Scientific Literature Review

Fatty Acid Amidopropyl Dimethylamines as Used in Cosmetics

February 13, 2012

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on this Scientific Literature Review and to identify additional published data that should be included or provide unpublished data which can be made public and included.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 All unpublished data submitted to CIR will be discussed in open meetings, will be available at the CIR office for review by any interested party and may be cited in a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

The 2012 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is F. Alan Andersen, Ph.D. This report was prepared by Christina Burnett, Scientific Analyst/Writer, and Bart Heldreth, Ph.D., Chemist CIR.

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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 scientific literature review is found in Table 1.

In December 2010, the Cosmetic Ingredient Review (CIR)'s Expert Panel issued a final amended safety assessment on cocamidopropyl betaine (CAPB) and related fatty acid amidopropyl betaines. The Expert Panel concluded that these ingredients "were safe in cosmetics as long as they are formulated to be non-sensitizing, which may be based on a quantitative risk assessment." The Expert Panel had expressed great concern related to the impurities that may exist in the amidopropyl betaines because of 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) on 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 that the Expert Panel reviewed in the CAPB safety assessment have been incorporated into this scientific literature review.

CHEMISTRY

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

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 amidization (i.e., amide forming condensation) of fatty acids with 3,3-dimethylaminopropylamine (DMAPA), most commonly under alkaline or acidic conditions (Figure 1).[1,2] The resultant ingredients have an identical core, with two primary functional groups, a secondary amide and a tertiary amine, separated by a propyl chain. These ingredients only differ by the identity of the fatty 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 98-99% pure fatty acid amidopropyl dimethylamines.[3] Accordingly, starting materials, such as DMAPA, represent the largest concern for impurities.

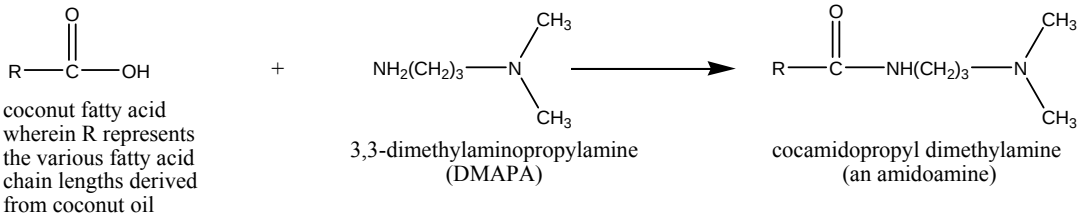


Figure 1. Synthesis of Cocamidopropyl Dimethylamine

Despite the long alkyl chains substituents therein, these ingredients are readily solubilized in water, as they are easily converted into quaternary ammonium salts (ie, cationic surfactants) at even mildly acidic pH values (ie, the tertiary amines are protonated to ammonium cations; these ingredients are alkaline materials with pK_b values in the range of 5-6).[2,3] Due to their high polarity, both as the free tertiary amines and as the quaternary ammonium salts formed in-situ, these ingredients perform excellently at dissipating Triboelectric charges (ie, static electricity), even at low concentrations (eg, 0.1% w/w).[3-5] 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.[3,3]

Method of Manufacturing

Cocamidopropyl Dimethylamine

According to a supplier, cocoamidopropyl dimethylamine is made by mixing together refined coconut oil with DMAPA and heating the mixture to > 75 °C and < 175 °C.[6] The progress of the reaction is followed using standard analytical tests until specifications are met. The product is then filtered and stored in lined steel drums. The composition of the final product is 83-90% cocamidopropyl dimethylamine, 8.9-9.4% glycerin, 1.0% (max) DMAPA, and 5.0% (max) glyceryl esters.

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.[7] Nitrosation can occur under physiologic conditions.[8] 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.[9] Accordingly, fatty acid amidopropyl dimethylamine should be formulated to avoid the formation of nitrosamines.

USE

Cosmetic

All but one of the 24 fatty acid amidopropyl dimethylamines included in this safety assessment function as antistatic agents in cosmetic formulations.[10] Brassicamidopropyl dimethylamine is reported to function as hair and skin conditioning agents. In addition to being an antistatic agent, stearamidopropyl dimethylamine is reported to function as a hair conditioning agent.

Table 3 presents the current product formulation data for these fatty acid amidopropyl dimethylamines. According to information supplied to the Food and Drug Administration (FDA) 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.[11] 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; 32 of those 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. At this time, the Personal Care Products Council is performing a use concentration survey and CIR is awaiting those results.

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.[12]

Non-Cosmetic

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.[13-18]

TOXICOKINETICS

Absorption, Distribution, Metabolism, Excretion

No studies were found on the absorption, distribution, metabolism, and excretion of fatty acid amidopropyl dimethylamines.

GENOTOXICITY

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

CARCINOGENICITY

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

IRRITATION AND SENSITIZATION

Sensitization

Ocular – Non-human

Dilinoleamidopropyl Dimethylamine

An eye irritation study of dilinoleamidopropyl dimethylamine in a 2% dilution with corn oil was performed in a single male rabbit (strain not described). [19] The right eye was the test eye, which was unwashed after the application of the solution. No irritation was observed 24 h after application.

Dermal – Human

Amidoamine

The North American Contact Dermatitis Group (NACDG) evaluated 25,813 patients for allergic contact dermatitis with patch tests from 1998 to 2007.[20] "Amidoamine" produced relevant allergic reactions in 0.5% of the seniors (20/4215; 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.

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.[21,22] Reactions were especially prevalent when 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 dimethylamine (0.05%), cocamidopropyl dimethylamine (0.1%), minkamidopropyl dimethylamine (0.1%), and palmitamidopropyl dimethylamine (0.025%). All 13 patients reacted to the oleamidpropyl 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 out of 12 tested, 75%), and myristamidopropyl dimethylamine (6 patients, 46%). Five patients reacted to isostearamidopropyl dimethylamine, minkamidopropyl dimethylamine, and cocamidopropyl dimethylamine (only 12 patients tested). The remaining substances elicited 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.

Oleamidopropyl Dimethylamine and Cocamidopropyl Dimethylamine

A 10-year retrospective study of patients with allergic eyelid dermatitis investigated the possible allergens.[23] Patch testing was performed in these patients with the NACDG's standard screening tray and other likely allergen trays. Out 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.

CLINICAL USE

Case Studies

Oleamidopropyl Dimethylamine

In the Netherlands, one medical practitioner reported on 3 cases of allergic contact dermatitis in patients that had used a body lotion.[24] In the first case, a 32-year-old female had itchy swelling of the eyelids. Both the upper and 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. 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 observed to hydroxycitronellal and quaterium-15. Further tests showed a positive reaction to oleamidopropyl dimethylamine. The itching improved after the patient discontinued using the body lotion.[24]

FATTY ACID AMIDOPROPYL DIMETHYLAMINES AS REPORTED IN CAPB SAFETY ASSESSMENT

The section below was originally included in the CIR's amended safety assessment of cocamidopropyl betaine (CAPB). Amidoamine herein refers to cocamidopropyl dimethylamine.

