Received: 14 September 2020 | Revised: 15 October 2020 | Accepted: 19 October 2020

DOI: 10.1111/cod.13728

ORIGINAL ARTICLE

CONTACT DERMATITIS WILEY

Contact allergy to polyhexamethylene biguanide (polyaminopropyl biguanide)

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Abstract

Background: Polyaminopropyl biguanide (INCI name) and polyhexamethylene biguanide (PHMB) are polymeric biguanides. PHMB is a broad-spectrum antimicrobial substance used as a preservative in many products. Due to our limited knowledge on PHMB contact allergy frequency and the fact that cases of allergic contact dermatitis to PHMB might be missed, we have included PHMB as a screening allergen since 2016.

Objective: To report the prevalence of positive patch test reactions to PHMB as a screening allergen in patients with suspected allergic contact dermatitis.

Methods: A retrospective analysis of 1760 patch tested patients from July 2016 to December 2018 was performed. Polyaminopropyl biguanide 2.0% aqua was included in the extended Malmö baseline series during the study period.

Results: Of all patients, 1204 (68.4%) were female. Positive patch test reactions were reported in 19 patients (1.1%). The most common sites of lesions were face, head, and neck (52.6%). There was a significant correlation between concomitant reactions to PHMB and other cosmetic-related allergens.

Conclusion: The prevalence of positive reactions to PHMB was higher than that previously reported. Patch testing with PHMB should be performed in patients with dermatitis who have lesions on the face, head, and neck.

KEYWORDS

allergic contact dermatitis, cosmetics, patch test, polyaminopropyl biguanide, polyhexamethylene biguanide, preservative, prevalence

1 | INTRODUCTION

Polyaminopropyl biguanide (INCI name; PAPB; CAS no. 133029-32-0) and polyhexamethylene biguanide (PHMB; CAS no. 27083-27-8, 28757-47-3, 32289-58-0 [PHMB HCl]) are polymeric biguanides comprising propyl biguanide or hexyl biguanide repeat units, respectively.[1] Both PAPB and PHMB are used as antiseptic substances and preservatives in products.[2] Low concentrations of PHMB demonstrated high antimicrobial efficacy against bacteria, whereas PAPB showed less or no antimicrobial effects.[2,3] Up until now there is no

This study was approved by the ethics committee of Faculty of Medicine, Lund University.

specific INCI name for PHMB. Accordingly, PAPB is usually used as a synonymous name for PHMB, and hence both cannot be entirely distinguished. Therefore, PHMB has been included in the opinion on PAPB by the Scientific Committee on Consumer Safety.[3] PHMB as an ingredient name in products will be used exclusively in this report. The chemical structures of PAPB and PHMB are shown in Figure 1.

Although PHMB has been used in many cleaning products, it had been found an uncommon allergen due to its low frequency of sensitization, with a prevalence of approximately 0.5% of tested patients in the past.[4] However, PHMB has been reported as a culprit allergen in cosmetic products and contact lens cleaning solutions in patients with allergic contact dermatitis (ACD).[5-8] PHMB has not only caused delayed-type hypersensitivity reactions, but cases of contact urticaria and anaphylaxis representing immediate-type hypersensitivity also have been reported.[9,10] Due to its bactericidal and fungicidal properties it has been used in wound dressings. Due to the impaired skin in connection to the wound area this may as such be a risk factor for sensitization from PHMB.[11,12] The knowledge about PHMB contact allergy frequency is still limited, and cases of ACD due to PHMB might be missed unless an allergy is specifically suspected, since PHMB is not present in baseline patch test series. Therefore, we wanted to investigate the prevalence of contact allergy reactions to PHMB in patients with eczema. This study aimed to report the prevalence and general information of patients with PHMB contact allergy by retrospectively analyzing the patch test results from consecutive dermatitis patients in a contact dermatitis clinic.

