Dermatological evaluation topical compatibility primary dermic irritation, accumulated and dermic sensitization (repeat insult patch test of a leave-on hair conditioner containing 0.5% Stearamidopropyl Dimethylamine). Unpublished data submitted by Personal Care Products Council. 2007.
53. Medcin Instituto da Pele S/C Ltda. Dermatological evaluation of topical compatibility primary and accumulated and dermic irritation and dermic sensitization (repeat insult patch test of a leave-on hair conditioner containing 0.5% Stearamidopropyl Dimethylamine). Unpublished data submitted by Personal Care Products Council. 2010.
54. Essex Testing Clinic, Inc. Clinical safety evaluation. Repeated insult patch test of a face and neck product containing 0.05% stearamidopropyl dimethylamine. EC Entry No.: 18513.03. Unpublished data submitted by the Personal Care Products Council on March 27, 2012: 12.
55. Harrison Research Laboratories Inc. Human repeated insult patch test of a hair conditioner containing 2% Stearamidopropyl Dimethylamine (product diluted to 30% (w/w) before testing). Unpublished data submitted by Personal Care Products Council. 1999: 93.
56. Hill Top Laboratories. Human repeat insult patch test of a hair conditioner containing 2% Stearamidopropyl Dimethylamine (product diluted to 30% (w/w) before testing). Unpublished data submitted by Personal Care Products Council. 1997.
57. North Cliff Consultants Inc. Human repeat insult patch test of a hair conditioner containing 2% Stearamidopropyl Dimethylamine (product diluted to 30% (w/w) before testing). Unpublished data submitted by Personal Care Products Council. 1997.
58. de Groot AC, Jagtman BA, van der Meeren HLM, et al. Cross-reaction pattern of the cationic emulsifier oleamidopropyl dimethylamine. *Contact Dermatitis*. 1988;19(4):284-289.
59. de Groot AC. Oleamidopropyl dimethylamine. *Derm Beruf Umwelt*. 1989;37(3):101-105.
60. de Groot AC, Liem DH. Contact allergy to oleamidopropyl dimethylamine. *Contact Dermatitis*. 1984;11(5):298-301.
61. Amin KA, Belsito DV. The aetiology of eyelid dermatitis: a 10-year retrospective analysis. *Contact Dermatitis*. 2006;55(5):280-285.
62. Bjerke D. PCPC task force on sensitization risk from CAPB impurities û presentation to CIR expert panel. Unpublished data submitted by Personal Care Products Council. 2008. 25 pages.
63. Api AM, Basketter DA, Cadby PA, et al. Dermal sensitization quantitative risk assessment (QRA) for fragrance ingredients. *Reg Toxicol Phamacol*. 2008;52(1):3-23.
64. Research Institute for Fragrance Materials. IFRA RIFM QRA Information Booklet Version 6.0. http://www.ifraorg.org/Upload/DownloadButtonDocuments/d9d4e420-8d2f-4290-a3fb-838d8449dc7d/22182_GD_2008_02_15_IFRA_RIFM_QRA_Information_booklet_V6.0_%2846th_IFRA_Amendment%29.pdf. Published May 12, 2006. Updated July 1, 2001. Accessed May 1, 2014.
65. CIR SSC. Skin sensitization quantitative risk assessment on stearamidopropyl dimethylamine. Unpublished data submitted by Personal Care Products Council. April 24, 2014: 6.
66. Advanced Chemistry Development (ACD/Labs). Advanced Chemistry Development software v11.02. 2012.
67. Hill Top Research, Inc. Delayed contact hypersensitivity study in guinea pigs of G0250.01 (stearamidopropyl dimethylamine). Report no. 83-1603-21. Unpublished data submitted by the Personal Care Products Council. 1984: 31.
68. Life Science Research. Delayed contact hypersensitivity in guinea-pigs (Buehler test) of palmityl/stearylamdiopropyl dimethylamine. Unpublished data submitted by the Personal Care Products Council on December 11, 2008: 40.
69. Personal Care Products Council. Summaries of two 1987 guinea pig maximization studies on amidoamine. Unpublished data submitted to the Personal Care Products Council. May 19, 2009: 4.
70. Wright ZM, Basketter DA, Blaikie L, et al. Vehicle effects on skin sensitizing potency of four chemicals: assessment using the local lymph node assay. *Int J Cosmet Sci*. 2001;23(2):75-83.
71. RCC Ltd. Local lymph node assay (LLNA) in mice of TEGO AMIDO S 18 (Sample ID: 14160). RCC study number A87884. Unpublished data submitted by the Personal Care Products Council. 2006: 48.
72. Degussa Goldschmidt Italia S.r.L. Certificate for analysis batch PA06303536 TEGO AMID S 18. Unpublished data submitted by the Personal Care Products Council. March 31, 2006: 1.
73. Calvert Laboratories, Inc. Local lymph node assay on amidoamine. Calvert Study No.: 0787MP72.001. Calvert Laboratories, Inc. Unpublished data submitted by the Personal Care Products Council on March 10, 2010. 2010: 59.
