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ORIGINAL ARTICLE

PILOT STUDY OF THE PREVALENCE OF CONTACT SENSITIZATION TO PRESERVATIVES AS COSMETIC INGREDIENTS IN OCCUPATIONAL AND EDUCATIONAL EXPOSURES

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Abstract. Aim: *To evaluate the prevalence of contact sensitization to selected preservatives as cosmetic ingredients among cosmeticians and cosmetology students and to identify the most common allergens in occupational and non-occupational exposures.* ***Materials and methods:*** *Skin patch testing with formaldehyde, quaternium-15, DMDM hydantoin, imidazolidinyl urea, methylisothiazolinone + methylchloro-isothiazolinone, iodopropynyl butylcarbamate, methyldibromoglutaronitrile, polyaminopropyl biguanide and paraben mix was performed among 109 participants – 37 cosmetology students, 26 cosmeticians, and 46 individuals – controls, occupationally unexposed to cosmetics. Fisher Exact Test and multiple binary logistic regression analysis were used.* ***Results:*** *Formaldehyde was the main contact sensitizer, with significantly higher prevalence of sensitization among the occupationally exposed cosmeticians and cosmetology students if compared to the controls (p = 0.005) [OR = 0.290 (95% CI: 0.092-0.916]). The positivity prevalence to DMDM hydantoin was 11%, with equal rates of sensitization to quaternium-15, methylisothiazolinone + methylchloroisothiazolinone and methyldibromo-glutaronitrile (9.2%). A significantly higher prevalence of co-sensitization to DMDM hydantoin and imidazolidinyl urea was revealed. The positivity rate to quaternium-15 was highest among cosmetology students – 13.5%. The frequency of positive reactions to imidazolidinyl urea was 2.7% for students and 11.5% for cosmeticians. Cosmetology students and cosmeticians were at risk of sensitization to DMDM hydantoin, and the cosmeticians – to methylisothiazolinone/methylchloro-isothiazolinone and methyldibromo glutaronitrile and parabens.* ***Conclusions:*** *This study established comparative high prevalence and risk of contact sensitization to the selected preservatives. Proper occupational risk information, developing and disseminating of practical tools for workplace risk assessment and management, with complex programs for prevention of occupational skin diseases should be provided.*

Key words: *contact sensitization, preservatives, cosmetics, occupational exposure, educational exposure*

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INTRODUCTION

According to the European legislation (REGULATION (EC) No 1223/2009) "cosmetic product" is any substance or mixture intended to be placed in contact with the external parts of the human body (epidermis, hair system, nails, lips and external genital organs) or with the teeth and the mucous membranes of the oral cavity with a view exclusively or mainly to cleaning them, perfuming them, changing their appearance, protecting them, keeping them in good condition or correcting body odours [1].

The Federal Food, Drug & Cosmetic Act (FD&C Act) defines cosmetics as “articles intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body... for cleansing, beautifying, promoting attractiveness, or altering the appearance.” Included in this definition are products such as skin moisturizers, perfumes, lipsticks, fingernail polishes, eye and facial makeup preparations, shampoos, permanent waves, hair colors, toothpastes, deodorants, as well as any material intended for use as a component of a cosmetic product [2].

The use of cosmetics among the general population nowadays is ubiquitous, with more and more products being produced and presented at the market, together with their enhanced media exposure. Most of these products contain ingredients capable of causing skin sensitization. Allergic contact dermatitis is a common adverse reaction caused by cosmetics and is increasingly being observed, up to 25% of the patients investigated [3]. According to a recent study, highest patch test positivity rate over 30 years was in the cosmetics series (70.2%), and the top three most common allergens during each five-year period, except from three metals, were cosmetics ingredients – two fragrances (fragrance mixed I, linalool hydroperoxide) and two preservatives (paraben mix, methylisothiazolinone). The variations in the positivity rates to cosmetics ingredients depends on the specificity of exposures, the popularity of cosmetic products in each country, regional legislation, and the tested population [4].

