

Benzalkonium Chloride: An Irritant and Sensitizer

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Background: Benzalkonium chloride (BAK) is a known irritant, and potentially cross-reacting quaternary ammonium compounds are commonly used as preservatives in personal care products.

Objective: The aim of the study was to review positive reactions to BAK in 615 patients patch tested for suspected allergic contact dermatitis.

Methods: A retrospective chart review was performed in 615 patients patch tested from June 2015 to October 2016. All patients were tested to a Modified American Contact Dermatitis Society core series of 70 allergens including BAK (0.1% aqueous). Initial readings were performed at 48 hours with final readings performed between 72 and 168 hours. Results were graded as + (weak: papules and erythema), ++ (strong: papules and edema or vesicles), or +++ (extreme: coalescing vesicles, spreading or bullous reactions).

Results: A total of 141 men (23%) and 475 women (77%) were tested (mean age, 49 years). Four hundred thirty-two (70%) were atopic. Of 615 patients, 198 (32%) tested positive to BAK, and 64 (10%) had ++ or +++ reactions at their final reading. On average, BAK-positive patients were using at least 1 product containing BAK or possible cross-reactors.

Conclusions: Widespread exposure to irritants in dermatitis patients can predispose to sensitization. Products containing BAK or potential cross-reactors should be used carefully in patients with compromised skin barriers.

Benzalkonium chloride (BAK) is a cationic quaternary ammonium compound (QAC) commonly used as a preservative in various personal care products (PCPs), pharmaceutical preparations such as ophthalmic solutions, nasal sprays, and cleaning agents. Although its disinfectant and antimicrobial properties are useful for the prevention of infectious disease transmission, growing evidence suggests that it may induce contact allergy at a higher rate than previously anticipated.¹ As a highly hydrophilic and large molecular compound, BAK is thought to have limited diffusion into healthy skin; however, its absorption profile may differ on a compromised skin barrier.^{2–4} Instances of eyelid contact dermatitis have already been reported in the literature in addition to cases of conjunctivitis, cheilitis, stomatitis, and hand dermatitis from occupational exposures.^{5–7} Another study determined that

BAK induced severe DNA damage in human respiratory epithelial cell cultures in vitro and could possibly damage the nasal mucosa.⁸

Recent investigations are currently challenging the previous belief that BAK is solely a skin irritant with low potential for sensitization and advocating for its recognition as a novel contact allergen.^{1,9} The aims of this study were to retrospectively evaluate the prevalence of BAK contact allergy in a broad cohort of dermatitis patients and to assess their exposures through personal care, household, and/or occupational products.

METHODS

A retrospective chart review was conducted in 634 consecutive patients patched tested in our outpatient clinic between June 1, 2015, and October 1, 2016, for suspected allergic contact dermatitis (ACD). Nineteen patients were removed from analysis because they were not tested to at least our entire standard series, leaving a total of 615 patients. This study was approved by the Brigham and Women's Hospital Institutional Review Board (no. 2016P000718).

All patients were patch tested to a modified American Contact Dermatitis Society (ACDS) core "standard" series of 70 allergens, as well as additional series based on clinical history and physical examination. Our standard series included BAK at a 0.1% concentration in aqueous solution (Chemotechnique MB Diagnostics AB, Vellinge, Sweden). Finn Chambers (SmartPractice, Phoenix, AZ) were used to occlude all allergens. At 48 hours, patches were removed, and patients were evaluated for an initial reading. Final readings were performed from 72 hours (day 3) to 168 hours (day 7) after placement. Reactions were graded according to the International

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TABLE 1. Patch Test Results for 615 Patients Tested to a Modified Core ACDS Series Containing BAK 0.1% Aqueous

BAK Patch Test Results	Patients, n (%)
–	280 (45.5)
+/–	138 (22.4)
+	134 (21.8)
++	58 (9.4)
+++	6 (1.0)
No. positive and doubtful reactions	336 (54.6)
No. positive reactions (+, ++, +++)	198 (32.1)
No. strong reactions (++, +++)	64 (10.4)

Contact Dermatitis Research Group with +/- (doubtful reactions) defined as macular erythema only; + reactions as papules and erythema; ++ reactions as edematous papules and/or vesicles within the disc site; and +++ reactions as coalescing vesicles, bullous, or extreme reactions spreading beyond the disc site.

