

Allergy to cocamidopropyl betaine may be due to amidoamine: a patch test and product use test study

JOSEPH F. FOWLER¹, LYNN M. FOWLER¹ AND J. EDWARD HUNTER²

¹Family & Occupational Dermatology, Inc., 310 E. Broadway, Suite 100,
Louisville, Kentucky 40202, USA

²The Procter & Gamble Company, 11511 Reed Hartman Highway, Cincinnati, Ohio 45241-9974,
USA

Cocamidopropyl betaine (CAPB) is an amphoteric surfactant commonly used in personal care products and surface cleaners. Patch testing with commercially-available CAPB has yielded occasional reactions indicative of allergic contact dermatitis. To determine if subjects with previous positive patch tests would react in provocative use tests of products containing CAPB, and to study various contaminants in commercial CAPB supplies for allergenicity in these subjects, 10 subjects previously positive to CAPB on patch testing used a hair shampoo, hand soap, and body wash containing CAPB for 1-6 weeks or until a reaction developed. Later, they were patch tested to 2 different purity grades of CAPB and 3 possible manufacturing contaminants (dimethylaminopropylamine, amidoamine, and sodium monochloroacetate). 7 of the 10 subjects developed dermatitis from 1 or more CAPB-containing products at some point during the study. 9 of the 10 use-test subjects were then patch tested, and 6 of these subjects showed a reaction to amidoamine (0.1% aq.). None reacted to dimethylaminopropylamine (0.1% pet.). 1 subject reacted to CAPB but not to amidoamine. In the follow-up patch testing with CAPB that was free of amidoamine, there were no positive reactions. Most subjects who were patch-test-positive showed a reaction when using CAPB-containing skin and hair care products. The chemical amidoamine, which is used in the synthesis of CAPB and which is a known contaminant of CAPB preparations, is likely to be the actual sensitizer in most cases rather than CAPB itself. The results do not rule out the possibility that CAPB itself may be an allergen in rare cases.

Key words: cocamidopropyl betaine; amidoamine; DMAPA; allergic contact dermatitis; provocative use test; cosmetics; surfactants. © Munksgaard, 1997.

Accepted for publication 26 August 1997

Cocamidopropyl betaine (CAPB) is an amphoteric surfactant that has come into popularity with manufacturers of personal care products, especially hair care products. CAPB and other betaines are often favored over other surfactants because they are less irritating to the skin and eyes. Case reports have appeared in the contact dermatitis literature of allergy to CAPB in shampoos, skin cleansers, makeup removers, and contact lens solutions (1-9). Based on data voluntarily submitted by the cosmetic industry to the FDA, the % of personal care products using CAPB increased from 3.3% in 1989 to 6.2% in 1994 (personal communication, Cosmetic Ingredient Review) (Table 1). This study was designed to determine whether provocative use testing with CAPB-containing prod-

ucts would result in dermatitis in treated areas. Furthermore, patch testing with contaminants of commercial CAPB supplies, as well as with perfumes and a preservative used in several personal care products, was undertaken to attempt to identify the true allergens.

Materials and Methods

Subjects were identified who had been found to have a positive reaction on routine patch testing to CAPB 1% aq. (Chemotechnique, Malmo, Sweden) and were invited to participate. A total of 14 agreed to enter the study. Some of the subjects have been described previously (1). 10 controls, patch test negative to CAPB, were also enrolled.

Table 1. Growth in usage of cocamidopropyl betaine (CAPB) in personal care products 1989–94

Year	Total no. of formulations considered*	Total no. of formulations containing CAPB*	% of formulations containing CAPB
1989	8098	267	3.30
1994	9707	605	6.23

*Data based on information on cosmetic products voluntarily reported to FDA by the cosmetic industry. Product categories include: hair shampoos; hair conditioners; other hair preparations; bubble bath products; other bath preparations; skin cleansing creams, lotions; other personal cleanliness preparations; skin care preparations. Source of 1989 data: Cosmetic ingredient review, *Final report on the Safety assessment, of cocamidopropyl betaine*, report #5030, p. 5, 5 June 1990.

Source of 1994 data: Cosmetic ingredient review (personal communication), September 1994.

Subjects tested with CAPB more than 2 years previously were retested before starting the study. 3 prototype test products (a shampoo, a liquid hand soap, and a body wash) were specially formulated by The Procter & Gamble Company, Cincinnati, Ohio, with commonly used cosmetic ingredients, including CAPB F grade (from Goldschmidt Chemical Corporation, Hopewell, VA). The active level of CAPB in the shampoo was 5.0% and that in the liquid hand soap and body wash was 5.2%.