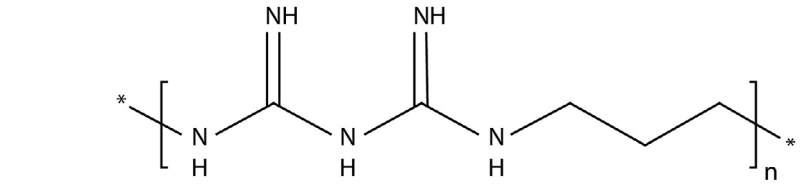
2 | MATERIALS AND METHODS

A retrospective analysis of 1760 patients patch tested from July 2016 to December 2018 at the Department of Occupational and Environmental Dermatology, Malmö, Sweden, was performed. All patients with suspicion of contact dermatitis were tested with the Swedish baseline series, with additional allergens based on experience of the clinic and local exposures (the extended Malmö baseline series), other suspected allergens, and personal products. In addition, PAPB (INCI), as PHMB HCl, CAS no. 27083-27-8, at the concentration of 2.0% w/v in water was included in the extended Malmö baseline series during the study period. The patch test solution was kindly provided by professor An Goossens, Contact Allergy Unit, Department of Dermatology, Katholieke Universiteit Leuven, Belgium. The patch test preparation was applied on the upper back of the patients with 15 μL in 8 mm Finn Chambers (Epitest, Tuusula, Finland, or SmartPractice, Phoenix, Arizona) mounted on Scanpor tape (Norgeplaster, Oslo, Norway). The patch tests were removed on day (D) 2. Dermatologists performed patch test readings on D3/4 and D7, according to the classification suggested by the International Contact Dermatitis Research Group.[13] Patch test data and patients' characteristics were recorded in a computer system, DALUK. Reported reactions included negative, irritant, doubtful (?+), weak positive (+), strong positive (++), and extreme positive (+++) reactions.

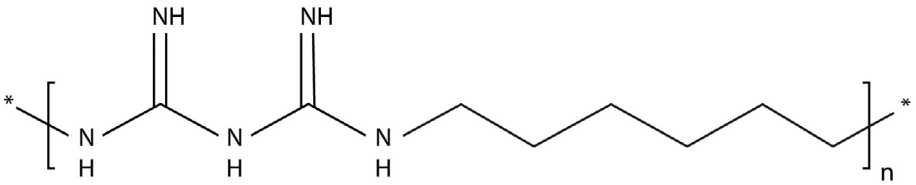
Data were analyzed using PASW Statistics, version 18.0 (SPSS, Chicago, Illinois). Descriptive statistics were presented as frequency and percentage, or as mean ± standard deviation. The chi-square test or Fisher exact test was used to compare the prevalence of positive patch test reactions to other concomitant allergens between patients with positive or doubtful and negative reactions to PHMB.

3 | RESULTS

Of all 1760 tested patients, 1204 (68.4%) were female. Positive patch test reactions to PHMB were reported in 19 (1.1%) of all tested patients. Contact allergy was more common in female than in male patients: 1.2% versus 0.9% (*P*-value >.3; Fisher exact test, two-sided). The mean age (± SD) was 51.4 (±19.1) years. Of these, 11 patients



Polyaminopropyl biguanide
$(C_5H_{11}N_5)_n$



Polyhexamethylene biguanide
$(C_8H_{17}N_5)_n$

FIGURE 1 Chemical structures of polyaminopropyl biguanide and polyhexamethylene biguanide

(57.9%) demonstrated weak positive reactions (+), 6 (31.6%) strong (++), and 2 (10.5%) extreme positive (+++) reactions. Doubtful reactions were reported in 37 patients (2.1%). An irritant reaction was demonstrated in one female patient. The most common sites of lesions were the face, head, and neck (52.6%), followed by hands (26.3%). About two-thirds (68.4%) of these patients reacted to at least three allergens. Common concomitant positive allergens were nickel sulfate (36.8%), sodium tetrachloropalladate (26.3%), *Myroxylon pereirae* resin (balsam of Peru; 21.1%), Amerchol L-101 (15.8%), gold sodium thiosulfate (15.8%), hydroperoxides of limonene (15.8%), hydroperoxides of linalool (15.8%), and methyldibromo glutaronitrile (15.8%). Table 1 demonstrates the prevalences of positive patch test reactions to concomitant allergens of patients who reacted with a positive or doubtful reaction to PHMB compared with the patients with negative

TABLE 1 A comparison of the prevalence of positive patch test reactions to other allergens between patients who had positive or doubtful, and negative reactions to polyhexamethylene biguanide