Animal Studies

Hill Top Research, Inc. performed a delayed contact hypersensitivity study of stearamidopropyl dimethylamine in guinea pigs.[25] A pre-induction primary irritation study was conducted to determine the concentration for the induction phase of the study. Twenty Hartley outbred guinea pigs were treated with 1.0% w/v stearamidopropyl dimethylamine in 80% ethanol/20% distilled water. The test material was applied for 6 h at a dose volume of 0.3 ml using 25 mm diameter occluded Hill Top chambers on clipped, intact skin on the left shoulder. [Estimated dose/unit area = 6.1 x 10^2 μg/cm^2]. The exposure sites were rinsed after removal of chambers and re-exposed once a week for a total of 3 exposures. A control group of 10 guinea pigs received the vehicle alone. After a 2-week rest period, the animals received primary challenge patches of 0.25% w/v stearamidopropyl dimethylamine in acetone on naïve skin. [Estimated dose/unit area = 1.5 x 10^2 μg/cm^2]. One guinea pig had delayed contact hypersensitivity to the test material. The control animals had no reactions. A rechallenge was conducted in 6 guinea pigs 13 days after the primary challenge with 0.25%, 0.125%, and 0.0625% w/v stearamidopropyl dimethylamine. 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.

Palmityl/stearylamidopropyl dimethylamine at a concentration of 25% active in 8.95% phosphoric acid and 66.05% water was studied for delayed contact hypersensitivity using albino Dunkin/Hartley guinea pigs.[26] A preliminary irritation test was conducted to determine the maximum concentration for the induction and challenge phases of the study. In the induction phase, 10 male and 10 female animals received 0.4 ml of test material on a 4 cm^2 patch on the clipped skin of the left shoulder for a period of 6 h. [Estimated dose/unit area = 2.5 x 10^4 μg/cm^2]. The patches were occluded. An additional 5 male and 5 female animals were left untreated as the controls. A total of 3 induction patches were applied, once weekly, for 3 weeks. Following a 2-week rest period, all animals received primary challenge patches of 0.4 ml of test material on the right flank for 6 h. The test sites were scored at 24 and 48 h post-application. All but 3 of the 20 guinea pigs had patchy to severe erythema at the 24 and 48 h observation periods. Four control animals had slight to moderate patchy erythema during the observation periods. Rechallenges were conducted on 0.25% active and 0.5% active palmityl/stearylamidopropyl dimethylamine. No sensitization was observed with the 0.25% active material, but 0.5% active material elicited reactions in sensitized animals. The study concluded that palmityl/stearylamidopropyl dimethylamine had the potential to cause delayed contact hypersensitivity in guinea pigs.

Two guinea pig maximization studies to assess the skin sensitization potential of amidoamine were evaluated.[27] In the first study, preliminary tests determined the maximum concentrations of intradermal injections, topical induction, and challenge applications. Ten albino Dunkin/Hartley guinea pigs (6 females and 4 males) received two 0.1 ml injections of 50% Freund's complete adjuvant at the first pair of sites, two 0.1 ml injections of 0.1% amidoamine at the second pair of sites, and two 0.1 ml injections of amidoamine in DOBS/saline vehicle and Freund's complete adjuvant (50/50 ratio) to yield a final concentration of 0.1% amidoamine at the third pair of sites. One week following the injections, a single occlusive 48-h induction patch (2 x 4 cm) of 0.2-0.3 ml amidoamine 5% in acetone/PEG400 vehicle was applied to the same shaved area. Four male control animals received intradermal injections and induction patches using only the vehicles. Two weeks after the induction patch, all animals received a single occlusive 24-h challenge patch (8 mm diameter patch in a Finn chamber) saturated with 0.5% amidoamine in acetone/PEG 400 on a clipped and shaved flank. The treatment sites were examined 24 and 48 h after patch removal. Two 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 of $\geq$ 0.5 at 24 h after the removal of the patch. After 48 h, 6 animals had a reaction $\geq$ 0.5. Three out of 10 animals had a reaction score of 2. At the second challenge, 7 guinea pigs had a score of $\geq$ 0.5 at 24 h after patch removal. These scores were consistent at the 48 h reading. Five out of 10 animals had a reaction score of 2. At the third challenge, all 10 guinea pigs had a score $\geq$ 1 at 24 h after patch removal. These score remained largely consistent at the 48 h reading. Eight of the 10 animals had a reaction score of 2. The study concluded that amidoamine was a moderate sensitizer.[27]

The second maximization study was conducted in the same manner as the first with the only changes being that 0.025% amidoamine was used in the intradermal injections instead of 0.1%, 1% amidoamine was used in the topical induction, only 2 challenges were made, and 4 female guinea pigs were used as controls.

At the first challenge, 3 animals had a reaction score of $\geq$ 1 at both the 24 and 48 h readings, with one of the animals scoring a 2. At the second challenge, 3 animals had a reaction score of $\geq$ 1 at 24 and 48 h readings,

although 1 animal had no reaction at 48 that had one at 24 h while another that had no reaction at 24 h had one at 48 h. The study concluded that amidoamine was a moderate sensitizer.[27]

Wright et al. reported on the results of an LLNA study performed on 4 chemicals that are recognized human contact allergens, including DMAPA (99.0+% pure).[28] The chemicals were tested in 7 different vehicles: acetone, olive oil [4:1], dimethylsulfoxide, methethylketone, dimethyl formamide, propylene glycol, and 50:50 and 90:10 mixtures of ethanol and water. Groups of 4 female CBA/Ca mice were exposed topically on the dorsum of both ears to 25 µL of 0.5%, 1.0%, 2.5%, 5.0%, or 10.0% of the test material, or to an equal volume of the appropriate vehicle alone, daily for 3 consecutive days. Five days after the initial topical treatment, all animals were injected intravenously with 20 µCi of [^{3}H] methyl thymidine. Approximately 5 h after injection, the animals were killed and the auricular lymph nodes were excised. Single cell suspensions were prepared from pooled lymph nodes, with the cells precipitated by trichloroacetic acid (TCA), and radioactivity measured by liquid scintillation. The stimulation indices (SI) were calculated, and at 10.0% DMAPA ranged from 2.2 in propylene glycol to 15.7 in dimethyl formamide. The estimated concentrations for a SI of 3 (EC_3) ranged from 1.7% (in dimethyl formamide) to >10% (in propylene glycol).

An LLNA study was performed using stearamidopropyl dimethylamine (TEGO AMID S 18).[29] A certificate of analysis reported that the DMAPA level conformed to the $\leq$ 20 ppm limit, the amine value was 150.8 mg KOH/g (limit range = 148.0-152.0 mg KOH/g), and the melting point was 68.0°C (limit range 66.0-69.0°C).[30] CBA/Ca female mice were divided into 5 groups of 4 and received 0.1%, 0.5%, 1%, 2.5%, or 5% (w/v) of the test material in ethanol/water (7/3, v/v) on the dorsum of each ear lobe (25 µl per ear, diameter ~ 8 mm) once daily for 3 consecutive days. A control group of 4 mice was treated with the vehicle only. The positive control group received α-hexylcinnamaldehyde in acetone:olive oil (4:1, v/v). The mice were treated with [^{3}H] methyl thymidine, killed, and the lymph nodes were prepared in the manner as described in the previous study.