The provocative use test was divided into 3 phases. Before and after each phase, and at other times if a reaction occurred, the subjects and controls were evaluated by the investigator. Product usage was monitored by weighing returned containers and by a daily diary completed by the subjects. Use testing was followed by 3 additional phases: patch testing (phase 4); repeated forearm wash test in 1 subject (phase 5); and follow-up patch testing using a highly purified CAPB (phase 6).

Phase 1 – forearm wash test. Product A (a hair shampoo) was diluted to 10% in tap water by each subject at each washing. 2× daily for 6 consecutive days, the left forearm was “washed” with the solution for about 10 s, then rinsed and dried gently.

Phase 2 – shampoo use. If no reaction occurred to product A, the subject used product A as a shampoo for 2 weeks. The hair was shampooed in the subject’s normal manner at least 3× times per

week. No other hair care preparations were allowed during this time.

Phase 3 – shampoo, hand soap, body wash use. Those subjects not showing any reaction to Product A in phases 1 or 2 continued to use Product A for shampooing for 3 more weeks. In addition, Product B, a liquid hand soap, and Product C, a body wash, were used during these 3 weeks. The hand soap was used as desired by the subjects and other hand cleansing products were prohibited. The body wash was used 1× daily, applied by a soft nylon “bath puff.” No other bathing products were permitted.

Phase 4 – patch testing. At least 2 months after the completion of the product use test, subjects were patch tested to 2 purity grades of CAPB (1% aq.), possible contaminants of CAPB preparations (dimethylaminopropylamine 0.1% pet.; amidoamine 0.1% aq.; and sodium monochloroacetate 0.1% aq.), the preservatives used for CAPB (a proprietary mixture of benzoic acid, tetrasodium EDTA, and benzyl alcohol), and other potential allergens (perfumes and preservative (DMDM hydantoin)) used in the test products. These patch test materials were all supplied by The Procter & Gamble Company, Cincinnati, Ohio. Test materials were applied to Finn Chambers on Scanpor tape (Hermal, USA, Oak Hill, New York) to the backs of the subjects and left in place for 2 days. Readings were performed at removal (D2) and again at either 4 or 7 days and were graded on the usual North American Contact Dermatitis Group scale (0–3+). Control subjects were tested only to CAPB 1% aq. The patch testing was conducted in a blinded manner.

Phase 5 – 1 of the 2 subjects who reacted during phase 1 agreed to a forearm wash test with the shampoo containing CAPB, and a similar test on the opposite arm with an identical product except for the absence of CAPB.

Phase 6 – Additional patch testing was conducted in 7 subjects to determine if those who reacted positively to commercial CAPB (containing residual amidoamine) and to amidoamine in previous patch testing also reacted to CAPB that was essentially free of amidoamine. Purified CAPB containing only about 1 ppm amidoamine (in contrast to the typical level of 3000 ppm in Goldschmidt’s purest commercial “F grade”) was prepared

Table 2. Typical contaminant levels in cocamidopropyl betaines^{a)} (ppm)

Contaminant	S	Grade of cocamidopropyl betaine		
		L-7	F	F-50
amidoamine	30,000 max	15,000 max	3000 max	3000 max
Na monochloroacetate	5 max	5 max	5 max	5 max
dimethylaminopropylamine	3 max	3 max	3 max	3 max

^{a)}Data provided by Goldschmidt Chemical Corporation, Hopewell, VA, USA.

Table 3. Analyzed contaminant levels in CAPB material used in this study*

Ingredient	CAPB-S	CAPB-F w/pres	CAPB-F w/o pres
active amidoamine	27.3% 9000 ppm	30.3% 2700 ppm	30.3% 3200 ppm
DMAPA	below limit of detection	below limit of detection	below limit of detection

^a)Data provided by Goldschmidt Chemical Corporation, Hopewell, VA, USA.

for us by Dr. Burghard Gruning, Goldschmidt Chemical Corporation, Essen, Germany. This "amidoamine-free" CAPB and F grade CAPB were patch tested at 1% aq. along with 2 concentrations of amidoamine (0.1% and 0.01% aq.).

Analysis of test materials

Typical "contaminant" levels of various grades of CAPB are listed in Table 2. Table 3 lists levels of these contaminants in the materials used for testing in this study. (These analyses were conducted by the Goldschmidt Chemical Corporation, Hopewell, VA.).