74. Hill Top Research, Inc. Human repeated insult patch test of stearamidopropyl dimethylamine. Report no. 84-0162-72-B. Unpublished data submitted by the Personal Care Products Council. 1984: 13.

75. Inveresk Research Institute. HRIPT on palmityl/stearylamidopropyl dimethylamine. Report no. 1995. Unpublished data submitted by the Personal Care Products Council. 1981: 39.
76. Foti C, Rigano L, Vena GA, Grandolfo M, Liquori G, Angelini G. Contact allergy to oleamidopropyl dimethylamine and related substances. *Contact Dermatitis*. 1995;33(2):132-133.
77. Pigatto PD, Bigardi AS, Cusano F. Contact dermatitis to cocamidopropyl betaine is caused by residual amines: relevance, clinical characterization, and review of literature. *Am J Contact Dermat*. 1995;6:13-16.
78. Angelini G, Foti C, Rigano L, Vena GA. 3-Dimethylaminopropylamine: a key substance in contact allergy to cocamidopropyl betaine? *Contact Dermatitis*. 1995;32(2):96-99.
79. Angelini G, Rigano L, Foti C, Rossi P, Vena GA. Pure cocamidopropyl betaine is not the allergen in patients with positive reactions to commercial cocamidopropyl betaine. *Contact Dermatitis*. 1996;35(4):252-253.
80. Angelini G, Rigano L, Foti C, Vena GA, Grandolfo M. Contact allergy to impurities in structures: amount, chemical structure, and carrier effect in reactions to 3-dimethylaminopropylamine. *Contact Dermatitis*. 1996;34(4):248-252.
81. Angelini G, Rigano L, Foti C, Grandolfo M, Gruning B. Carrier and inhibitory effects of surfactants on allergic contact reactions to 3-dimethylaminopropylamine. *Contact Dermatitis*. 1998; 39(3):152-153.
82. Uter W. Lack of patch test reactivity to 3-dimethylaminopropylamine in German hairdressers. *Contact Dermatitis*. 1999;41(4):231.
83. McFadden JP, Ross JS, White IR, Basketter DA. Clinical allergy to cocamidopropyl betaine: reactivity to cocamidopropylamine and lack of reactivity to 3-dimethylaminopropylamine. *Contact Dermatitis*. 2001;45(2):72-74.
84. Foti C, Bonamonte D, Mascolo G, et al. The role of 3-dimethylaminopropylamine and amidoamine in contact allergy to cocamidopropyl betaine. *Contact Dermatitis*. 2003;48(4):194-198.
85. Brey NL, Fowler JF. Relevance of positive patch-test reactions to cocamidopropyl betaine and amidoamine. *Dermatitis*. 2004; 15(1):7-9.
86. Fowler JF, Zug KM, Taylor JS, et al. Allergy to cocamidopropyl betaine and amidoamine in North America. *Dermatitis*. 2004; 15(1):5-6.
87. Pratt MD, Belsito DV, Deleo VA, et al. North american contact dermatitis group path-test results, 2001-2002 study period. *Dermatitis*. 2004;15(4):176-183.
88. Li LF. A study of the sensitization rate of cocamidopropyl betaine in patients patch tested in a university hospital in Beijing. *Contact Dermatitis*. 2008;58(1):24-27.
89. Fowler JF, Fowler LM, Hunter JE. Allergy to cocamidopropyl betaine may be due to amidoamine: a patch test and product use test study. *Contact Dermatitis*. 1997;37(6):276-281.
90. Hunter JE, Fowler JF. Safety to human skin of cocamidopropyl betaine: a mild surfactant for personal-care products. *J Surfactants and Detergents*. 1998;1(2):235-239.
91. Fartasch M, Diepgen TL, Kuhn M, Basketter DA. Provocative use tests in CAPB-allergic subjects with CAPB-containing product. *Contact Dermatitis*. 1999;41(1):30-34.
92. Speight EL, Beck MH, Lawrence CM. Occupational allergic contact dermatitis due to 3-dimethylaminopropylamine. *Contact Dermatitis*. 1993;28(1):49-50.
93. Kanerva L, Estlander T, Jolanki R. Occupational allergic contact dermatitis from 3-dimethylaminopropylamine in shampoos. *Contact Dermatitis*. 1996;35(2):122-123.
94. Fowler JF. Cocamidopropyl betaine. *Dermatitis*. 2004;15(1):3-4.
95. Moreau L, Sasseville D. Allergic contact dermatitis from cocamidopropyl betaine, cocamidoamine, 3-(dimethylamino)-propylamine, and oleamidopropyl dimethylamine: co-reactions or cross-reactions? *Dermatitis*. 2004;15(3):146-149.
96. Hervella M, Yanguas JI, Iglesias Z, Larrea M, Ros C, Gallego M. Alergia de contacto a 3-dimetilaminopopilamina y cocamidopropil betaina (Contact allergy to 3-dimethylaminopropylamine and cocamidopropyl betaine). *Actas Dermosifiliogr*. 2006;97(3): 189-195.
97. Knopp E, Watsky K. Eyelid dermatitis: contact allergy to 3-(dimethylamino)propylamine. *Dermatitis*. 2008;19(6):328-333.