No deaths occurred during the treatment period in any dose group. 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 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. This persisted for 2 days in the 1% dose group and until treatment end in the 2.5% and 5% dose groups. Body weight development was not affected in any of the animals. The SI were1.4, 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 at 1.4%. The positive control group had expected results and validated the study. The study concluded that steramidopropyl dimethylamine (TEGO AMID S 18) was a potential skin sensitizer in this LLNA test.[29]

Calvert Laboratories, Inc. performed an LLNA study using amidoamine (~99% C12-C18).[31] A preliminary dose range study was performed. In the main study, groups of 5 mice received 0%, 0.1%, 0.5%, 1%, 2.5%, or 5% of the test material in ethanol/water, 7:3 (v/v) neutralized to pH 6.0 with citric acid monohydrate. An additional 5 mice received the positive control, 35% hexylcinnamaldehyde. The mice were treated on the dorsal surface of both ears (25 µl/ear) once daily for 3 days. On day 6, the mice were injected i.v. with 20 µCi of ^{3}H-thymidine. Five hours later, the mice were killed and the draining auricular lymph nodes were removed, processed and assessed for lymphocyte proliferation. No mortality or adverse effects were observed throughout the study. Very slight erythema was observed on day 3 and very slight erythema and edema were observed on days 4-6 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 3-6, 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 for amidoamine was calculated at 0.98%. The positive control group had expected results and validated the study. This LLNA study concluded that amidoamine has skin sensitizing activity.

Human Studies

Hill Top Research, Inc. performed an investigation of the potential of stearamidopropyl dimethylamine to induce skin sensitization in 112 human subjects. [32] Applications contained a concentration of 0.25% w/v of the test material in undiluted mineral oil. Induction applications of 0.3 ml were made to the same site with a Webril patch for a total of 9 applications. Challenge applications were made to naïve alternate sites. Frequent incidences of slight to moderate irritation, including erythema, some edema, papules, glazing, and cracking, were observed during the induction period, but were considered transient. Five subjects had a reaction of Grade 1 or greater during the challenge phase. The responses to stearamidopropyl dimethylamine were indicative of primary irritation rather than contact sensitization.

In a study by Inveresk Research International, the sensitization potential of a 4% aqueous liquid fabric softener formulation containing 0.5% stearyl/palmitylamidopropyl dimethylamine was investigated using 77 subjects.[33] During the induction phase, the test material was applied at a dose volume of 0.5 ml with a ¾ inch square Webril pad to the dorsal surface of the upper arm. [Estimated dose/unit area = 6.9 x 10^2 µg/cm^2]. Patches

were applied for a duration of 24 h, 9 times over a period of 3 weeks. The test material caused some degree of irritation in most volunteers. After a rest period of 2 weeks, the subjects received challenge patches with the same concentration of test material on both arms. Patch sites were graded 48 and 96 h after patching. Eight subjects reacted at challenge, and 7 submitted to rechallenge with 4% and 0.4% aqueous formulations. No reactions indicative of sensitization occurred at rechallenge. The test formulation containing stearyl/palmitylamidopropyl dimethylamine had no significant sensitization potential.

Foti et al. patch tested 285 consecutive dermatitis patients with the European standard series supplemented with oleamidopropyl dimethylamine (0.5% aq.), CAPB (1% aq.), and DMAPA (1% aq.).[34] The standard patching technique was employed and test sites were scored on days 2, 3, 4, and 7. 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 by DMAPA (6 ppm or 0.12% of the sample) and indicates that the allergic responses in the last group were not due to cross-reaction. (From the study documentation, it was not possible to determine whether the administered CAPB concentration was 1% active or 1% aqueous, which equated to 0.3% active).

In a 2-year study by Pigatto et al., 1190 eczema patients were patch tested with 1% aq. CAPB using standard technique and grading according to the European Contact Dermatitis Group (ECDG).[35] From this patch test, 17 patients were diagnosed with allergic contact dermatitis to CAPB. Relevance was established with an additional positive patch test of 2+ or more to at least one personal care product containing CAPB used by the patients. Fifteen patients were further tested with CAPB 0.01%, 0.5%, 1% (from 2 different manufactures), and 2% in water; and DMAPA at 0.05%, 0.1%, and 1% in petrolatum; and, if possible, the patients' reported cosmetics diluted in water at 1:10, 1:100, and 1:1000.

In 12 patients tested with their own personal cosmetics, 9 had positive reactions to at least one 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%. Only 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. These positive reactions from DMAPA suggest that the positive reaction to CAPB-containing products was likely due to a certain concentration of DMAPA that was an impurity. DMAPA was measured in the products at 50 - 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 detection level (level not reported) in the other type. The authors stated that the sensitizing agent in CAPB allergy is DMAPA, although their findings did not exclude the role of CAPB itself from causing allergic dermatitis.[35] (From the study documentation, it was not possible to determine whether the administered CAPB concentration was 1% active or 1% aqueous, which equated to 0.3% active).

A study of sensitization to commercially available CAPB in patients with dermatitis was performed by Angelini et al.[36] Twelve hundred consecutive patients with dermatitis of various types were patch tested with the European standard series and CAPB 1% aq. (30% active ingredient). Some of the patients that 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 were observed in 46 subjects (3.8%) while irritant reactions were recorded in 15 subjects (1.25%). Of these 46 subjects, 30 had positive reactions to DMAPA 1% aq. In these 30 subjects, 3 and 16 were positive to the purer grade of CAPB 0.5% aq. and CAPB 1% aq., respectively. Patients with irritant reactions had negative reactions to the synthetic materials and to the 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. The authors concluded that the results suggested that DMAPA impurity was responsible for CAPB allergy.[36] (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 equated to 0.15% active and 0.3% active, respectively).

A further study by Angelini et al. was performed to determine if CAPB or an impurity of CAPB was responsible for cases of contact dermatitis.[37] In this study, thin-layer chromatography was employed to analyze a sample of CAPB (Tego Betaine F 30% solution) and isolate and identify unknown impurities other than DMAPA, chloroacetic acid, and amidoamine found in the CAPB solution. An infrared spectrum analysis was used to confirm the presence of the sodium salt of N, N-dimethyl-propylene-diaminotriacetic acid.

Upon identifying the impurity, 30 patients with a history of contact allergy to 1% aq. CAPB and 1% DMAPA were patch tested with pure CAPB and a blend containing sodium chloride and N, N-dimethyl-propylene-diaminotriacetic acid (both at 1%). None of the subjects reacted to any of the chemicals. The authors suggested that

pure CAPB, chloroacetic acid, amidoamine, and N, N-dimethyl-propylene-diaminotriacetic acid were not the components responsible for CAPB sensitivity and the involvement of DMAPA cannot be ruled out.[37] (From the study documentation, it was not possible to determine whether the administered CAPB concentration was 1% active or 1% aqueous, which equated to 0.3% active).

In another study by Angelini et al., DMAPA was tested at varying concentrations with other tensioactive chemicals to determine if they enhanced sensitivity to DMAPA.[38] Thirty-four subjects with confirmed contact allergy to 1% aq. DMAPA were patch tested with DMAPA in water, DMAPA in a SLES 2% aq. solution, and DMAPA in a polysorbate 20 2% aq. solution, all in decreasing concentrations from 0.1% to 0.00005%. The subjects were also patch tested with CAPB and a series of 10 substances chemically related to DMAPA. Test sites were occluded for 2 days and the sites were measured for reactions on days 2, 3, 4, and 7.