Clinical relevance for BAK and potential cross-reactors was established according to the following scheme: definite relevance (positive patch test with product or positive repeat open application test [ROAT] with the product), probable relevance (BAK or potential cross-reactor present in PCP and distribution of rash in vicinity of use), possible relevance (not present in patient's current PCPs, but possible exposure in the past and use of the product in vicinity of dermatitis), and unknown relevance (no known exposure to allergen, or exposure to allergen but not consistent with distribution of clinical dermatitis). Patients were instructed to bring all their PCPs and medications to their final visit for assessment of exposure and clinical relevance. All statistical analyses were carried using IBM SPSS software, version 22 (IBM Corp, Armonk, NY), and results were analyzed

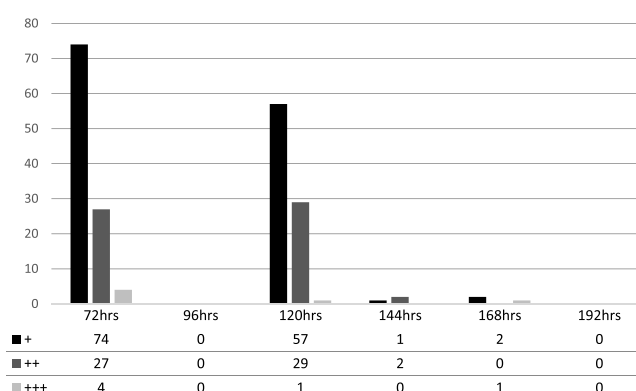


Figure 1. Positive patch test results to BAK at various final reading hours. There was no statistically significant difference between the number of positive reactions or intensity of reactions at 72 and 120 hours ($P=0.41$).

using a Fisher exact test where statistical significance was established at a $P < 0.05$.

RESULTS

Of 615 patients, 198 (32%) had positive patch test reactions to BAK (Table 1). Our cohort was predominantly female (77% [475/615]) and in majority white (76% [468/615]); 70% (432/615) had an atopic diathesis; 27% (164/615) reported a previous history of childhood atopic dermatitis, and the mean age was 49 years (Table 2). Reactions were graded as negative in 46% (280/615) of our cohort, doubtful in 22% (138/615), + in 22% (134/615), ++ in 9% (58/615), and +++ in 1.0% (6/615). There were no statistical differences in our BAK-positive patients versus our BAK-negative patients in reference to sex, age, atopic dermatitis, or ethnicity (Table 2). Based on the collected data, we calculated a positivity

TABLE 2. Demographics for 615 Patients Patch Tested to a Modified Core ACDS Series Containing BAK 0.1% Aqueous

Characteristics	n (%)	BAK+	BAK–	P
Age, mean, y	49	47	49	0.05
Female	475 (77.1)	145	328	0.18
Male	141 (22.9)	52	88	0.18
Atopic diathesis	434 (70.1)	139	295	0.92
Atopic dermatitis	164 (26.6)	56	108	0.56
Race and/or ethnicity				
American Indian or Alaska Native	1 (0.2)	1	0	0.15
Asian	39 (6.5)	18	21	0.05
Black or African American	29 (4.7)	8	21	0.59
Hispanic or Latino	32 (5.2)	14	18	0.15
Native Hawaiian or other Pacific Islander	0 (0.0)	0	0	n/a
White	468 (76.0)	141	327	0.05
Other	7 (1.1)	2	5	0.83
Declined or NA	39 (6.3)	14	25	0.61
No. patients	615	198	417	<0.01

NA, not applicable.