Normal usage of personal care products by subjects

Prior to the start of the use study, the subjects filled out questionnaires identifying brands of shampoo, hand soap, and body wash products that they were currently using. The subjects were also asked if they had ever experienced any adverse skin reactions to

any of these products and, if yes, to identify the product. The packages of the subjects' current products were subsequently examined to determine whether CAPB was listed as an ingredient.

Results

Controls

All 10 control subjects completed the full study. There were no reactions to any of the products used. All 10 remained negative to CAPB at the final patch testing.

Subjects

Of the 14 previously positive subjects, 4 were negative on patch testing with CAPB 1% aq. and were dropped from the study. The remaining 10 subjects entered the use study.

Use test results

3 previously positive subjects completed the entire study and showed no reaction during any of the 3 phases (Table 4). 7 subjects reacted to 1 or more of the products during the use tests. 2 subjects (#6, #24) reacted during phase 1, both within several days. Dermatitis with erythema, scaling, and pruritus was noted on the treated, but not on the control, arms. These subjects did not proceed to phase 2.

2 subjects (#2, #17) reacted during phase 2 with dermatitis and pruritus of the face and neck. 1 subject (#23) reacted with scalp, face, and/or neck

Table 4. Product use test reactions

Subject	Phase 1	Phase 2	Phase 3	Comments
1	NR	NR	NR	
2	NR	mild itching	face/scalp dermatitis; body: no reaction	facial reaction identical to patient's original presenting complaint 3 years previously
4	NR	NR	scalp dermatitis; scattered dermatitis on neck and arms	
5	NR	NR	dermatitis hands/ scalp; generalized itching	
6	dermatitis and severe pruritus 3-4 days	NT	NT	
7	NR	NR	NR	
16	NR	NR	NR	
17	mild, transient erythema lasting several hours	pruritus, dermatitis face, scalp, neck	NT	
23	NR	NR	facial dermatitis and itching	
24	Moderately severe dermatitis within 3-4 days	NT	NT	dermatitis took several weeks to resolve even with topical steroid cream

NR: no reaction. phase 2: shampoo usage. NT: not tested. phase 3: shampoo, liquid soap, body wash usage. phase 1: forearm wash.

Table 5. Patch test reactions (D4)

Allergen	No. subjects having reaction grade			
	0	±	1+	2+
CAPB-F 1% aq., w/preservative	6	1	2	0
CAPB-F 1% aq., w/o preservative	5	1	3	0
preservative	8	0	1	0
CAPB-S 1% aq., w/o preservative	7	1	1	0
DMAPA 0.1% pet.	7	2	0	0
amidoamine 0.1% aq.	2	1	3	3

0: negative reaction. ±: questionable reaction. 1+: positive reaction. 2+: strong positive reaction.

Table 6. Follow-up patch test reactions (D4)

	Subject no.						
allergen	1	2	4	5	6	7	17
CAPB-F 1% aq.	±	±	1+	1+	1+	-	-
CAPB amidoamine free 1% aq.	-	±	-	±	-	-	-
amidoamine 0.01% aq.	1+	1+	1.5+	2+	-	-	-
amidoamine 0.01% aq.	-	-	1+	1+	-	-	-

-: negative reaction. ±: questionable reaction. 1+: positive reaction. 2+: strong positive reaction.

dermatitis during phase 3 but did not display symptoms elsewhere on the body. The final 2 subjects (#4, #5) developed dermatitis on the head and/or neck along with dermatitis and/or pruritus on the body during phase 3.

Both subjects who reacted during phase 1 were asked to complete phase 5, but 1 declined. The remaining subject (#6) reacted on both forearms shortly after using the products with and without CAPB. The product containing CAPB caused a reaction at D2, whereas the product lacking CAPB caused a reaction at D5. The patch tests in this subject showed a reaction to the preservative system used in the F grade CAPB but no reaction to CAPB, and only a questionable reaction to amidoamine.

Patch test results

9 of the initial 10 subjects participated in patch testing. Patch test results are given in Table 5. Of 9 subjects tested, 6 reacted to amidoamine 0.1% aq. 5 of these 6 had reacted during the product use testing. There were 2 reactions to CAPB-F grade with preservative, 3 to CAPB-F grade without preservative, 1 to CAPB-S grade, and 1 to the preservative system used for CAPB-F grade (benzoic acid,

benzyl alcohol, tetrasodium EDTA). 6 subjects were tested with other individual constituents of the test products (perfumes and preservative) and no reactions were seen. 2 subjects (#4, #5) had questionable responses to DMAPA but no subjects reacted to sodium monochloroacetate. Both of these materials are used in the synthesis of CAPB.