Eighteen subjects had positive reaction 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 in 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 in 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. The authors concluded that tensioactives such as SLES and polysorbate 20 may enhance the risk of sensitization to DMAPA at low concentrations. They also concluded that the primary amine and the tertiary amine groups (dimethyl-substituted) are the sensitizing chemical structures in DMAPA and related molecules when they are separated by 2 or 3 carbon atoms.[38]

In another study by Angelini et al., 20 patients (ages 17-51 years, 13 females and 7 males) with confirmed contact allergy to DMAPA (1% aq.) and CAPB (1% aq.) were tested.[39] All the patients had intolerance to detergents and shampoos and none were sensitized through an occupation. The patients were patch tested using serial dilutions of DMAPA (100 ppm) in surfactant solutions (1% or 2% w/w surfacatants) that included purified CAPB (DMAPA < 1 ppm), SLES, polysorbate 20 (Tween 20), lauryl polyglucoside (APG), SLES/CAPB 3:1 (w/w), and APG/CAPB 3:2 (w/w). The test sites were scored on days 2, 3, 4 and 7. (From the study documentation, it was not possible to determine whether the administered CAPB concentration was 1% active or 1% aqueous, which equated to 0.3% active).

Positive reactions were observed in serial dilutions of DMAPA in 1% CAPB at 1 ppm and higher (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 in serial dilutions of 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. The authors concluded that the concentration limit for DMAPA in 1% CAPB or 1% SLES/CAPB 3:1 should be 0.5 ppm (corresponding to 15 ppm and 60 ppm, respectively) and that betaine should be blended with non-ionic surfactants to reduce allergy risks.[39] (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 equated to 0.3% active and 0.6%, respectively).

Uter studied 80 subjects (mainly hairdressers) with dermatitis from 1996 to 1999.[40] During this period the subjects were patch tested with the hairdresser's series supplemented with DMAPA (1% pet. and 1% aq.). The hairdresser's series contained CAPB (1% aq.) that had a maximum residual DMAPA of <15 ppm. Of the 80 subjects, 6 had + to +++ reactions to CAPB, but none of the six 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 equated to 0.3% active).

McFadden et al. studied 7 subjects that had relevant dermatitis to CAPB.[41] The dermatitis occurred after use of liquid soaps, and in one case an eye make-up remover that contained CAPB. Four of the 7 subjects were patch tested with partially purified CAPB (1% aq.) containing <0.5% cocamidopropylamine and to 0.1% and 0.01% cocamidopropylamine. The patch sites were read at day 2 and day 4 after the initial patching. One subject had a positive reaction that appeared only to cocamidopropylamine. Another had a reaction only to CAPB; however irritancy could not be ruled out since the subject's patch sites were only read on day 2. The other 2 patients had positive reactions to cocamidopropylamine and CAPB. Control subjects had negative patch results.

Six out of the 7 original subjects with dermatitis were patched tested with DMAPA along with controls on normal and tape stripped skin at 0 ppm to 10,000 ppm. The subjects were also tested with DMAPA in the presence of 0.2% aq., sodium lauryl sulfate (SLS), or in the presence of 1.0% pure CAPB (<0.3% cocamidopropylamine, <10 ppm DMAPA). The patch sites were again read on day 2 and day 4 after the patch applications. One of the 6 subjects reacted to DMAPA on normal and tape-stripped skin at concentrations >1000 ppm. Three of the 6 subjects reacted to DMAPA in the presence of 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. The authors concluded that the sensitization experienced by the subjects to the CAPB products was likely due to the residual intermediates from the CAPB production, with reaction to cocamidopropylamine more likely than DMAPA.[41] (From the study documentation, it was not possible to determine whether the administered CAPB concentration was 1% active or 1% aqueous, which equated to 0.3% active).

The impurities DMAPA and amidoamine in CAPB were further analyzed for sensitization potential in 10 subjects with CAPB allergy.[42] The subjects that had all tested positive to CAPB 1% aq. (Firma type) were patch tested with CAPB 1% aq. (Chemotechnique type), DMAPA 1% aq., and purified amidoamine at 0.5%, 0.25%, and 0.1% aq. 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. Four patients had positive reactions (++) to the purified amidoamine at 0.1%. No reactions were observed to the CAPB from Chemotechnique, which was suggested to have a higher purity by the authors. Control patches in 20 volunteers were negative for amidoamine. The authors concluded that cross-reactivity between DMAPA and amidoamine causes CAPB allergy. They also suggested that DMAPA is the true sensitizing material and amidoamine aids in the trans-epidermal penetration of DMAPA. (From the study documentation, it was not possible to determine whether the administered CAPB concentration was 1% active or 1% aqueous, which equated to 0.3% active).

Brey and Fowler performed a retrospective study of patients that had positive patch test results to 1.0% aq. CAPB and/or 1.0% amidoamine in the year 2001.[43] Reactions to other allergens were also recorded. Out of 957 patients patch tested in 2001, 49 had positive reactions to CAPB, amidoamine, or both. A follow-up evaluation in 35 patients was performed to establish relevance of reactions to CAPB and amidoamine with use of products containing these chemicals. Fifteen patients (42.9%) reacted to CAPB, 12 patients (34.3%) reacted to amidoamine, and 8 patients (22.8%) 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 equated to 0.3% active).

Fowler et al. performed a retrospective study of patients with CAPB and/or amidoamine contact allergy in 2001.[44] Out of 975 patients, 15 had a positive patch test reaction to 1.0% CAPB only, 25 had a positive patch test reaction to 0.1% 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. This study also evaluated formaldehyde allergy. Of the 58 patients, 12.7% were also allergic to formaldehyde. This was compared to the 10.1% of the total 975 patients that had formaldehyde allergy. The authors suggested that there is no significant relationship between CAPB or amidoamine allergy and formaldehyde allergy. (From the study documentation, it was not possible to determine whether the administered CAPB concentration was 1% active or 1% aqueous, which equated to 0.3% active).

The NACDG evaluated 4913 patients for allergic contact dermatitis with an extended screening series of 65 allergens from January 1, 2001 to December 31, 2002. CAPB (1% aq.) and the by-product of CAPB production, amidoamine (0.1% aq.), were both included in this screening series. Positive results for CAPB were observed in 2.8% of the patients while 2.3% were positive for amidoamine. The relevance of the CAPB and amidoamine reactions (present and past) was 90.9% and 85%, respectively.[45] (From the study documentation, it was not possible to determine whether the administered CAPB concentration was 1% active or 1% aqueous, which equated to 0.3% active).

In a study by Li to determine the sensitization rate of CAPB in China and to analyze the relationship between CAPB and DMAPA, 429 patients (105 male, 324 female; 9-81 years old) with suspected contact allergy were patch tested with 1% aq. CAPB (purified) and 1% aq. DMAPA.[46] The patients were also tested with the European standard series.

Of the 429 subjects tested, 9 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. Twenty-seven of these subjects and 15 (out of 353) of the subjects with cosmetic allergic contact dermatitis 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. Because the subjects of this study had positive reactions to both CAPB (purified) and DMAPA, the authors recommended that patch tests in cases of suspected cosmetic allergic contact dermatitis contain both CAPB and DMAPA.[46] (From the study documentation, it was not possible to determine whether the administered CAPB concentration was 1% active or 1% aqueous, which equated to 0.3% active).

