

Is cocamidopropyl betaine a contact allergen? Analysis of network data and short review of the literature

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Summary

Background. There is no general agreement on whether cocamidopropyl betaine (CAPB) is a skin sensitizer.

Objective. To examine the evidence for CAPB being a (non-)sensitizer.

Methods. This was a retrospective analysis of data on patch testing with CAPB 1% aqua collected by the Information Network of Departments of Dermatology from 1996 to 2009, with a focus on the patch test reaction profile, and demographic and clinical features of CAPB positives, supplemented by a literature review.

Results. Eighty-three thousand eight hundred and sixty-four patients were patch tested with CAPB 1% aqua, yielding 2.16% [95% confidence interval (CI) 2.06–2.26%] positive (2.03% + and 0.13% ++/+++) and 4.6% non-allergic reactions. Thus, the reaction index was –0.368 and the positivity ratio was 94.2%. Reproducibility on synchronous patch testing (n = 6534) was poor [Cohen's kappa: 0.29 (95% CI 0.25–0.32)] and results upon retesting (n = 1157) were almost non-reproducible [kappa: 0.12 (95% CI 0.05–0.19)]. Multifactorial logistic regression analysis revealed an increased risk associated with being male and aged ≥40 years, with atopic dermatitis, with scalp dermatitis, with being a hairdresser, and with a 48-hr patch test application. When only ++ or +++ reactions were used as a conservative outcome, only the elevated risk in males and in patients with atopic dermatitis remained significant.

Conclusion. The vast majority of positive reactions to CAPB are presumably false positive. Allergic reactions are very rare. This would support the notion of CAPB being 'not a significant skin sensitizer', in line with current classification systems.

Key words: cocamidopropyl betaine; contact allergy; patch test; skin irritant; surfactant.

Cocamidopropyl betaine (CAPB; coconut oil amidopropyl betaine, CAS 61789-40-0) is a pseudo-amphoteric zwitterion detergent used in cosmetics and personal hygiene

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products, mainly in rinse-off products such as shampoos, but also in roll-on deodorants, contact lens solutions, toothpaste detergents, makeup removers, bath gels, skincare products, cleansers, liquid soaps, and antiseptics (1, 2). The use of CAPB has increased exponentially since the 1970s in the United States. Of the 19 000 cosmetic products registered in 1980, 47 contained CAPB. By October 2005, 1242 of 22 016 products were listed as containing CAPB according to the Food and Drug Administration data Voluntary Cosmetic Registration Program (2). This increase in use was explained by the substitution of anionic (such as sodium lauryl sulfate) and cationic surfactants, which are considered to be more

irritating than CAPB (2). Another analysis of data provided by a US pharmacy company (Walgreens) revealed that 53% of shampoos (95/179) contained CAPB (3). No data on the use of CAPB in Europe are available.

CAPB is derived from long-chain alkylbetaines. The first step in its synthesis consists of the reaction of coconut fatty acid (with chain lengths varying between C-8 and C-18) with 3-dimethylaminopropylamine (DMAPA), giving cocamidopropyl dimethylamine ('amidoamine'). This amidoamine is converted to CAPB by the reaction with sodium monochloroacetate. Thus, CAPB is a mixture of several compounds with the same basic structure and different lipophilic ends.

Both DMAPA and amidoamine may be present as impurities in commercial products, and are thought to be the sensitizers (1), whereas the role of pure CAPB itself as a sensitizer is thought to be minimal (2, 4–6).

We wondered whether the results of patch testing with CAPB 1% in aqua obtained by one major manufacturer, collected in a large multicentre surveillance network, could contribute to answering the question 'Is CAPB really an allergen'?

Materials and Methods

The multicentre project Information Network of Departments of Dermatology (IVDK) is an instrument of epidemiological surveillance of contact allergy and has been described in detail elsewhere (7, 8). Patch tests are performed in accordance with the recommendations of the International Contact Dermatitis Research Group (9) and the German Contact Dermatitis Research Group (DKG) (10). Patch test material is obtained from Hermal/Reinbek, Germany. Patch test preparations are applied for 24 or 48 hr. Readings are performed until at least 72 hr, using the following gradings: negative, ?, +, ++, +++, IR (see Table 1 footnote), and follicular. The patch test results of every reading, a standardized history (comprising age, sex, atopic diseases, current and former occupation(s), and presumptive causal exposures) and final diagnoses and site(s) of dermatitis are assessed and documented. All data are transferred to the data centre in Göttingen in an anonymized format every 6 months.