Studies aiming to evaluate occupationally induced contact dermatitis are directed mainly to hairdressers, nail technicians/manicurists and beauticians/cosmetologists. Among the latter professional groups, apart from the consumer exposures, occupational ones start at the beginning of their practical education. No data was found in the available literature regarding the rates of sensitization among students of cosmetology.

Therefore, the aim of the present study was to evaluate the prevalence of contact sensitization to selected preservatives as cosmetic ingredients among cosmeticians and cosmetology students and to identify the most common allergens in occupational and non-occupational exposures.

MATERIALS AND METHODS

A cross-sectional study was conducted in the period October – December 2022 upon obtaining approval from the Medical Ethics Board at Medical University – Sofia and in accordance with the Helsinki Declaration. A total of 109 participants (8 men and 101 women) were included in the study. They were divided into 3 groups – 37 cosmetology students from the Medical College, Medical University – Sofia, 26 occupationally exposed cosmeticians, and 46 individuals without occupational exposure to cosmetics served as a control group. The demographic characteristics of the groups are presented in Table 1.

Table 1. Demographic characteristics of the studied population

Group	N	Age		
		Mean ± SD	Min	Max
Cosmetology students	37	23.70 ± 6.62	18	41
Occupationally exposed cosmeticians	26	32.77 ± 9.60	20	51
Controls	46	31.98 ± 14.54	17	62
Total	109	29.48 ± 11.84	17	62

All the participants were informed about the purpose of the study and gave their written informed consent before its commencement.

All the participants were skin patch tested with the following haptens: preservatives – formaldehyde (2.0% aq), quaternium-15 (1.0% pet), DMDM hydantoin (1.0% pet), imidazolidinyl urea (2.0% pet), methylisothiazolinone + methylchloroisothiazolinone (0.01% aq), iodopropynyl butylcarbamate (0.2% pet), methyldibromoglutaronitrile (0.5% pet), polyaminopropyl biguanide (2.5% aq), Paraben mix (12.0% pet) – Chemotechnique Diagnostics, by placing the haptens in IQ Ultimate hypoallergenic patches of Chemotechnique Diagnostics (IQ Chambers®, Vellinge, Sweden). Lack of anti-allergic medication one week before and during the testing was a mandatory requirement. Patches were applied on the upper back of the tested individuals and left for 48 hours. Patch test reading was performed on day (D)3 or D4 and on D7. The reactions were interpreted as negative, doubtful, weakly positive (+), strongly positive (++), extremely positive (+++), and irritant reactions, as recommended by the International Contact Dermatitis Research Group (ICDRG). For the statistical analyses, as positive reactions were counted reactions

with at least one plus (+) on D3/4 or D7, whereas negative, doubtful, and irritant reactions were concluded as negative.

Statistical analyzes were performed using statistical software SPSS for Windows version 20.0. Continuous variables were presented as mean ± standard deviation (SD). The category variables were presented as a percentage. The relationship between preservatives and groups was evaluated by Fisher's exact test. Multivariable binary logistic regression was used to evaluate the risk between the positive reactions and groups. A two-tailed p-value < 0.05 was considered statistically significant.

RESULTS

Regarding the age characteristics of the tested groups, the mean age of the students was significantly lower if compared to the control group (p = 0.006) and the one of the occupationally exposed cosmeticians (p = 0.008). No significant differences between the controls and cosmeticians were observed (p = 0.957).

Data on the prevalence of sensitization to the selected cosmetics ingredients in the defined groups are presented in Table 2.

Regarding the ingredients used as preservatives, formaldehyde was identified as a main contact sensitizer. Moreover, the multivariable binary logistic regression analysis demonstrated that the prevalence of contact sensitization to formaldehyde was significantly higher among the groups of occupationally exposed cosmeticians and cosmetology students if compared to the controls (p = 0.005) [OR = 0.290 (95% CI: 0.092-0.916)] – Table 3.

The prevalence of positive skin patch tests to *DMDM hydantoin* was high (11%), with equal rates of sensitization to *quaternium-15, methylisothiazolinone + methylchloroisothiazolinone* and *methyldibromo-glutaronitrile* (9.2%). No significant differences between the studied groups were revealed.