Provocative Use Studies

A provocative use study of products containing CAPB was performed by Fowler et al.[47] Ten subjects were identified through positive reactions to 1% aq. CAPB in routine patch testing. Ten control subjects negative to CAPB were also enrolled. The provocative use test was divided into 3 phases, with 3 different test products (shampoo, liquid hand soap, and body wash) used in each phase. The products were specially formulated with CAPB-F grade (active level of CAPB in shampoo was 5.0%; active level in hand soap and body wash was 5.2%). 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: 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 grades F and S (both 1% aq.), DMAPA (0.1% pet), amidoamine (0.1% aq.), sodium monochloroacetate (0.1% aq.), 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 0.1% 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, one reacted to the CAPB-S grade, and one reacted to the proprietary preservative mixture. Two 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 equated to 0.3% active).

A follow-up patch test with 7 of the subjects was performed using purified CAPB (containing only 1 ppm amidoamine), CAPB-F grade (with approximately 3000 ppm amidoamine), and 2 concentrations of amidoamine (0.1% and 0.01% aq.). 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. The authors concluded that the impurity amidoamine may be the causative allergen in CAPB sensitivity and they recommend that cosmetics and personal care products should be formulated to minimize contamination with this impurity. In addition, the authors could not rule out the possibility that CAPB alone was not an allergen to pre-sensitized individuals.[47,48]

Another provocative use test was conducted by Fartasch et al.[49] Subjects with eczema were tested for CAPB allergy while undergoing patch testing for the standard allergen series. Out of 1063 patients, 13 were identified with a positive patch reaction; however, relevance could only be established in 4 of the subjects. Another 6 patients were referred to the study for eczematous eruptions of the scalp and/or hand dermatitis and had positive 1% aq. CAPB patch test reactions. Twenty volunteers served as controls for the study.

The product use study consisted of 3 phases. In Phase I, a 0.1 ml test sample of shower gel containing CAPB (25% dilution; DMAPA below 1 ppm) was applied, lathered for 1 minute, and rinsed on the subjects' forearms twice daily for 7 days. The second phase of the study consisted of patch testing in order to differentiate irritant reactions from allergic reactions and to reconfirm sensitivity to CAPB and DMAPA. The subjects were patch tested with 0.1%, 0.3%, and 1.0% dilutions of CKKB (Tegobetaine CKKB5; 1.1 ppm DMAPA) and DMAPA, respectively. Patch sites were read on days 2, 3, and 4 following application. Subjects that had no allergic reactions in Phase I participated in Phase III. In this phase, the subjects used the shower gel as they would in normal daily hygiene practices for 4 weeks.

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 out of the 10 subjects had a positive

reaction to 1% CAPB and another 3 had marginal 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. The authors concluded that CAPB as tested may be used safely in individuals with CAPB sensitivity.[49] (From the study documentation, it was not possible to determine whether the administered CAPB concentration was 1% active or 1% aqueous, which equated to 0.3% active).

Case Reports

Speight et al. reported on two case studies of occupational allergic contact dermatitis.[50] In the first case study, a 50-year-old man who worked in a chemical factory (which produced amines) developed a red itchy face. The reaction cleared after treatment with topical corticosteriods 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 for 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 case study, a 54-year-old man who worked with DMAPA and CAPB developed an itchy red scaly face and right palm that cleared over 2 weeks. However, 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.[50]

A 34-year-old woman employed as an assistant nurse developed dermatitis on both hands without earlier skin symptoms. The dermatitis 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. The authors stated that the dermatitis was from occupational exposure to shampoos and hand cleansers that may have contained DMAPA as a contaminant.[51]

A 37-year-old woman with no history of atopic or seborrheic dermatitis was reported by Fowler to have a 5 month history of eyelid dermatitis.[52] 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). CAPB was present in the baby shampoo used by the patient. The dermatitis cleared after discontinuing use of the product.

A 39-year-old woman with personal history of eczema and asthma reported with a 6 month history of persistent dermatitis of the face and eyelids.[53] The patient complained of a burning sensation, pruritus, erythema, and occasional swelling of the eyelids. The dermatitis would worsen when the patient's hair contacted her face. 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.

Hervella et al. reported on 3 cases of allergic contact dermatitis.[54] The patients (a 58-year-old housewife, a 36-year-old male office worker, and a 24-year-old hairdresser) 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 response 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 equated to 0.3% active).

A 42-year-old female reported with a 4 month history of severe recalcitrant eyelid dermatitis.[55] 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.

SUMMARY

The fatty acid amidopropyl dimethylamines, referred to as "amidoamines" function primarily as antistatic agents in cosmetic products. The CIR Expert Panel had expressed great concern related these chemicals in a safety assessment of fatty acid amidopropyl betaines where 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 (i.e., amide forming condensation) of fatty acids with 3,3-dimethylaminopropylamine (DMAPA), most commonly under alkaline or acidic conditions. Although nitrosamine content has not been reported, 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; 355 of those uses are in rinse-off formulations. Behenamidopropyl dimethylamine has the second greatest number of overall uses reported, with a total of 35; 32 of those uses 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. At this time, the Personal Care Products Council is performing a use concentration survey and CIR is awaiting those results.

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 biocide in contact lens disinfecting solution.

No studies were found on the toxicokinetics, genotoxicity, or carcinogenicity of fatty acid amidopropyl dimethylamines.

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

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

A 10-year retrospective study found that out 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.

In numerous animal, human, and clinical studies related to research of CAPB, DMAPA and/or amidoamine were found to be the responsible agent for contact allergy to CAPB.

DATA NEEDS

Data will be obtained from an industry survey of current uses and use concentrations as a function of cosmetic product type. Any available additional safety data involving dermal exposure would be useful as would information on the amount of DMAPA impurities in cosmetic grade fatty acid amidopropyl dimethylamines.

TABLES AND FIGURES

Table 1. Names, CAS registry numbers, and definitions.[10] (wherein the italicized or bracketed text has been added by CIR staff)