Allergens with concomitant reactions	Concentration and vehicles	PHMB negative PT reactions (n = 1704) n	(%)	PHMB positive PT reactions (n = 19) n	(%)	*P*-value[a]	PHMB doubtful PT reactions (n = 37) N	(%)	*P*-value[b]
Cosmetic-related									
Fragrances									
Myroxylon pereirae	25% pet.	114	(6.7)	4	(21.1)	**.036**	9	(24.3)	**<.001**
Hydroperoxides of limonene	0.3% pet.	75	(4.4)	3	(15.8)	.051	3	(8.1)	.22
Hydroperoxides of linalool	1% pet.	109	(6.4)	3	(15.8)	.12	8	(21.6)	**.002**
Cinnamyl alcohol	2% pet.	15	(0.9)	2	(10.5)	**.014**	1	(2.7)	.30
Fragrance mix I	8% pet.	87	(5.1)	1	(5.3)	>.999	10	(27.0)	**<.001**
Citral	2% pet.	6	(0.4)	1	(5.3)	.075	1	(2.7)	.14
Hexyl cinnamal	10% pet.	2	(0.1)	1	(5.3)	**.033**	1	(2.7)	.064
Preservatives									
Methyldibromo glutaronitrile	0.5% pet.	36	(2.1)	3	(15.8)	**.008**	3	(8.1)	**.048**
Methylchlorothiazolinone/methylisothiazolinone	0.02 % aq.	66	(3.9)	2	(10.5)	.17	9	(24.3)	**<.001**
Formaldehyde	2% aq.	53	(3.1)	2	(10.5)	.12	5	(13.5)	**.006**
Others									
Amerchol L-101	50% pet.	5	(0.3)	3	(15.8)	**<.001**	2	(5.4)	**.009**
p-Phenylenediamine	1% pet.	37	(2.2)	1	(5.3)	.35	1	(2.7)	.56
Colophonium	20% pet.	49	(2.9)	1	(5.3)	.43	3	(8.1)	.094
Non-cosmetic-related									
Nickel sulfate	5% pet.	253	(14.8)	7	(36.8)	**.016**	10	(27.0)	**.024**
Sodium tetrachloropalladate	3% pet.	146	(8.6)	5	(26.3)	**.020**	6	(16.2)	.12
Gold sodium thiosulfate	2% pet.	222	(13.0)	3	(15.8)	.73	2	(5.4)	.31
Caine mix 2	10% pet.	21	(1.2)	2	(10.5)	**.025**	0	(0)	-
Cobalt chloride	0.5% pet.	71	(4.2)	2	(10.5)	.19	2	(5.4)	.66
Benzisothiazolinone	0.1% pet.	18	(1.1)	1	(5.3)	.19	0	(0)	-
Carba mix	3% pet.	24	(1.4)	1	(5.3)	.24	2	(5.4)	.11
4,4′ -Diaminodiphenylmethane	0.5% pet.	17	(1.0)	1	(5.3)	.18	0	(0)	-
Epoxy resin	1% pet.	20	(1.2)	1	(5.3)	.21	1	(2.7)	.39
Phenol formaldehyde resin (PFR2)	1% pet.	7	(0.4)	1	(5.3)	.085	2	(5.4)	**.015**
Potassium dichromate	0.5% pet.	58	(3.4)	1	(5.3)	.49	2	(5.4)	.36
Neomycin sulfate	20% pet.	13	(0.8)	1	(5.3)	.14	0	(0)	-
Palladium chloride	2% pet.	123	(7.2)	1	(5.3)	>.999	7	(18.9)	**.013**
Textile dye mix	6.6% pet.	41	(2.4)	1	(5.3)	.38	2	(5.4)	.23

Abbreviations: aq, aqueous; pet, petrolatum; PHMB, polyhexamethylene biguanide; PT, patch test.

[a]Comparison between positive and negative patch test reactions to PHMB.

[b]Comparison between doubtful and negative patch test reactions to PHMB; *P*-value <.05 indicates statistical significance.

reactions. The prevalences of positive patch test reactions to the following allergens were significantly more common in patients who positively reacted to PHMB: *Myroxylon pereirae* resin, cinnamic alcohol, hexyl cinnamal, methyldibromo glutaraldehyde, Amerchol L-101, nickel sulfate, sodium tetrachloropalladate, and caine mix 2 (*P*-values <.05). In those with doubtful reactions, a comparison with negative reactions also showed significantly higher numbers of positive reactions to several allergens.