The CAPB patch test preparation used in this study was 1% aq. (Hermal/Trolab Germany), prepared from CAPB (brand name 'Dehyton K') obtained from Henkel Germany (the question of possible impurities in patch test preparations is discussed below). Between 1996 and 2009, this patch test preparation was part of a special series of the DKG (cosmetic ingredient series), and was applied in 56 departments of dermatology of the IVDK.

Frequencies of sensitization (as percentage of patients tested) were primarily calculated as crude proportions not

further standardized for sex and age (11). The reaction index (RI), relating the number of allergic reactions to the number of doubtful or irritant reactions (12, 13), and the positivity ratio (PR), relating the frequency of + reactions to the total number of allergic reactions (14), were calculated as parameters to assess the patch test preparation. For data management and analysis, the statistical software package SASTM (version 9.2; SAS Institute, Cary, NC, USA) was used.

Results

Patch test reactions

Our present analysis of 83 864 patients patch tested with CAPB 1% aq. yielded 1812 positive reactions [2.16%, 95% confidence interval (CI) 2.06–2.26%], namely, 1706 + (2.03%) and 106 stronger (++/+++) positive reactions (0.13%, (95% CI 0.10–0.15%). In comparison, non-allergic reactions were much more common (4.6%); The negative RI (−0.368, 95% CI −0.392 to 0.344) and the high PR (94.2%, 95% CI 94.1–94.3%) raise suspicion that many of the 'positive' reactions probably have to be considered as irritant/false positive (Table 1) (14).

Reproducibility of patch test reactions

Another important aspect of the 'quality' of a patch test preparation, and its ability to diagnose contact sensitization, is reproducibility. In the IVDK database, 6534 patients were identified who were tested synchronously in duplicate (e.g. with CAPB in the 'hairdressers series' and in the 'topicals' series) or, in 180 cases, even in triplicate. The 'minimum' and the 'maximum' reactions observed during these tests were analysed, for the assessment of synchronous reproducibility (Table 2). Cohen's simple kappa

Table 1. Profile of reactions to the patch test preparation cocamidopropyl betaine 1% aq.

Reading	Frequency	Percentage	Cumulative frequency	Cumulative percentage
+	1706	2.03	1706	2.03
++	102	0.12	1808	2.16
+++	4	0.00	1812	2.16
?	2612	3.11	4424	5.28
f	109	0.13	4533	5.41
IR	1202	1.43	5735	6.84
Negative	78 129	93.16	83 864	100.00

?, erythema only, no infiltrate; f, few follicular papules; +, erythema, infiltrate, discrete papules; ++, erythema, infiltrate, papules, vesicles; +++, erythema, infiltrate, confluent vesicles; IR, soap effect, ring effect, blister, necrosis.

Table 2. Comparison of patch test reactions to cocamidopropyl betaine 1% aq. upon synchronous testing (asymmetry is introduced by design, as the minimum reaction is contrasted with the maximum reaction); Cohen's simple kappa was 0.29 (95% confidence interval 0.25–0.32), indicative of quite limited concordance

Maximum reaction	Minimum reaction					Total
	Negative	IR	?	+	++	
Negative	5898	—	—	—	—	5898
IR	122	23	—	—	—	145
?	358	2	73	—	—	433
+	168	1	16	42	—	227
++	6	0	0	4	1	11
Total	6552	26	89	46	1	6714

?, erythema only, no infiltrate; +, erythema, infiltrate, discrete papules; ++, erythema, infiltrate, papules, vesicles; IR, soap effect, ring effect, blister, necrosis.

was 0.29 (95% CI 0.25–0.32), indicative of quite limited concordance. Regarding an aggregated outcome of + to +++ reactions versus the remainder, Cohen's simple kappa improved slightly to 0.32 (95% CI 0.25–0.39).

Moreover, some patients (1157) were tested on at least two different occasions at least 30 days apart, with a mean latency of 1130 days (first quartile, 412 days; third quartile, 1602 days). This allowed the analysis of metachronous reproducibility (Table 3). In this setting, Cohen's simple kappa was only 0.12 (95% CI 0.05–0.19). Of 1054 negatives in the first testing, 22 (2.1%) became positive in the second testing; of 23 initial '+' reactions, 2 remained positive (8.7%); and of 2 '+' reactions, none was confirmed in retesting (Table 3).