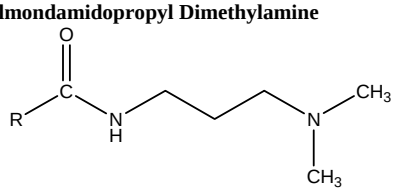
Ingredient & CAS No.	Definition
Almondamidopropyl Dimethylamine	Almondamidopropyl Dimethylamine is the amidoamine that *results from the reaction of DMAPA and* the fatty acids derived from almond oil.
Avocadamidopropyl Dimethylamine	Avocadamidopropyl Dimethylamine is the amidoamine that *results from the reaction of DMAPA and* the fatty acids derived from Persea Gratissima (Avocado) Oil.
Babassuamidopropyl Dimethylamine	Babassuamidopropyl Dimethylamine is the amidoamine that *results from the reaction of DMAPA and* the fatty acids derived from Orbignya oleifera (babassu) oil.
Behenamidopropyl Dimethylamine 60270-33-9 [872429-01-1]	Behenamidopropyl Dimethylamine is the amidoamine that *results from the reaction of DMAPA and behenic acid.*
Brassicamidopropyl Dimethylamine	Brassicamidopropyl Dimethylamine is the amidoamine that *results from the reaction of DMAPA and* the fatty acids derived from Brassica Campestris (Rapeseed) Seed Oil.
Cocamidopropyl Dimethylamine 68140-01-2	Cocamidopropyl Dimethylamine is the amidoamine that *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 aminopropyldimethylamine. *Dilinoleamidopropyl Dimethylamine is the amidoamine that results from the reaction of DMAPA and the 36-carbon dicarboxylic acid, formed by the catalytic dimerization of linoleic acid.*
Isostearamidopropyl Dimethylamine 67799-04-6 [3432-14-2]	Isostearamidopropyl Dimethylamine is the amidoamine that *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 results from the reaction of DMAPA and lauric acid.*
Linoleamidopropyl Dimethylamine 81613-56-1	Linoleamidopropyl Dimethylamine is the amidoamine that *results from the reaction of DMAPA and linoleic acid.*
Minkamidopropyl Dimethylamine 68953-11-7	Minkamidopropyl Dimethylamine is the amidoamine that *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 *results from the reaction of DMAPA and myristic acid.*
Oatamidopropyl Dimethylamine	Oatamidopropyl Dimethylamine is the amidoamine that *results from the reaction of DMAPA and* the fatty acids derived from Avena Sativa (Oat) Kernel Oil.
Oleamidopropyl Dimethylamine 109-28-4 [149879-92-5] [126150-52-5]	Oleamidopropyl Dimethylamine is the amidoamine that *results from the reaction of DMAPA and oleic acid.*
Olivamidopropyl Dimethylamine	Olivamidopropyl Dimethylamine is the amidoamine that *results from the reaction of DMAPA and* the fatty acids derived from olive oil.
Palmitamidopropyl Dimethylamine 39669-97-1 [872428-99-4]	Palmitamidopropyl Dimethylamine is the amidoamine that *results from the reaction of DMAPA and palmitic acid.*
Ricinoleamidopropyl Dimethylamine 20457-75-4	Ricinoleamidopropyl Dimethylamine is the amidoamine that *results from the reaction of DMAPA and ricinoleic acid.*
Sesamidopropyl Dimethylamine	Sesamidopropyl Dimethylamine is the amidoamine that *results from the reaction of DMAPA and* the fatty acids derived from sesame oil.

Table 1. Names, CAS registry numbers, and definitions.[10] (wherein the italicized or bracketed text has been added by CIR staff)

Ingredient & CAS No.	Definition
Soyamidopropyl Dimethylamine 68188-30-7	Soyamidopropyl Dimethylamine is the amidoamine that *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 *results from the reaction of DMAPA and stearic acid.*
Sunflowerseedamidopropyl Dimethylamine	Sunflowerseedamidopropyl Dimethylamine is the amidoamine that *results from the reaction of DMAPA and* the fatty acids derived from sunflowerseed oil.
Tallamidopropyl Dimethylamine 68650-79-3	Tallamidopropyl Dimethylamine is the substituted amine that *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 *results from the reaction of DMAPA and* the fatty acids derived from tallow.
Wheat Germamidopropyl Dimethylamine	Wheat Germamidopropyl Dimethylamine is the amidoamine that *results from the reaction of DMAPA and* the fatty acids derived from wheat germ oil.

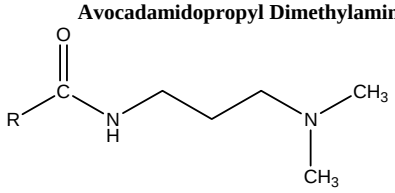
Figure 2. Structures

1. Almondamidopropyl Dimethylamine



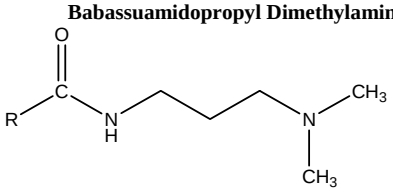
wherein RC(O) represents the fatty acid residue derived from almond oil

2. Avocadamidopropyl Dimethylamine



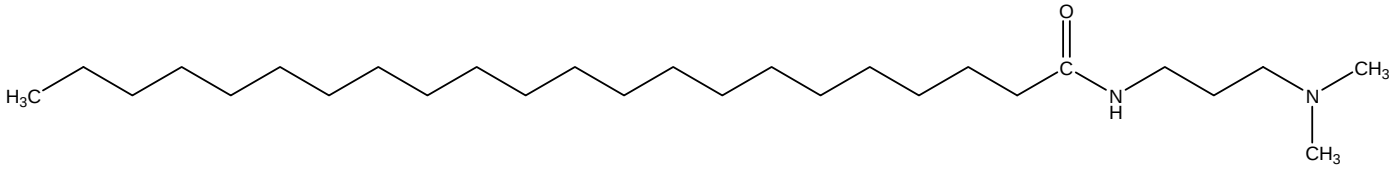
wherein RC(O) represents the fatty acid residue derived from Persea Gratissima (Avocado) Oil

3. Babassuamidopropyl Dimethylamine

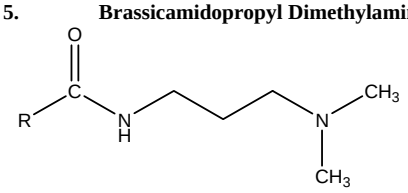


wherein RC(O) represents the fatty acid residue derived from Orbignya oleifera (babassu) oil

4. Behenamidopropyl Dimethylamine

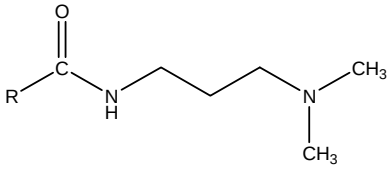


5. Brassicamidopropyl Dimethylamine



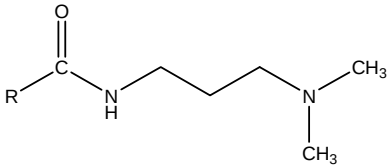
wherein RC(O) represents the fatty acids acid residue from Brassica Campestris (Rapeseed) Seed Oil

6. Cocamidopropyl Dimethylamine



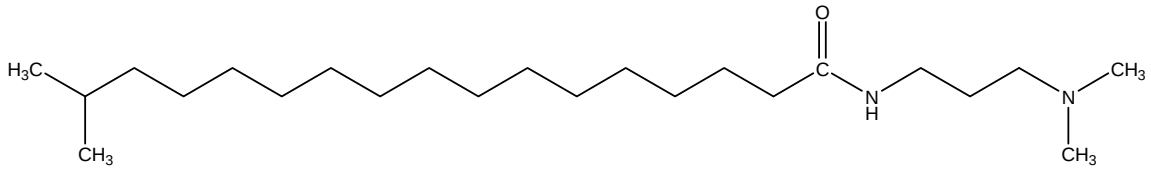
wherein RC(O) represents the fatty acid residue derived from coconut oil

7. Dilinoleamidopropyl Dimethylamine

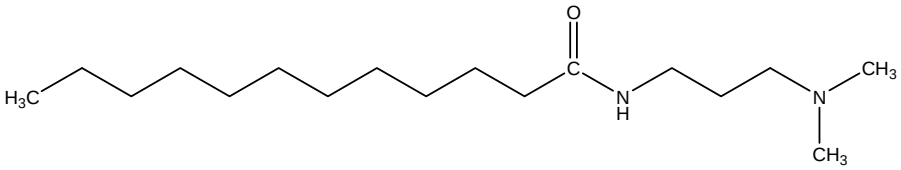


wherein RC(O) represents the variety of 36-carbon dicarboxylic acid residues, formed by the catalytic dimerization of linoleic acid