Furthermore, we evaluated the prevalence of co-sensitization to formaldehyde and formaldehyde releasers – Table 4. The statistical analysis revealed a significantly higher prevalence of co-sensitization to DMDM hydantoin and imidazolidinyl urea.

Table 2. Prevalence of sensitization to the selected preservatives in the defined groups

Positive reactions to:	Controls	Cosmetology students	Occupationally exposed cosmeticians	Total	p-value
	N (%)	N (%)	N (%)	N (%)	
Preservatives					
Formaldehyde	2a (4.3)	10b (27.0)	8b (30.8)	20 (18.3)	0.005*
Quaternium-15	3 (6.5)	5 (13.5)	2 (7.7)	10 (9.2)	0.587
DMDM hydantoin	3 (6.5)	6 (16.2)	3 (11.5)	12 (11.0)	0.341
Imidazolidinyl urea	3 (6.5)	1 (2.7)	3 (11.5)	7 (6.4)	0.419
Methylisothiazolinone + Methylchloroisothiazolinone	4 (8.7)	3 (8.1)	3 (11.5)	10 (9.2)	0.837
Iodopropynyl butylcarbamate	2 (4.3)	2 (5.4)	1 (3.8)	5 (4.6)	1.000
Methyldibromoglutaronitrile	4 (8.7)	3 (8.1)	3 (11.5)	10 (9.2)	0.837
Polyaminopropyl biguanide	5 (10.9)	4 (10.8)	0	9 (8.3)	0.213
Paraben mix	1 (2.2)	2 (5.4)	2 (7.7)	5 (4.6)	0.529

Note: *Fisher's Exact Test; Different letters show a statistically significant difference between the proportions (%) in the groups (p < 0.05), and the identical letters indicate that there is no significant difference.

Table 3. Prevalence of sensitization to formaldehyde in the defined groups – multivariable binary logistic regression analysis

Dependent variable	Factors	Negative	Positive	OR	95% CI		p
Formaldehyde	Control group, N	44	1	1,000			
	Students, N	27	10	6,686	1,321	33,842	0,022
	Occupationally exposed cosmeticians, N	18	8	12,200	2,109	70,564	0,005
	Age, Mean (SD)	30,6 (12,4)	24,9 (7,8)	0,935	0,870	1,004	0,063

Table 4. Distribution of the concomitant sensitization to the studied allergens among the patch tested individuals

Allergen	Quaternium 15	Formaldehyde	DMDM hydantoin	Imidazolidinyl urea
Quaternium 15	10	2	2	1
Formaldehyde	2	20	3	2
DMDM hydantoin	2	3	12	5* p < 0,001
Imidazolidinyl urea	1	2	5* p < 0,001	7

Note: to be read as follows: horizontally – subjects sensitized to allergen 1 co-react with allergen 2 in x-number of cases; vertically: subjects sensitized to allergen 2 are also sensitized to allergen 1 in x-number of cases.

One person, previously diagnosed with atopic dermatitis manifested positive reactions to formaldehyde and all the formaldehyde releasers.

DISCUSSION

Contact sensitization is a latent form of delayed type hypersensitivity to low-molecule substances, the so-called haptens, acting as contact allergens. After sensitization, a subsequent exposure exceeding the individual elicitation threshold results in manifestation of clinically observable disease – allergic contact dermatitis [5, 6]. Contact dermatitis is often under recognized.

Contact sensitization is not uncommon. Multicenter epidemiological studies, based on patch tests results, outline the dynamics of its prevalence in different population groups, incl. occupationally exposed, and the pattern of the most frequent and/or relevant contact sensitizers.

A recent study presented the results of patch testing of 22 581 patients with the European Baseline Series, obtained in 53 departments in 13 European countries during 2019 and 2020. Regarding the preservatives, the rate of positive reactions to formaldehyde at 2% aq. was 2.49% vs. 1.59% for 1% concentration; methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) and MI alone up to around 5% positives [7].