Clinical and demographic factors

Regarding the factors of the MOAHLFA index, males (2.7% versus 1.9%), patients with atopic dermatitis (2.6%

Table 3. Comparison of patch test reactions to cocamidopropyl betaine 1% aq., upon retesting; no significant asymmetry ($p = 0.53$, Bowker's test); Cohen's simple kappa 0.12 (95% confidence interval 0.05–0.19), close to 'non-reproducible'

First reading	Second reading					Total
	Negative	IR	?	+	++	
Negative	991	12	29	21	1	1054
IR	15	0	0	0	0	15
?	50	2	9	2	0	63
+	17	0	4	2	0	23
++	1	0	1	0	0	2
Total	1074	14	43	25	1	1157

?, erythema only, no infiltrate; +, erythema, infiltrate, discrete papules; ++, erythema, infiltrate, papules, vesicles; IR, soap effect, ring effect, blister, necrosis.

Table 4. The distribution of MOAHLFA factors among patients with + to +++ reactions to cocamidopropyl betaine (CAPB) as compared with those patients tested with CAPB 1% aq.

		CAPB positive		CAPB non-positive	
		n	%	n	%
Male	M	798	44.04	29 783	36.30
Occupational dermatitis	O	299	16.50	12 786	15.58
Atopic dermatitis	A	418	23.07	15 890	19.37
Hand dermatitis	H	553	30.52	24 513	29.87
Leg dermatitis	L	259	14.29	10 926	13.32
Face dermatitis	F	286	15.78	14 091	17.17
Age 40 years and above	A	1277	70.47	54 890	66.89

versus 2.1%) and patients aged >40 years (2.3% versus 2.2%) had positive reactions to CAPB significantly more often, whereas in those with occupational dermatitis and dermatitis of the hands, face, and legs, CAPB positivity was not increased. The MOAHLFA index of patients tested with CAPB, and of patients reacting + to +++ to CAPB, is shown in Table 4.

According to bivariate analyses, hairdressers (2.8% versus 2.1%) and masseurs (5% versus 2.1%) were slightly more often affected by CAPB sensitization (considering + to +++ reactions). However, regarding the ++/+++ reactions (as unequivocally allergic), sensitization was no longer increased in these two occupations. The scalp was the only site of dermatitis that was slightly associated with CAPB sensitivity (2.9% versus 2.2% in all other localizations). Of 19 965 patients who were exposed for 24 hr, 1.4% had a positive reaction, whereas of patients exposed for 48 hr (60 670), 2.2% reacted positively.

For further exploration of the association between positive reactions and important clinical or demographic factors, a multifactorial logistic regression analysis was performed. As explanatory factors, age (dichotomized at age 40 years), sex, the three 'MOAHLFA' anatomical sites, hairdressing (current or previous) versus all other occupations, and duration of patch test application were used. A significantly increased risk was associated with being male and age 40 years and above, respectively, with atopic dermatitis, with scalp dermatitis, with being a hairdresser, and with the longer patch test application. With a ++ or +++ patch test reaction as a more conservative outcome definition, only the elevated risk in males and in patients with atopic dermatitis remained significant (Table 5).

Discussion

Analysis of the results of patch testing of more than 80 000 patients with CAPB yielded 2.16% positive reactions. However, only 0.13% were ++ or stronger reactions. The

Table 5. Results of two logistic regression analyses, using + to +++ and ++/+++ reactions, respectively, as outcome, and the factors listed as explanatory factors; the association was quantified with adjusted odds ratios (ORs) with accompanying 95% confidence intervals (CIs)