TABLE 3. Anatomical Localization of Dermatitis for 64 Patients With ++ and +++ to BAK

Location	n (%)
Scattered generalized*	24 (37.5)
Trunk	22 (34.4)
Lower extremity	19 (29.7)
Upper extremity	18 (28.1)
Face	15 (23.4)
Hand	15 (23.4)
Back	14 (21.9)
Eyelids	13 (20.3)
Neck	8 (12.5)
Genitals	6 (9.4)
Scalp	5 (7.8)
Mouth/lips	5 (7.8)
Feet	5 (7.8)

*Dermatitis involving 3 or more anatomical sites or 3 sites if the sites were trunk, arms, and legs.

ratio (PR) of 67.68 and a reaction index (RI) of 0.17. Moreover, most had their final reading at either 72 hours (day 3) or 120 hours (day 5) (47% and 42%, respectively). There was no statistical difference between the number of positive reactions or strength of reactions at either interval ($P = 0.41$) (Fig. 1). On average, our patients were using at least 1 product containing BAK or a potential cross-reactor.

Among the 198 patients with positive testing to BAK, 32% (64/198) had either ++ or +++ reactions, representing 10% (64/615) of the entire study population. For these patients with ++/+++ reactions, the most frequent locations of dermatitis in descending frequency were scattered generalized, trunk, lower extremities, and upper extremities (Table 3). Most of our ++/+++ reactors had experienced dermatitis symptoms for 1 to 5 years before their diagnosis (Table 4). Patients with ++/+++ reactions were exposed to BAK or a potential cross-reactor through both leave-on (39%) and wash-off (61%) products, the majority from hair conditioners, shampoos, and body lotions (Fig. 2). In 31% of our ++/+++ patients, reactions intensified from negative reactions at their 48-hour reading to either ++ or +++ at final reading day, 36% were from a doubtful reaction to a ++ or +++ reaction, 6% were from a + to a ++ or +++ reaction, and 9% either remained at a ++ or increased to a +++ reaction (Fig. 3). Furthermore, contact allergy was determined to be probably relevant in 58% of patients with ++/+++ reactions to BAK, possibly relevant in 3%, and of unknown relevance in 39%.

ILLUSTRATIVE CASES

Case 1

A 76-year-old white man underwent patch testing at another institution with the North American (NA) 80 comprehensive series and a cosmetic series for an eczematous eruption of his trunk and legs for 4 months requiring 2 prednisone tapers and topical steroid

creams. Readings were performed at days 2 and 4. At day 4, he showed the following reactions: + nickel sulfate hexahydrate, ++ cobalt hexahydrate, and + BAK. He had been using an Aveeno eczema cream containing BAK. Benzalkonium chloride was felt to be a clinically relevant allergen, and he was given a Contact Allergen Management Program (CAMP) listing suggesting products without his allergens.

He continued to be very symptomatic with dermatitis of his trunk and extremities 15 months after his initial patch testing, despite using products recommended to him via his CAMP listing and following low-nickel and low-cobalt diets.

He was sent to us for consultation with complaints of “hypersensitive skin” and clothing intolerance. We found that he was using CeraVe moisturizing cream containing behentrimonium methosulfate, a potential BAK cross-reactor. We recommended that he stop using CeraVe and use Vaseline as a moisturizer.

He returned in follow-up for patch testing 2 months after consultation, and his symptoms had markedly improved with only discontinuing CeraVe. We patch tested him with a modified ACDS core series and textile series. Readings were performed at days 2 and 3, and photographs were reviewed at day 7. We did not rechallenge him to cobalt, because this had been ++ on his previous testing. See Figures 4A and B, for days 2 and 7 BAK photographs, respectively.

He showed the following reactions on his day 3 reading: ++ 2-bromo-2-nitropropane-1,3-diol (bronopol), ++ glyceryl monoethioglycolate, +++ BAK, + neomycin sulfate, + paraben mix, + fragrance mix I, +/- nickel sulfate 2.5%, +/- potassium dichromate, and +/- formaldehyde. On day 7 photographs, nickel and potassium dichromate both became ++.