Formaldehyde and formaldehyde releasers (FRs) are ubiquitous in the environment and are pointed out as major contact sensitizers. Formaldehyde could be detected in air, foods and many consumer products – cosmetics, household detergents, as well as in industrial products such as metalworking fluids [8]. Occasionally, de novo formation of formaldehyde from oxidation of high purity polyoxyethylene surfactants in cosmetics and detergents was described [9]. In Europe, the use of free formaldehyde in cosmetics is forbidden and has been replaced by FRs. Among the most relevant FRs applied in cosmetics and included as test haptens in our study are: quaternium-15 (forbidden in the EU since 2019) [10], DMDM hydantoin and imidazolidinyl urea. Quaternium-15 still can be found in US cosmetics [11].

The reported prevalence of sensitization to formaldehyde varies in different countries. Higher sensitization frequencies were attributed to the use of the nowadays recommended 2% aq. test preparation, detecting more contact allergies [12]. Reactions to formaldehyde were positive in 5.6% of patients in a recent study [13]. Another recent study reported 2.49% positivity rate to formaldehyde at 2% aq [7].

Our study results indicate a statistically significant relationship between occupational exposure (existing, even shorter as duration among the group of students as well) and prevalence of contact sensitization. We could speculatively contribute these results to a more intensive occupational exposure to potential sources, incl. cosmetics. On the other hand, formaldehyde is a well-known irritant and we could not exclude the possibility that some of our weak positive reactions could have been irritant ones. Concerning the prevalence of sensitization to formaldehyde in the control group our findings are similar to those reported by other authors [13].

Quaternium-15 is the most common sensitizer among the FRs in the United States – sensitization rate 7.7% in general population [14]. In Europe, according to recent studies, the prevalence of positive tests is 0.5-1.3% [7, 13]. Our results on sensitization rates to quaternium-15 are approaching the US reports, with highest positivity among cosmetology students.

Sensitization rates to the widely used formaldehyde releaser *imidazolidinyl* urea are reported to be between 2% and 3% in the United States and between 0.4% and 1% in Europe [7, 11, 13]. According to our findings, the frequency of positive reactions varied from 2.7% among the students to 11.5% among occupationally exposed cosmeticians. A possible explanation could be the longer and more intensive exposure to cosmetics and other imidazolidinyl urea containing consumer products.

The maximum allowed concentrations of *DMDM hydantoin* in EU cosmetics is 0.6%, but it should be noted that the exposure is ubiquitous. A big variety of products, incl. such for professional use may contain the substance – shampoos, conditioners, liquid hand soaps, facial cleansers, moisturizers, makeup removers, styling products, etc., suggesting their possible role for the established in our study high rates of positivity, especially among students and cosmeticians.

Regarding the co-sensitization between the FRs, our results indicate that, with high statistical significance, co-reactivity is most likely to be observed between DMDM hydantoin and imidazolidinyl urea.

Due to the wide use of *methylisothiazolinone* (MI), alone or in combination with *methylchloroisothiazolinone* (MCI) in cosmetics (e.g. hair care, personal hygiene products, facial cleansers), as well as in industrial and household products, it is considered that allergic reactions can occur even in inhalation exposure. Leave-on cosmetics are believed to be the main cause of contact allergy to MI. Rinse-off products, however, through repeated or cumulative use can also cause sensitization. In 2017, in Annex V of Regulation (EC) No 1223/2009 of the European Parliament and of the Council on cosmetic products MI was banned in leave-on products and allowed a maximum of 15 ppm in rinse-off products [15]. According to the last update (28/09/2022) of Annex V, the maximum concentration in ready for use preparation (rinse-off) of a mixture in the ratio 3:1 of MCI and 2-methylisothiazoline is 0.0015% [16].

Recent data from European studies show positivity rates to MI + MCI 3.41% – 6.91% [7, 13]. According to a study from the United States, among the preservatives, most frequent were patch test reactions to MI 0.2% aq (12.2%), and 3.8% for MCI/MI 0.01% aq [14]. Our results demonstrate higher prevalence of sensitization to MCI/MI (0.01% aq), with the group of occupationally exposed cosmeticians being at particular risk. We could suppose the role of the occupational exposure to cosmetics, as well as hidden exposures such as MI emanating from freshly painted walls [17], the use of isothiazolinones in dish-washing and washing-machine liquids, cleaning agents for dental care, and their general presence in multi-purpose household detergents, which may elicit (airborne) allergic contact dermatitis [18].