Factor	%	+ to +++ reaction: OR (95% CI)	++ or +++ reaction: OR (95% CI)
Age $\geq$ 40 years	67.3	1.29 (1.16–1.44)	1.52 (0.96–2.47)
Male sex	36.5	1.43 (1.30–1.58)	1.89 (1.26–2.82)
Atopic dermatitis (past or present)	19.5	1.38 (1.23–1.55)	1.94 (1.21–3.03)
Hairdresser (yes versus no)	2.8	1.67 (1.28–2.15)	2.35 (0.70–5.89)
Site			
Hand	29.9	1.03 (0.91–1.16)	0.65 (0.38–1.07)
Face	17.1	0.98 (0.84–1.12)	0.82 (0.45–1.44)
Leg	13.3	1.14 (0.98–1.32)	0.96 (0.51–1.70)
Scalp	2.8	1.53 (1.18–1.96)	1.04 (0.25–2.85)
Other than hand, face, leg, or scalp	36.8	1.00 (reference)	1.00 (reference)
Patch test application: 2 days (versus 1 day)	72.2	1.61 (1.43–1.82)	1.15 (0.74–1.84)

majority of reactions (4.67%) were doubtful or irritant, yielding a markedly negative RI, and the vast majority or positive reactions were + reactions (PR = 94.2%). Such a reaction pattern is typical for problematic patch test preparations such as octyl gallate (RI = -0.368; PR = 94.2%) or propylene glycol (RI = 0.0; PR = 95.7%), indicating that many of the positive reactions probably have to be considered as irritant/false positive (Table 1) (14, 15). Furthermore, the shorter patch test exposure time of 24 hr (versus 48 hr) almost significantly and relevantly reduced the odds of a + to +++ reaction (Table 5); the reversed odds ratio (OR) is 0.62 (95% CI 0.55–0.70). This is very similar to what is seen with a typical irritant such as sodium lauryl sulfate (SLS), with an OR of 0.52 (95% CI 0.44–0.62) for the 24-hr exposure (16). There were unequivocal positive reactions to CAPB at least in terms of ++ reactions, albeit very rarely (0.1%); however, the occurrence of erythematous, infiltrated – i.e. morphologically ‘positive’ – reactions at day 3 has been observed with clear-cut irritants (17), rendering the distinction between irritant and allergic reactions on the sole basis of morphology or even time-course unreliable – at least for a limited set of ‘difficult’ allergens (18).

In addition to atopic dermatitis being a risk factor (Table 5), a further finding hints at the role of endogenous factors, as male sex was a weak but significant risk factor, both in SLS [OR 1.38 (95% CI 1.21–1.56)] (16) and in CAPB (Table 5). A review compiling results from nine acute irritation patch test studies concluded that males were significantly more reactive to irritant chemicals than were females (19). This is in contrast to sensitization, for which female sex can be regarded as an endogenous susceptibility factor (20). The notion of increased susceptibility in CAPB reactors is supported by another study from the IVDK, using the concomitant reactions to SLS as an indicator of increased reactivity to irritants. In SLS

negatives, there were 1.1% (95% CI: 0.7–1.5) ‘+’ reactions to CAPB, whereas in SLS positives, 3.8% (95% CI: 2.6–5.0) displayed a ‘+’ reaction (15). Synchronous reproducibility of reactions to SLS is rather poor (21), namely kappa 0.35 (95% CI 0.17–0.53) for 0.125% SLS at day 3, and kappa 0.36 (95% CI 0.10–0.62) for 0.0625% SLS at day 3 (recalculated). This is quite similar to the synchronous reproducibility of CAPB observed in our study, also using the aggregated outcome, and far from the kappa values observed when ‘proper’ allergens, such as *p*-phenylene diamine (kappa 0.86; 95% CI 0.79–0.92) or fragrance mix (kappa 0.78; 95% CI 0.73–0.84), are synchronously tested (22). In metachronous patch testing, the results of the first patch testing were close to ‘not reproducible’, and it is noteworthy that the patients who were negative in the first patch testing and later reacted ‘positively’ were as frequent as in the total patch test population (22/1054; 2.1%).

If the majority of positive reactions are interpreted as ‘false positive’, and actually irritant, these irritant reactions should be distributed equally among subgroups defined by, for example, different occupation or site of eczema. However, this is not really the case: in the one occupation that can be regarded as involving professional exposure to CAPB, namely hairdressing, the prevalence of + to +++ reactions to CAPB was increased, as confirmed by a significantly increased risk in the adjusted, multifactorial analysis, although, with the more conservatively defined outcome, the increased risk estimate was no longer significant. This can be attributed to the relatively small size of this subgroup, and to the fact that the estimate relies on only 1 ++ reaction in a hairdresser. Moreover, on comparison of hairdressers with female clients, who very probably have differing exposures to shampoos, reactions to CAPB were slightly more common in hairdressers than in clients, namely, 3.2% versus 1.9% in the period 1995–2002 and 3.4% versus 2.9% in the period

2003–2006 (23, 24), even though this difference was not significant. Hence, the contribution of intense exposure to shampoo found in hairdressers, possibly somewhat lessened by occupational hygiene measures, to CAPB sensitization risk can probably not be excluded.