His intolerance to various clothing items was felt to be likely secondary to textile formaldehyde. In addition, we found formaldehyde-releasing preservatives (quaternium 15 and 1,3-dimethylol-5,5-dimethyl hydantoin) in his Nizoral shampoo and Selsun shampoo, respectively. We found parabens in his Hydrolatum and behentrimonium methosulfate (a potential BAK cross-reactor) in his CeraVe moisturizing cream, which we had had him discontinue on initial consultation. His reaction to glyceryl monoethioglycolate and neomycin was not clinically relevant.

We generated a product list for him from SkinSAFE free of his allergens and recommended appropriate textiles unlikely to be finished with formaldehyde. He has been free of dermatitis more than 2 years after testing. At our request, he performed a ROAT

TABLE 4. Duration of Dermatitis for 64 Patients With ++ and +++ to BAK

Duration, y	n (%)
<1	16 (25)
1–5	27 (42)
5–10	7 (11)
10+	7 (11)
Uncertain	7 (11)

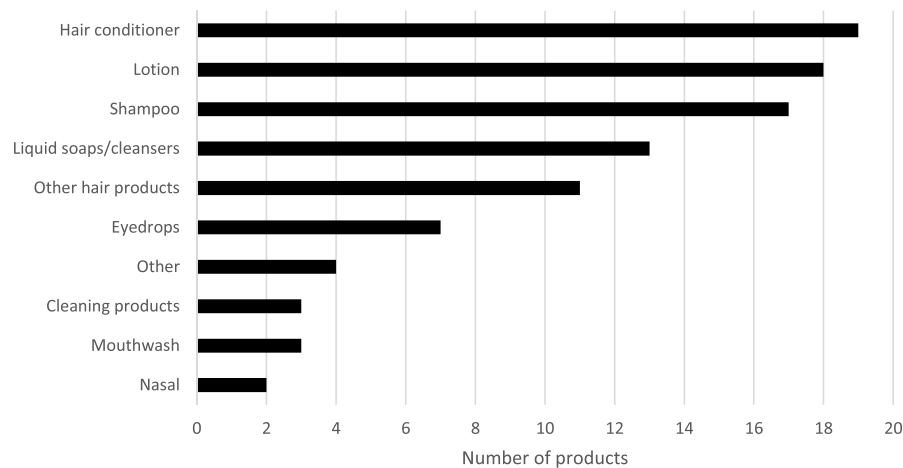


Figure 2. Exposures from PCPs containing BAK or related compound in 64 patients with ++ or +++ reactions to BAK.

with CeraVe cream 2 years after his initial testing with negative results. Retest of paraben mix (under patch occlusion for 48 hours) was also negative. He had not been required to adhere to low-nickel or low-cobalt diets.

Case 2

A 47-year-old Asian atopic nurse with facial dermatitis for 11 months has been reported previously by our group.¹⁰ She had been tested 5 months earlier at another institution to an NA standard series (50 allergens, BAK not present), an extended cosmetic series, and plant series, with completely negative results reported. On patch testing at our institution (days 3 and 5 readings), she had ++ BAK at the final read. Among her duties was the frequent use of disinfectant wipes from “purple top” dispensers to clean surfaces. The active ingredients of the wipes were the QACs benzyl-C12-18-alkyldimethyl ammonium chlorides and C12-18-alkyldimethyl chlorides. We postulated that her BAK reaction was a relevant

occupational allergen due to structural similarity to the QACs in the disinfectant wipes. She cleared completely with avoidance of the disinfectant wipes after having had significant facial dermatitis for a total of 15 months.