Follow-up patch test results

7 of the 10 subjects participated in follow-up patch testing. To the amidoamine-free CAPB, there were 2 questionable reactions and 5 negative reactions (Table 6). In contrast, there were 3 positive reactions to the commercial CAPB, 4 positive reactions to the higher concentration of amidoamine, and 2 positive reactions to the lower concentration of amidoamine.

Discussion

Cocamidopropyl betaine has been shown to cause occasional cases of allergic contact dermatitis since the early 1980s (2-9). The purpose of our study was to determine whether individuals who had shown a possible sensitization response to CAPB in previous diagnostic patch testing(1) could use personal care products containing typical levels of this surfactant without dermatological reactions. We found that most, but not all, of our subjects who previously had been patch test positive to CAPB responded unfavorably when they used the test products. Post-study patch testing to identify possible causes of these responses suggested that they were more likely due to amidoamine, a material used in CAPB synthesis and a contaminant of CAPB preparations, rather than to CAPB itself. Only 1 subject reacted to 1 of the CAPB test materials without reacting to amidoamine. The post-study patch testing further suggested that other CAPB synthesis components and potential contaminants, specifically dimethylaminopropylamine (DMAPA) and sodium monochloroacetate, were probably not responsible for the unfavorable reactions to these test products. Our follow-up patch testing (Table 6) further supports the likelihood that amidoamine is an allergen and may be responsible for many of the previously reported reactions to CAPB.

Manufacturers of CAPB frequently make several purity grades available depending on intended use. Purer grades are generally preferred for personal care and health care products because of their lower irritation and sensitization potential. Our use test products were made with the purest grade of CAPB (F grade) available. CAPB-S grade typically contains a higher level of amidoamine

compared to F grade (Table 2). Analyses by the Goldschmidt Chemical Corporation verified that the amidoamine used in our patch testing had a very low DMAPA content of 34 ppm. Goldschmidt scientists indicated to us that a CAPB made from this material would have a DMAPA level of about 1 ppm maximum.

We are unable to explain the slightly greater patch test responsiveness to CAPB F grade than to less pure CAPB S grade. This apparent difference in responsiveness between the F and S grades was small and may have occurred because we patch tested only a small number of subjects, and/or because there was a smaller than expected difference in amidoamine content between the F and S grade samples used in patch testing (Tables 2, 3).

Other investigators have suggested that DMAPA may be the cause of CAPB-related contact dermatitis. Pigatto et al. (10) reported that 12 subjects with contact allergy attributed to CAPB reacted to DMAPA (1%, 0.5% and 0.1% pet.) on patch testing. In addition, cosmetics from 4 subjects were indicated to contain DMAPA at levels ranging from 50–150 ppm. The investigators evaluated the presence of DMAPA in CAPB samples used in their tests. CAPB from Firma (Florence, Italy) was reported to contain 200 ppm of DMAPA, while DMAPA in CAPB from Aldrich (Milan, Italy) was nondetectable. 15 CAPB-positive subjects reacted to the high DMAPA-containing CAPB from Firma, while only 1 of the 15 responded to the Aldrich CAPB. These investigators did not test with amidoamine, however. Therefore, their variation in results could have been due to amidoamine rather than DMAPA.

Amidoamine is typically present as an impurity in CAPB preparations at much higher levels ranging from 3000 to 30,000 ppm. This information suggests that the analytical procedure used by Pigatto et al. (10) that reported high DMAPA levels in several cosmetic products and in samples of CAPB from Firma, may not be sufficiently sensitive to differentiate between DMAPA and amidoamine. Effects observed by Pigatto et al. (10) could have been due to amidoamine or to a combination of amidoamine and DMAPA.

Angelini et al. (11) conducted patch testing on 30 subjects with contact allergy attributed to CAPB with substances used in the synthesis of CAPB (including DMAPA (0.1% aq.), amidoamine (0.05% aq.), and monochloroacetic acid (0.1% aq.) together with a sample of CAPB (0.5% and 1% aq.) declared by the supplier to be of greater purity than the grade to which all the subjects had previously reacted. All of the subjects experienced positive reactions to DMAPA, while the purer grade of CAPB at 0.5% and 1% gave positive reac-

tions in 10% and 53% of subjects, respectively. There were no reactions to amidoamine or to monochloroacetic acid at the concentrations used. The investigators suggested that DMAPA present as an impurity in commercial CAPBs may be responsible for CAPB allergy.