These results are similar to those found in patients patch tested with benzalkonium chloride. Considering the allergenic properties of this well-known irritant, we found that the risk of reacting to benzalkonium chloride was significantly higher in the group exposed to, and therefore tested with, disinfectants than in those tested with the topical drugs and the ophthalmic series. The difference was even more prominent regarding ++/+++ reactions. It was concluded that the irritant benzalkonium chloride might (very rarely) exhibit sensitizing properties (18). Likewise, a further finding from another study of the IVDK relating eczema localization ('scalp dermatitis') and reactions to CAPB may support the notion of CAPB being an allergen (25). The risk of reacting positively to CAPB was significantly increased in patients with scalp dermatitis according to this previous analysis [OR 2.37 (95% CI 1.74–3.16)], whereas the association observed here – also restricted to ++ to +++ reactions – is more limited (Table 5). In any case, the evidence to be drawn from this association might be weaker than that from the association with occupation. As 'scalp dermatitis' was not necessarily allergic contact dermatitis, both associated reactions (dermatitis and patch test) may have been irritant reactions, possibly because of higher susceptibility, as was also discussed in the case of benzalkonium chloride (18).

Our results can be summarized as follows:

1. CAPB, which is not 100% pure (as in the patch test and in commercial products) is an irritant compound, and can, as such, cause slight irritant reactions in predisposed individuals under patch test conditions.
2. Many erythematous/infiltrated reactions (+), interpreted as allergic on morphological grounds, are most likely false positive (in view of the RI and PR).
3. Positive reactions are only weakly associated with specific anatomical sites (such as specific sites of exposure).
4. Positive reactions are only weakly associated with highly exposed occupations (hairdressers).
5. Risk factors for + to +++ reactions identified by multiple regression analysis were no longer significant when the less disputable stronger reactions (++/+++) were used as outcome, except for the susceptibility factors atopic dermatitis and male sex.

6. In contrast to reactions to clear-cut contact allergens (22, 26), (positive) patch test reactions to CAPB were very poorly reproducible.

Therefore, the evidence for CAPB being an allergen is very limited, according to the present analysis.

Reports from larger patch test populations

CAPB was first recognized as a contact allergen some 20 years ago (27). Later, a few publications reported on larger groups of patients reacting to CAPB patch test preparations. Of 957 patch-tested patients, 49 had a positive reaction to either CAPB or 'amidoamine' or both (with regard to amidoamine, see below). Of these patients, 35 were available for follow-up. Twenty-nine identified the surfactant in their home products. In all of these patients, the dermatitis was felt to be caused, in whole or in part, by CAPB exposure (28). In The Netherlands, 883 patients were patch tested and 20 reacted to CAPB. All patients had used shampoos containing the surfactant, and 8 of the patients were hairdressers (29). Armstrong et al. reported on patch testing with CAPB during an 8-year period in St John's, London (30). From 1991 to 1994, Tegobetaine® 1% aq. was used, and from 1995 to 1998 CAPB 1% aq. (Hermal) was used. The former was said to contain significantly higher levels of reactants and intermediate residues. In total, 10 798 patients were tested. Twenty-nine (0.3%) showed a positive reaction. During 1991–1994, there were 24 positive responses, and from 1995 to 1998, 5 reactions were noted. The reactions were regarded as relevant (past or present) in 23 cases (79%). The commonest sites were the face and neck (30). Hillen et al. analysed the data of the IVDK recorded between 1993 and 2003 in patients with scalp dermatitis (25). CAPB was tested in 1021 of these patients, and 48 (5.0% standardized for sex and age) reacted positively (for comments, see above).

Most recently, Suuronen et al. from the Finnish Institute of Occupational Health reported on the patch testing of 1092 patients with fatty acid derivatives, among them CAPB, between 2000 and 2009 (31). The vast majority of reactions were interpreted as irritant (4–25%). Two patients (0.2%) reacted positively to CAPB. Higher frequencies of positive reactions to other coconut fatty acid derivatives were noted.