The previous 2 cases illustrate the following important points: (1) for patient 1, being generated a CAMP listing, which did not remove CeraVe cream that contains behentrimonium methosulfate, a potential BAK cross-reactor, contributed to his generalized dermatitis for an additional 15 months before consultation with us; (2) for patient 2, the absence of testing to BAK in the NA standard 50 led to missing an important occupational allergen for her; and

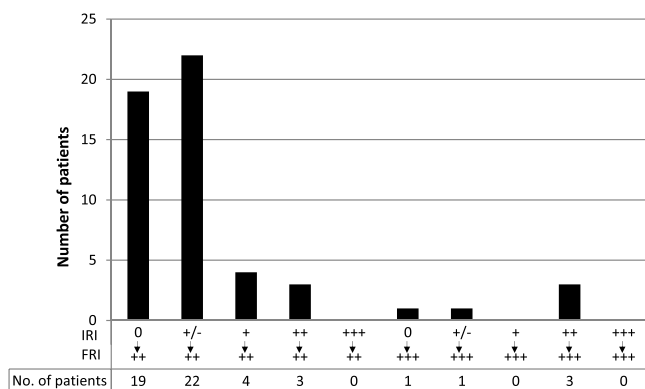


Figure 3. Graph illustrating the intensity of reactions observed at the 48-hour initial reading and the final reading for 64 patients with ++ or +++ reactions to BAK (eg, 19 patients had their reaction intensity from 0 to ++ at their final reading appointment). Eleven patients did not present to clinic for their initial reading visit and thus were excluded from this graph.

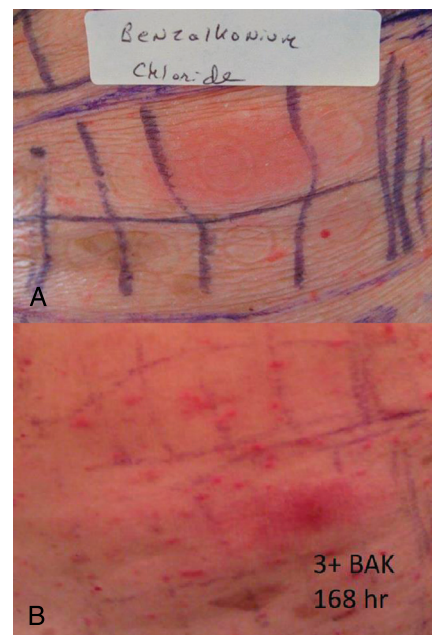


Figure 4. A, Clinical photograph showing ++ reaction to BAK 0.1% aqueous day 2 after placement. B, Same reaction portrayed in (A) progressing to a +++ reaction on day 3 and still present on day 7 after placement.

(3) there can be false-negative results with a ROAT. For both patients, once items with potential BAK cross-reactors were removed from their PCPs and occupational exposures (patient 2), they both cleared after having had dermatitis for more than 1 year each.

DISCUSSION

Benzalkonium chloride is a known irritant that can, in certain cases, also act as a contact allergen, making the distinction between its irritant and allergenic nature particularly complex.^{6,11} In previous studies, cytokine assays favored a more irritant profile, whereas sensitization assays in animal models were ambivalent and ultimately could not confirm or dispute the allergenicity of this chemical.^{11–16}

This retrospective chart review of 615 dermatitis patients patch tested to a modified ACDS core series for a 16-month period from 2015 to 2016 showed 10% patients with ++/+++ reactions to BAK. Most patients had their final reading date at either day 3 or day 5. Although slightly more patients had their final evaluation at day 3, we observed no statistically significant differences between the strength of reactions or number of positive BAK reactions between day 3 or day 5. This result suggests that even at our later final reading time we were still able to elicit strong or extreme positive reactions to BAK, making these reactions likely to be true positives and not simply irritant reactions. Of our BAK reactions greater than +, 58 (29%) were ++ and 6 (3%) were +++. Two thirds of our patients progressed from no or doubtful reactions at their initial 48-hour reading to a ++ or +++ reaction at their final reading date. These results are thus consistent with a crescendo effect seen with true contact allergic reactions. Moreover, BAK was the number 1 preservative allergen in our full cohort of 615 dermatitis patients, illustrating its importance as a sensitizer (Table 5). Three of our 5 top preservative allergens are also among the top 5 North American Contact Dermatitis Group (NACDG) preservative allergens¹⁷ including formaldehyde 1%, methylisothiazolinone (MI), and methylchloroisothiazolinone/methylisothiazolinone (MCI/MI). The NACDG standard does not include BAK, and our standard series does not include formaldehyde 2%, but rather formaldehyde 1% (Table 5).