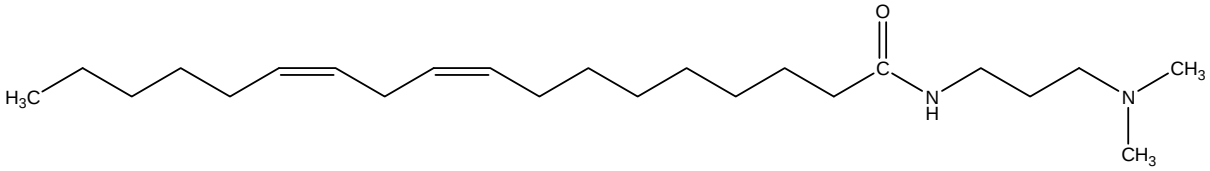
8. **Isostearamidopropyl Dimethylamine** (one example of an "iso")



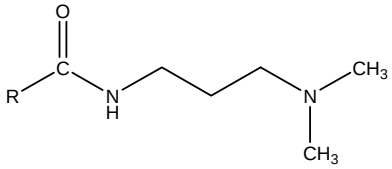
9. **Lauramidopropyl Dimethylamine**



10. **Linoleamidopropyl Dimethylamine**

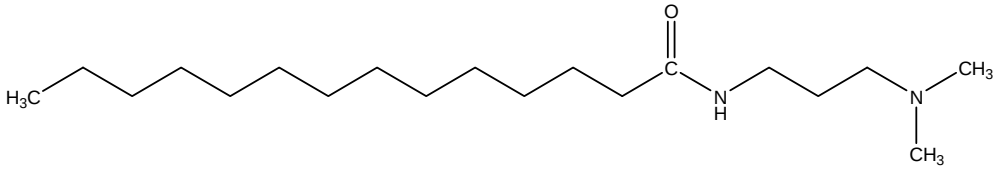


11. **Minkamidopropyl Dimethylamine**

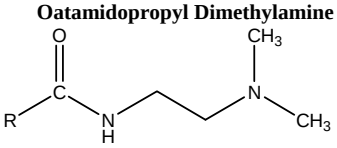


wherein RC(O) represents the fatty acid residue derived from mink oil

12. **Myristamidopropyl Dimethylamine**

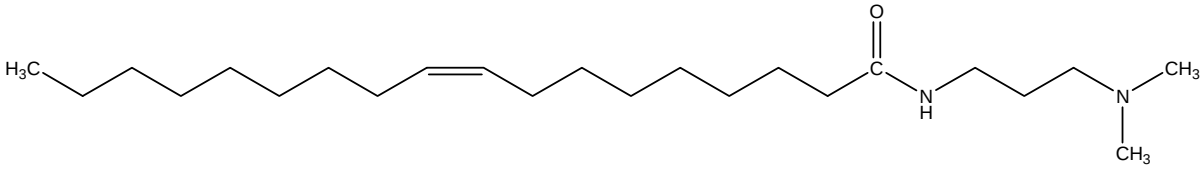


13. **Oatamidopropyl Dimethylamine**

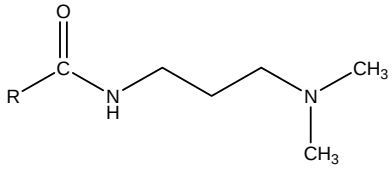


wherein RC(O) represents the fatty acid residue derived from Avena Sativa (Oat) Kernel Oil

14. **Oleamidopropyl Dimethylamine**

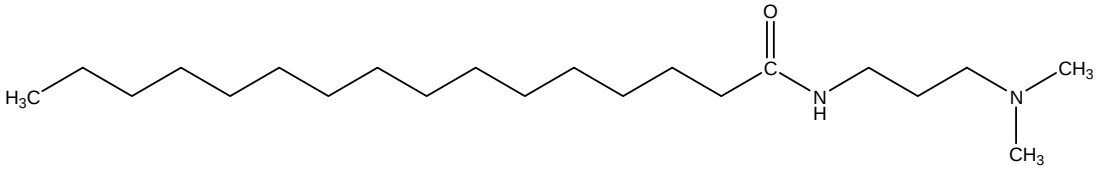


15. **Olivamidopropyl Dimethylamine**

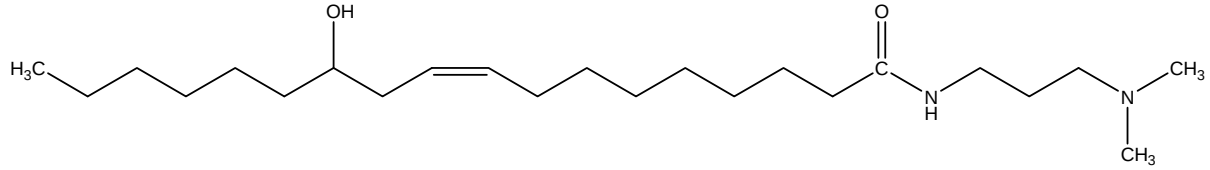


wherein RC(O) represents the fatty acid residue derived from olive oil

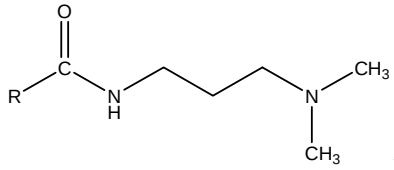
16. **Palmitamidopropyl Dimethylamine**



17. Ricinoleamidopropyl Dimethylamine

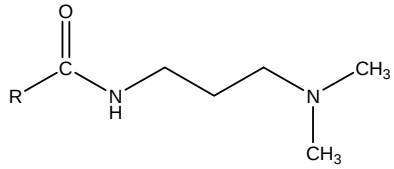


18. Sesamidopropyl Dimethylamine



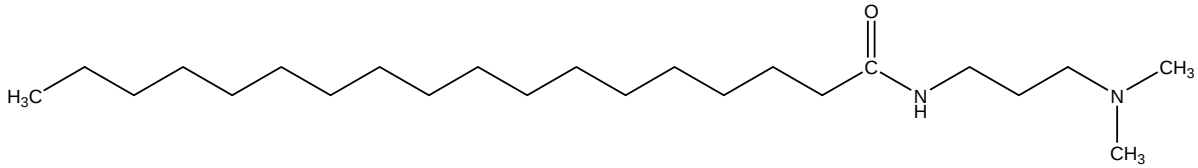
wherein RC(O) represents the fatty acid residue derived from sesame oil