In North America, where it is considered to be a more important allergen, CAPB is tested routinely. In the 2004, it was nominated as 'Contact allergen of the year' (32). Fowler et al. analysed patch test data from 975 consecutive patients patch tested during 2001 recorded by the North American Contact Dermatitis Group (NACDG) (33). Fifteen (1.5%) reacted to CAPB 1% only,

25 (2.6%) to 'amidoamine' only, and 18 (1.8%) to both (total of 5.9%). Sixteen of 33 CAPB-positive reactions were considered to be of definite (3) or probable (13) relevance, that is, 9% and 39% of positive reactions. Again, the face (30.2%) and neck (14.3%) were most often affected anatomical sites. However, a scattered picture [scattered (generalized) distribution of dermatitis] (23.8%) was also frequently noted (33). Zug et al. analysed patients with scattered generalized dermatitis in detail (34). One thousand four hundred and ninety-seven of 10 061 patients (14.9%) had scattered generalized dermatitis only. Of these patients, 3.6% reacted positively to CAPB. NACDG patch test results from 2005 to 2006 from 13 centres in North America were reported and compared with pooled test data from the previous 10 years (35). Four thousand four hundred and thirty-six patients were tested with CAPB 1% aq., and 1.8% reacted positively. The clinical relevance of patch test reactions was considered to be 'definite' in 1.3% (probable, 30.4%; possible, 59.5%; and past, 2.5%). Thus, the frequency of 'definite relevant' positive reactions would be 0.02%.

The question of impurities

Positive reactions to patch test preparations containing CAPB were suspected to be caused by impurities remaining from the synthesis, namely DMAPA and amidoamine. The issue of the real sensitizer has been a matter of controversy for many years. Numerous US studies demonstrated that amidoamine was the cause of allergic contact dermatitis, whereas numerous European studies demonstrated that DMAPA was the sensitizer (2).

Fowler et al. studied patients with previous positive patch test reactions to CAPB in a provocative use test with products containing CAPB (hair shampoo, hand soap, and body wash) (4). Later, 9 were patch tested with CAPB of two different purity grades as well as with three possible impurities (amidoamine, DMAPA, and sodium monochloroacetate). Seven of the 10 reacted to the use test. Patch test reactions to amidoamine were seen in 6 patients, but none to DMAPA, and none to CAPB free of amidoamine.

Foti et al. tested 10 patients with contact allergy to commercial CAPB with DMAPA 1% aq. and with pure amidoamine at concentrations ranging from 0.5% to 0.1% in aq. 0.5% (5). All patients reacted to DMAPA, and concomitantly to amidoamine. Four of these 10 even reacted to amidoamine at a concentration of 0.1%. However, none reacted to highly purified CAPB. The investigators concluded that DMAPA was indeed the true sensitizing substance, whereas amidoamine, which may release DMAPA *in vivo* by enzymatic hydrolysis, was said to be implicated in the transdermal penetration of

this sensitizing agent (5). However, the role of DMAPA was not confirmed by other studies (4, 6, 36). Uter tested 80 hairdressers with CAPB 1% aq. contained in a hairdresser's series, and with DMAPA 1% aq. (36). Seven reacted to CAPB (6 + and 1 +/+ +/+ +), and none reacted to DMAPA; amidoamine was not tested in this study. Similar (DMAPA-negative, CAPB-positive) results were obtained by McFadden et al. (6).

In several studies, it was shown that, most frequently, patients react to more than one coconut fatty acid derivative, such as CAPB, amidoamine, coconut diethanolamide, and oleamidopropyl dimethylamine (31, 37, 38). These substances are also used in hand cleaners and protective creams, and may be the primary sensitizers or may contain amidoamine as an impurity (37). The reactions to commercial (impure) CAPB might result from co-sensitizations or cross-reactions.

It has repeatedly been shown that CAPB patch test positives do not (or very rarely) react to highly purified CAPB (4–6). In predictive animal testing, it was classified as a non-sensitizer (39). In experiments using CAPB contaminated to a higher degree, it was observed that sensitization rates were much higher (30, 38). Is it thus possible that commercial CAPB, which may still contain impurities, caused sensitization and elicitation through DMAPA and/or amidoamine? According to the main manufacturers, the raw material of CAPB today contains a maximum of 15 ppm DMAPA and a maximum of 0.3% amidoamine. The maximum recommended dose of CAPB in rinse-off and leave-on products is 3.0% (40).