++ And +++ BAK Reactions

It is also worth noting that 58% of patients had a probably relevant exposure to BAK, meaning that either BAK or potential cross-reactor was identified in their PCPs and used in the distribution

of their dermatitis. In addition, the more frequent locations of dermatitis such as the trunk and extremities corresponded to areas that would be exposed to the more prevalent classes of products containing BAK or potential cross-reactor (ie, body lotion, shampoos, and conditioners, the latter two potentially contributing to the face, neck, and upper back dermatitis.). Most products were classified as wash-off products (61%) versus leave-on products (39%). Considering that exposure was mainly secondary to wash-off products, BAK may be problematic not only from leave-on formulations such as lotions but also from wash-off products. Possibly, residues may linger on areas of impaired skin barrier, become occluded under clothing creating a situation of irritancy initially, and then with continued exposure predispose to the development of true contact allergy in areas such as the trunk or extremities. For dermatitis of the face, the thinner skin in that location could allow penetration of BAK or cross-reactors even from wash-off products such as shampoos and hair conditioners.

Our findings of, on average, at least 1 product containing BAK or potential cross-reactors in our full cohort of 198 BAK-positive patients attest to the widespread exposure to BAK and cross-reactors within PCPs. We have observed BAK or potential cross-reactors in many popular products marketed specifically for “eczema” and “sensitive skin” patients. The Personal Care Council Database offers an extensive list of potential BAK cross-reactors including, among others, behentrimonium methosulfate, distearylethyl dimonium chloride, cetrimonium (cetrimide) chloride, and benzethonium chloride (BEC).¹⁸ The CAMP database (<http://www.contactderm.org>), however, does not currently list all of the previously mentioned ones as potential cross-reactors (Table 6).¹⁹

At this time, the SkinSAFE database includes all the previously mentioned QACs as potential cross-reactors with BAK (<http://www.SkinSAFEproducts.com>) and contains approximately 20% of products with BAK or similar compounds (e-mail communication, Dr. J. Yiannias with P.L.S., February 2017) demonstrating the pervasiveness of this preservative in PCPs.

Dao et al²⁰ investigated allergy to BAK and BEC using different concentrations and vehicles for BAK and BEC. They found that 75% patients with possible ACD to BAK coreacted with BEC. They reported that approximately 58% of patients with definite or possible ACD to BAK would not have been identified if only BAK 0.1% aqueous was tested. They thus recommended testing to BAK 0.15% in both aqueous and petrolatum formulations to optimize the sensitivity of patch testing to this allergen. More importantly,

TABLE 5. Top 5 Preservative Allergens Among 615 Patients Patch Tested to a Modified Core ACDS Series

Rank	Modified ACDS Core Series	+, n (%)	++, n (%)	+++, n (%)	Positive Reactions, n
1	BAK 0.1% aq	134 (67.7)	58 (29.3)	6 (3.0)	198
2	Formaldehyde 1% aq	81 (62.8)	39 (30.2)	9 (7.0)	129
3	MI 0.2% aq	67 (54.9)	20 (16.4)	35 (28.7)	122
4	2-Bromo-2-nitropropane-1,3-diol (bronopol) 0.5% pet	50 (68.5)	21 (28.8)	2 (2.7)	73
5	MCI/MI 0.01% aq	33 (54.1)	20 (32.8)	8 (13.1)	61

aq, aqueous; pet, petrolatum.