19. Soyamidopropyl Dimethylamine

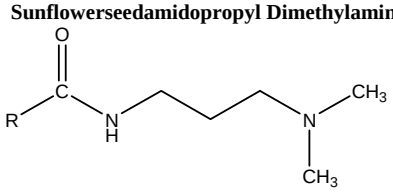


wherein RC(O) represents the fatty acid residue derived from soy

20. Stearamidopropyl Dimethylamine

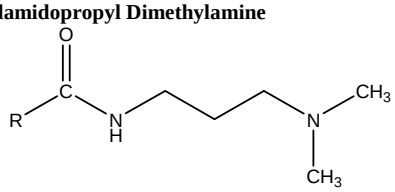


21. Sunflowerseedamidopropyl Dimethylamine



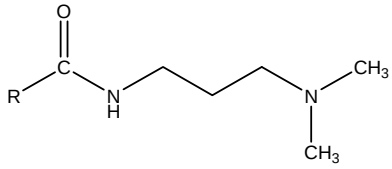
wherein RC(O) represents the fatty acid residue derived from sunflowerseed oil

22. Tallamidopropyl Dimethylamine



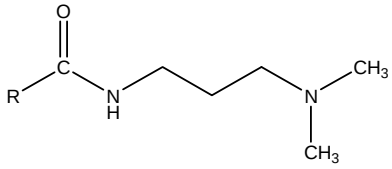
wherein RC(O) represents the fatty acid residue derived from tall oil

23. Tallowamidopropyl Dimethylamine



wherein RC(O) represents the fatty acid residue derived from tallow

24. Wheat Germamidopropyl Dimethylamine



wherein RC(O) represents the fatty acid residue derived from wheat germ oil

Table 2. Physical and chemical properties.

Property	Value	Reference
Behenamidopropyl Dimethylamine		
Molecular Weight g/mol	424.75	[56]
Molecular Volume cm^3/mol @ 20 ºC	487.4	[56]
Density/Specific Gravity g/cm^3 @ 20 ºC	0.871	[56]
Vapor pressure mmHg@ 25 ºC	6.30×10^{-12}	[56]
Boiling Point ºC	544.8	[56]
log P @ 25 ºC	9.656	[56]
Cocamidopropyl Dimethylamine		
Appearance	Clear liquid	[6]
Odor	Mild amine	[6]
Density/Specific Gravity g/cm^3 @ 25 ºC	0.98-1.02	[6]
Vapor pressure mmHg	< 0.01	[6]
Boiling Point ºC @ 760 mmHg	> 100	[6]
Melting Point ºC	< 25	[6]
Solubility in water	Soluble	[6]
pH	~ 9	[6]
Lauramidopropyl Dimethylamine		
Molecular Weight g/mol	284.48	[56]
Molecular Volume cm^3/mol @ 20 ºC	322.3	[56]
Density/Specific Gravity g/cm^3 @ 20 ºC	0.882	[56]
Vapor pressure mmHg@ 25 ºC	3.17×10^{-7}	[56]
Boiling Point ºC	418.9	[56]
Melting Point ºC	28.5-30.0	[3]
log P @ 25 ºC	4.561	[56]
Linoleamidopropyl Dimethylamine		
Molecular Weight g/mol	364.61	[56]
Molecular Volume cm^3/mol @ 20 ºC	408.6	[56]
Density/Specific Gravity g/cm^3 @ 20 ºC	0.892	[56]
Vapor pressure mmHg@ 25 ºC	2.69×10^{-10}	[56]
Boiling Point ºC	504.3	[56]
log P @ 25 ºC	6.805	[56]

Table 2. Physical and chemical properties.

Property	Value	Reference
Myristamidopropyl Dimethylamine		
Molecular Weight g/mol	312.53	[56]
Molecular Volume cm^3/mol @ 20 °C	355.3	[56]
Density/Specific Gravity g/cm^3 @ 20 °C	0.879	[56]
Vapor pressure mmHg@ 25 °C	3.84×10^{-8}	[56]
Boiling Point °C	445.8	[56]
log P @ 25 °C	5.580	[56]
Oleamidopropyl Dimethylamine		
Molecular Weight g/mol	366.62	[56]
Molecular Volume cm^3/mol @ 20 °C	414.9	[56]
Density/Specific Gravity g/cm^3 @ 20 °C	0.883	[56]
Vapor pressure mmHg@ 25 °C	2.57×10^{-10}	[56]
Boiling Point °C	504.8	[56]
log P @ 25 °C	7.209	[56]
Palmitamidopropyl Dimethylamine		
Molecular Weight g/mol	340.59	[56]
Molecular Volume cm^3/mol @ 20 °C	388.3	[56]
Density/Specific Gravity g/cm^3 @ 20 °C	0.876	[56]
Vapor pressure mmHg@ 25 °C	4.52×10^{-9}	[56]
Boiling Point °C	471.8	[56]
log P @ 25 °C	6.599	[56]
Ricinoleamidopropyl Dimethylamine		
Molecular Weight g/mol	382.62	[56]
Molecular Volume cm^3/mol @ 20 °C	412.8	[56]
Density/Specific Gravity g/cm^3 @ 20 °C	0.926	[56]
Vapor pressure mmHg@ 25 °C	8.20×10^{-14}	[56]
Boiling Point °C	537.9	[56]
log P @ 25 °C	5.395	[56]

Table 2. Physical and chemical properties.

Property	Value	Reference
Stearamidopropyl Dimethylamine		
Molecular Weight g/mol	368.64	[56]
Molecular Volume cm^3/mol @ 20 °C	421.7	[56]
Density/Specific Gravity g/cm^3 @ 20 °C	0.874	[56]
Vapor pressure mmHg@ 25 °C	5.19×10^{-10} - 9.03×10^{-10}	[56]
Boiling Point °C	490.6 - 496.9	[56]
Melting Point °C	58.5-59.5	[3]
log P @ 25 °C	7.618 - 7.629	[56]

Table 3. Frequency and concentration of use according to duration and type of exposure[11]

	# of Uses	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*
	Behenamidopropyl Dimethylamine		**Brassicamidopropyl Dimethylamine**		**Cocamidopropyl Dimethylamine**	
Totals*	**35**	**NR**	**1**	**NR**	**6**	NR
Duration of Use						
Leave-On	3	NR	NR	NR	3	NR
Rinse-Off	32	NR	1	NR	3	NR
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	NR
Dermal Contact	NR	NR	NR	NR	6	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	35	NR	1	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	1	NR
Baby Products	NR	NR	NR	NR	NR	NR

	Isostearamidopropyl Dimethylamine		**Lauramidopropyl Dimethylamine**		**Minkamidopropyl Dimethylamine**	
Totals*	**13**	**NR**	**1**	**NR**	**1**	**NR**
Duration of Use						
Leave-On	1	NR	NR	NR	NR	NR
Rinse Off	12	NR	1	NR	1	NR
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	NR
Dermal Contact	1	NR	NR	NR	NR	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	12	NR	1	NR	1	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR

	Oleamidopropyl Dimethylamine		**Palmitamidopropyl Dimethylamine**		**Stearamidopropyl Dimethylamine**	
Totals*	**12**	**NR**	**1**	**NR**	**427**	**NR**
Duration of Use						
Leave-On	5	NR	1	NR	72	NR
Rinse-Off	7	NR	NR	NR	355	NR
Diluted for (Bath) Use	NR	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	NR
Dermal Contact	NR	NR	NR	NR	28	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	12	NR	1	NR	315	NR
Hair-Coloring	NR	NR	NR	NR	83	NR
Nail	NR	NR	NR	NR	1	NR
Mucous Membrane	NR	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	1	NR

* Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types my not equal the sum of total uses.

NR – no reported uses

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