In patch testing, 1% CAPB is used. Thus, the concentrations of DMAPA to be expected would be 450 ppb in products, and 150 ppb in patch tests; both of these concentrations are most likely below any induction or elicitation threshold. In fact, more recent studies have been unable to support a causal role of DMAPA (see above).

However, the concentrations of amidoamine to be expected would be 90 ppm in products, and 30 ppm in patch tests. If amidoamine is a sensitizer, induction and elicitation in highly susceptible individuals cannot be excluded, notwithstanding the possibility of cross-sensitization or co-sensitization through other coconut fatty acid derivatives.

True allergies to CAPB?

Against this background, our results and the results regarding positive reactions reported in the literature cannot be neglected in their entirety as all being false positive/irritant. It was shown that commercial patch test preparations were able to identify cases reacting to products containing CAPB, probably both containing impurities to a sufficient degree. Thus, the patch test

reactions were regarded as 'relevant' (28). The notion that commercial CAPB containing impurities may cause allergic reactions might be supported by use tests. Seven of the 10 CAPB patch test-positive patients reacted to the use test. None reacted to a CAPB patch test free of amidoamine (4). On the other hand, Fartasch et al. showed that CAPB-positive patients tolerated (in a repeated open application test and an uncontrolled use test) CAPB-containing products, although, on retesting, 5/10 again reacted to CAPB patch tests at 1% (41).

However, even if there was agreement regarding reactions to commercial (probably contaminated) CAPB patch tests being very often irritant/false positive, and true allergic reactions being very rare, the question remains: how frequent (or infrequent) are true allergic reactions?

In principle, the percentage of relevant reactions might give clues regarding the question of false-positive reactions (42). If we consider, in a type of 'epidemiological relevance approach', only the group of patients in whom an increased risk had been shown (hairstylists, masseurs, and patients with scalp dermatitis), and take the total of the reactions in these groups all as 'relevant', then 160 cases with relevant reactions remain. This would obviously be a 'worst case ceiling estimate', as a certain proportion of false-positive reactions is very likely also in these subgroups. On the basis of such an estimate, which is admittedly somewhat daring, 91.2% of positive reactions would be false positive, and 8.8% positive and relevant. Although the above is a concept of relevance that is not directly comparable to that of individual clinical relevance, this finding would be quite compatible with the NACDG finding of relevant reactions in 1.8% (definite) to 30.4% (probable) of patients (35). With 8.8% of reactions assumed to be allergic, a frequency of sensitization to CAPB of 0.19% of patients tested would result. This would again be compatible with the most recent data from Finland (0.2%) (31), as well as with former results reported from St John's, London (0.3%) (30).

Conclusion

On the basis of our results and the accumulated knowledge on CAPB, the following can be concluded:

- CAPB is a recognized irritant substance (under patch test conditions). Pure CAPB was not shown to be a skin sensitizer, in either humans or animal tests.
- Both commercially marketed CAPB and CAPB patch test preparations incorporating CAPB from different sources probably contain impurities to different degrees. Among these, DMAPA is present at a concentration that is most likely far too low, whereas amidoamine may be present at a high enough concentration to cause sensitization and elicitation, at least in a small subgroup of susceptible individuals. Susceptibility may be acquired (e.g. pre-existent irritant dermatitis) or inherent (20), but may be an important risk that is not to be underestimated, especially with regard to weak sensitizers.
- As CAPB is an irritant, and in view of several parameters (PR, RI, reproducibility, concomitant reactions to SLS, and similar population characteristics as in SLS positives), and the rather infrequent definite relevance of the reactions, the vast majority of reactions to commercial CAPB must be considered to be false positive/irritant.
- However, one has to face the possibility that a very small subgroup of patients tested may give relevant and/or stronger (++) reactions.
- These characteristics are similar to those found in patients reacting to the irritant benzalkonium chloride, where it was concluded that benzalkonium chloride may act as a sensitizer, albeit very rarely (18).
- Both the EU and a working group of the World Health Organization consider compounds to be not significant skin sensitizers if a large number of individuals (e.g. 10^5) have frequent skin exposure, but only a few cases are observed (43, 44). In such cases, the German MAK Commission refrains from designating compounds as 'SH' (indicating 'skin sensitizer') (45).

Taking these findings together, we are tempted to consider CAPB as a 'non-allergen', despite the paradox of rare allergic reactions occurring.

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