TABLE 6. Partial Listing of Potential BAK Cross-Reactors From the PCP, SkinSAFE, and CAMP Databases

Potential BAK Cross-reactors	PCP Database	SkinSAFE Database	CAMP Database
Alkyldimethyl benzyl ammonium chloride	✓	✓	✓
Alkyldimethyl ethylbenzyl ammonium chloride	✓	✓	✓
Behentrimonium methosulfate	✓	✓	
BEC	✓	✓	✓
Cetrimonium (cetrimide) chloride	✓	✓	✓
Cetylpyridinium chloride	✓	✓	✓
Distearoylethyl dimonium chloride	✓	✓	
Guar hydroxypropyltrimonium chloride	✓	✓	

these authors found that 48% of their patients, even with doubtful reactions to BAK, had significant clinical improvement by avoiding QACs in their PCPs.²⁰

Benzalkonium chloride is presently not tested by the NACDG on their standard series because it was removed due to low rates of allergy in the past and concerns about irritancy potential. Based on criteria detailed by Warshaw et al,²¹ a “problematic” preparation displays a PR higher than 55% and an RI less than or equal to 0.46. Such allergens are characteristic of chemicals that produce many weak reactions and/or potentially false-positive reactions.^{1,21} In our cohort, we obtained values of 67.68 and 0.18 for both the PR and RI, respectively, which fall within the problematic range. This observation does raise a concern for false interpretation of patch testing results to BAK. Indeed, doubtful and + reactions to BAK should be interpreted with caution, and many + reactions may represent irritant reactions. However, given the high percentage (10%) of our dermatitis patients with ++/+++ reactions to BAK, together with exposure to BAK in PCPs and with most reactions occurring in a crescendo fashion, BAK should be considered an important contact allergen in our cohort.

In addition, other centers have also noticed an increased incidence of BAK contact allergy in recent years. The Mayo Clinic identified BAK among the top 5 allergens in a study of patients patch tested to a supplemental cosmetic series between 2000 and 2007.²² Another study by the Mayo Clinic¹ reported a statistically significant increase in BAK reactions when comparing 1998–2000 (5.5%) with 2006–2010 (8.8%, $P = 0.005$). They determined that testing for BAK was a useful addition to their standard series.¹

In vitro models showed a marked increase in the absorption of substances with an impaired barrier.^{2,3} It is known that even weak sensitizers such as parabens and lanolin can become allergenic when applied to areas of a perturbed skin barrier such as chronic dermatitis or ulcers.^{23,24} Moreover, other studies suggest that irritants also have the potential to become allergens when exposed to compromised skin.²⁵ This illustrates the need for more comprehensive absorption and toxicologic assays in both intact and compromised skin to evaluate safe concentrations to be used in both wash-off and leave-on products.

Limitations for this study include that this was not a multicenter study, which may have induced a regional bias in our analysis. In addition, our clinic is a tertiary care referral center,

whose data may not be applicable to a broader dermatology population. Some of our patients did not bring in all their products for inspection, which may have led to an underestimation of the true exposures to BAK or similar QACs and their clinical relevance. It is also possible that testing with 0.1% BAK in aqueous solution only and not at the higher concentration of 0.15% in both aqueous and petrolatum vehicles as recommended by Dao et al²⁰ falsely decreased positive reactions to BAK. Establishing a definite clinical relevance was also challenging, given our patients’ long history of dermatitis and their reluctance to perform ROATs to products containing BAK or related compounds for fear of exacerbating their symptoms. Therefore, it is possible that we may have underestimated the clinical relevance of some of our BAK-allergic patients.

Further studies including serial dilution assays and provocative use tests in patients with known allergy to BAK should be conducted in the future to differentiate irritant reactions from allergic ones and evaluate the true clinical relevance of positive patch test results.^{1,6,26} Such studies should also incorporate potential cross-reactors such as behentrimonium methosulfate, distearoylethyl dimonium chloride, cetrimonium chloride, and guar hydroxypropyltrimonium chloride because of their significant presence in the market.

In summary, BAK is an irritant, and weak patch test reactions need to be interpreted cautiously. However, given the high prevalence of ++/+++ reactions in our dermatitis patients, BAK and potential cross-reactors should be used cautiously in the setting of patients with compromised skin barriers. Additional studies with BAK cross-reactors in BAK-allergic patients should be conducted in the future.

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