In contrast to the reports of Pigatto et al. (10) and Angelini et al. (11), suggesting that DMAPA is a likely cause of positive reactions in CAPB preparations or in products containing CAPB, we found DMAPA to be essentially absent from the CAPB materials that we used. It may be that the positive results of Pigatto et al. Angelini et al. were irritant rather than allergic positives (10, 11). Furthermore, it may be that the true pattern of allergy differs in Europe because of different sources of supply of CAPB.

We selected a lower level of DMAPA (0.1% pet.) for patch testing as more relevant to evaluation of a potential relationship to CAPB-related clinical reactions and to reduce possible discomfort to our subjects. Our work suggests that amidoamine should be tested at a concentration of at least 0.1%. In our testing, only the subjects with the strongest reactions at 0.1% reacted to 0.01%. This may account for the lack of response seen by investigators testing with 0.05%.

In conclusion, we consider that this study indicates that most individuals with an apparent allergy to CAPB, as indicated by previous patch testing, will react when challenged with CAPB-containing products. However, the true allergen appears to be amidoamine, used in the synthesis of CAPB, rather than CAPB itself, in most cases. DMAPA is essentially not present in the CAPB materials that we used and none of our subjects reacted to DMAPA on patch testing. It may be that the true pattern of allergy differs in Europe because of different sources of supply of CAPB.

Contaminants remaining in finished CAPBs, specifically amidoamine and possibly DMAPA, appear to account for most of the allergic reactions found. Therefore, we recommend use of CAPBs with minimal levels of contaminants for formulation of cosmetics and other personal care products, especially for use on sensitive skin areas such as the face.

Acknowledgements

We are grateful to Mr. David T. Floyd, Goldschmidt Chemical Corporation, Hopewell, VA, for providing several patch testing materials (CAPB F grade without preservative, dimethylaminopropylamine, amidoamine, and sodium monochloroacetate), analytical data on CAPBs used in our patch testing, and typical contaminant levels in various

grades of CAPB. We also thank Dr. Burghard Gruning, Goldschmidt Chemical Corporation, Essen, Germany, for preparing for us for patch testing a sample of CAPB that was essentially free of amidoamine.

References

1. Fowler J F. Cocamidopropyl betaine: The significance of positive patch-test results in twelve patients. *Cutis* 1993; 52: 281-284.
2. Andersen K E, Roed-Petersen J, Kamp P. Contact allergy related to TEA-PEG-3 cocamide sulfate and cocamidopropyl betaine in a shampoo. *Contact Dermatitis* 1984; 11: 192-193.
3. Vilaplana J, Grimalt F, Romaguera C. Contact dermatitis from cocamidopropyl betaine. *Contact Dermatitis* 1990; 23: 274.
4. Peter C, Hoting E. Contact allergy to cocamidopropyl betaine (CAPB). *Contact Dermatitis* 1992; 26: 282-283.
5. Taniguchi S, Katoh J, Hisa T et al. Shampoo dermatitis due to cocamidopropyl betaine. *Contact Dermatitis* 1992; 26: 139.
6. Ross J S, White I R. Eyelid dermatitis due to cocamidopropyl betaine in an eye makeup remover. *Contact Dermatitis* 1991; 25: 64.
7. Sertoli A, Lombardi P, Palleschi G M et al. Tegobetaine in contact lens solutions. *Contact Dermatitis* 1987; 6: 111-112.
8. Cameli N, Tosti G, Venturo N et al. Eyelid dermatitis due to cocamidopropyl betaine in a hard contact lens solution. *Contact Dermatitis* 1991; 25: 261-262.
9. Van Haute N, Doods-Goossens A. Shampoo dermatitis due to cocobetaine and sodium lauryl ether sulphate. *Contact Dermatitis* 1983; 9: 169.
10. Pigatto P D, Bigardi A S, Cusano F: Contact dermatitis to cocamidopropyl-betaine is caused by residual amines: relevance, clinical characteristics and review of the literature. *Am J Contact Dermatitis* 1995; 6: 13-16.
11. Angelini G, Foti C, Rigano L, Vena GA: 3-Dimethylaminopropylamine: a key substance in contact allergy to cocamidopropylbetaine? *Contact Derm* 1995; 33: 419-422.

Address:

Joseph F. Fowler
Family and Occupational Dermatology, Inc.
310 E. Broadway, Suite 100
Louisville
Kentucky 40202
USA

This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.