4 | DISCUSSION

The prevalence of positive patch test reactions to PHMB in this study was 1.1%, which was higher than that reported in the past (0.5% tested with 2.5% aq. and 0.8% tested with 5% aq.).[5] In the results with patch testing in Europe during 2013–2014, about 40% of allergens (15 of 38 allergens in the European baseline series) demonstrated prevalences of test positivity less than the prevalence of positive reactions to PHMB found in this study (1.1%).[14] With regard to female patients, the prevalence was found to be even higher at 1.5%. Many factors determine whether an allergen should be included in the baseline series; the frequency of contact allergy in the exposed population is one and with the found frequency, PHMB certainly merits taking the allergen into consideration for inclusion. The reason behind a higher prevalence might be that PHMB is widely used as a broad spectrum preservative and disinfectant in many products such as cosmetics, personal care products, washing or cleaning agents, wound dressings, and many medical-grade materials[3-5] with which individuals easily come in contact, both occupationally and domestically. Recently, a commercial allergen for patch testing, PHMB at the concentration of 2.5% aq. was introduced in the cosmetic series C-1000 (Chemotechnique Diagnostics, Sweden).[15] However, contact allergy cases could be missed if not patients without suspicion of cosmetic allergy are not also tested. Thus a patch test with PHMB should be considered in all patients with suspected contact allergy, especially those with dermatitis of the face, head, and neck.

In the present study, about half of the patients with positive reactions had lesions in the face, head, and neck, which was different from the report in the previous study in 2007.[5] Moreover, many head and neck patients revealed positive reactions to at least three allergens, called polysensitization, and most of the common concomitant allergens were ingredients found in cosmetics. Correspondingly, there were significantly higher prevalences of positive patch test reactions to several cosmetic-related allergens in PHMB patch test-positive patients (Table 1). These might be correlated with the utilization of PHMB in cosmetic products, in which the clinical exposure and symptoms are often facial. The results show that co-sensitization among cosmetic-related allergens and PHMB might exist. According to the use in cosmetics, there exists the opinion of the Scientific Committee on Consumer Safety in PHMB. During 2014 to 2017, it could be used up to a maximum concentration of 0.3% in cosmetics.[3] Later in 2017, the committee adopted the final opinion that the use of PHMB as a preservative in all cosmetic products up to 0.1% is safe.[3] This might further lead to a lower prevalence of PHMB contact allergy in the same way as reported for methylisothiazolinone after restricting the use in cosmetics.[16,17] Nevertheless, it is essential to be aware that other products and materials might contain PHMB. Hence, continuous monitoring of contact allergy to PHMB should be performed to establish whether the prevalence will decrease.

Of interest, we found a high prevalence (2.1%) of doubtful reactions to PHMB in this study. Further analysis showed no significant difference between patients with positive and doubtful reactions in terms of gender (*P*-value = .96) and the main site of lesions (*P*-value = .69). Face, head, and neck dermatitis remained the most common locations of lesions in both groups (*P*-value = .29). Moreover, the result also showed significantly higher numbers of positive reactions to several cosmetic-related allergens in patients with doubtful reactions to PHMB. The nature of patients in both groups seemed to be similar, which might support the notion that doubtful reactions represent weak allergic reactions rather than unspecific, irritant reactions.

Concerning positive reactions to other allergens, nickel sulfate, phenol-formaldehyde resin (PFR2), and palladium chloride demonstrated a significantly higher prevalence of positive reactions in patients with doubtful reactions to PHMB. Although nickel has been categorized as a metal allergen, it could be found in many kinds of cosmetics, especially in makeup.[18] Nickel and palladium were also reported to be common allergens that show concomitant positive test reactions in patch testing.[19] When patch testing phenol-formaldehyde resin (PFR2), a substantial number of simultaneous positive reactions were noted for *Myroxylon pereirae* resin, colophonium, and fragrance mix I.[20,21] This association indicates that the cases with doubtful reactions to PHMB are related to cosmetic allergy.

The test concentration of 2.0% PHMB in water was used in this study being aware that the allergen might induce patch test sensitization in patients. In animal studies, PHMB is considered to be a moderate to strong sensitizer at concentrations above 1.2%, and the threshold for eliciting skin reactions is approximately 1%.[3] Therefore, the Scientific Committee on Consumer Safety concluded that PHMB at the concentration of 2.0% could cause skin sensitization.[3] On the other hand, many previous studies suggested that PHMB should be tested at 5.0% aq.[7,8,11,12] The prevalence of positive reactions at a tested concentration of 2.5% aq. and 5.0% aq. was reported to be 0.5% and 0.8% in 1975 patients, respectively.[5] In that study, 6 of 15 patients were missed when using only PHMB 2.5% aq.; however, false-positive reactions caused by PHMB 5.0% aq. might be another probable explanation.[5] One study reported that PHMB 2.0% aq. showed a negative result, whereas 5.0%, 10.0%, and 20.0% aq. gave weak, moderate, and extreme positive reactions, respectively.[8]

The ratios of the patch test concentration to the use concentration in products or materials might vary from 10 to 90.[22] For example, methylisothiazolinone 2000 ppm aq. has been tested since a maximum concentration of 100 ppm was allowed in cosmetic products in Europe.[23] Based on this and the references above it seemed appropriate to fix the concentration at 2% of PHMB in our study. Thus, a concentration 20 times higher than the restricted use concentration in cosmetic products (0.1%) was considered acceptable in our study.

However, when analyzing data, finding no cases of active sensitization, only one case of irritancy, and quite a few cases of doubtful reactions, one should presumably consider adjusting the test concentration to optimize this. Thus, it might be fruitful to evaluate the optimal patch test concentration further. Which reactivity that is clinically relevant is of course also of importance, and might be further explored in a repeat open application study using a leave-on product with the maximum allowed concentration of PHMB as a test product. In the individual case, a doubtful reaction might be further evaluated by increasing the patch test concentration if there is a high degree of clinical suspicion or performing a repeated open application test with the suspected product.

In conclusion, the prevalence of positive reactions to PHMB at the concentration of 2.0% aq. was higher than expected. Regarding those patients with doubtful reactions to the tested preparation, a further study retesting with higher tested concentrations might be required. We recommend that patients with clinically suspected cosmetic contact allergy, especially those who have lesions in the face, head, and neck should be tested with PHMB. However, testing with PHMB in other cases might also be beneficial, since it is contained in products other than cosmetics. Because PHMB can cause immediate hypersensitivity reactions, either open patch testing with early reading or a skin prick test is recommended in patients with a suspicion of urticaria, angioedema, or anaphylaxis. Further investigations are needed before PHMB can be recommended for inclusion into a baseline series.

CONFLICT OF INTEREST

All authors have no conflicts of interest or financial support to declare.

AUTHOR CONTRIBUTIONS

Thanisorn Sukakul: Data curation; methodology; validation; visualization; writing-original draft; writing-review and editing. **Jakob Dahlin:** Data curation; formal analysis; investigation; resources; software; validation; visualization; writing-review and editing. **Ann Pontén:** Conceptualization; data curation; investigation. **annarita antelmi:** Data curation; investigation. **Magnus Bruze:** Conceptualization; investigation; methodology; supervision; validation; visualization; writing-original draft; writing-review and editing. **Nils Hamnerius:** Data curation; investigation. **Inese Hauksson:** Data curation; investigation. **Marléne Isaksson:** Data curation; investigation. **Tina Lejding:** Data curation; investigation. **Cecilia Svedman:** Conceptualization; data curation; formal analysis; investigation; methodology; project administration; supervision; validation; visualization; writing-original draft; writing-review and editing.

DATA AVAILABILITY STATEMENT

All data analysed during this study are included in this published article. https://onlinelibrary.wiley.com/doi/10.1111/cod.13728.

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How to cite this article: Sukakul T, Dahlin J, Pontén A, et al. Contact allergy to polyhexamethylene biguanide (polyaminopropyl biguanide). *Contact Dermatitis*. 2021;84: 326–331. https://doi.org/10.1111/cod.13728