Methyldibromo glutaronitrile is used in consumer and industrial products and considered to be among the most frequent allergens at the beginning of this century. In 2008, this preservative was banned for use in cosmetics in Europe [19]. A decrease in the prevalence of positive reactions (from 6.0% in 1998-2000 to 2.5% in 2017–2018) was reported by the North American Contact Dermatitis Group, with personal care products being the most common source of exposure (53.2%) [20].

According to Uter et al. (2022), in Europe the prevalence of sensitization to methyldibromo glutaronitrile is still high, with 4.26% at 0.3% pet., and 5.64% at 0.5% pet. [7]. Luis-Gronau et al. (2021), reported an increasing incidence of patients with positive reactions, but not considered as clinically significant [21]. Recently presented results from the Swedish Patch Test Register for the period 2010 – 2017 also demonstrate an increased prevalence of positive reactions from 3.1% in 2010 to 4.6% in 2017 [22]. The positivity rate for Slovenia was recently reported to be 9.2% [13]. The results from the present cross-sectional study indicate some higher prevalence of sensitization if compared with the recent findings cited above. Though significant differences between the defined study groups were not established, the one of occupationally exposed cosmeticians seems to be at higher risk of sensitization.

Iodopropynyl butylcarbamate is a broad-spectrum preservative, used in cosmetics. Its concentrations have been limited by EU legislation (0.02% in rinse-off products, 0.01% in leave-on products, 0.0075% in deodorants/ antiperspirants) because of concerns related to its iodine content and release [23].

Recently presented results from the United States report lowest frequencies of positive reactions to paraben mix (1%) and iodopropynyl butylcarbamate 0.1% pet (0.4%) [14]. Similar results are obtained after the analysis of data collected by the European Surveillance System on Contact Allergies (ESSCA) network between 2009 and 2012 from 12 European countries [24]. Our results also demonstrate that the positivity rate to iodopropynyl butylcarbamate (together with paraben mix) is among the lowest. We should note the fact that positive reaction was observed only in one occupationally exposed cosmetician.

Polyaminopropyl biguanide (CAS Numbers: 32289-58-0 [PHMB HCl]; 27083-27-8 [PHMB HCl]; 28757-47-3 [PHMB]) is the name of the cosmetic ingredient identified by the International Nomenclature of Cosmetic Ingredients (INCI). The chemical name that corresponds to the cosmetic ingredient is polyhexamethylene biguanide hydrochloride (PHMB HCl). Comments on the identity of polyaminopropyl biguanide were received from a chemical supplier, which stated that, effectively, all polyaminopropyl biguanide is PHMB HCl (ie, C6 alkyl chains linked together by biguanide groups), and no propyl biguanide groups are present. The INCI name is an artifact of arbitrarily choosing the middle of the C6 alkyl chains to identify the polymer repeating units of the ingredient [25]. Since until now there is no specific INCI name for PHMB, PAPB is usually used as a synonymous name for PHMB, and hence both cannot be entirely distinguished [26]. Safety Assessment of PHMB as used in cosmetics was performed, and PHMB has been included in the opinion on PAPB by the Scientific Committee on Consumer Safety [27].

Polyaminopropyl biguanide is broad-spectrum antimicrobial agent used as antiseptic in a variety of non-cosmetic products, such as contact lens cleaning solutions, skin disinfectant solutions, incl. such approved by the European Chemical Agency and the US Environmental Protection Agency for use against SARS-CoV-2, and wound dressings [25, 28]. In cosmetics it is used as a preservative, mostly in leave-on products, as well as in rinse-off products (ie, hair dyes and colors, and in skin cleansing products) and lipstick [25, 29]. Polyaminopropyl biguanide is listed in Annex V of the European Commission Regulation No. 1223/2009 as a preservative to be used in all cosmetic products at a maximum concentration of 0.1% [30].

Data about PHMB contact allergy frequency is still limited. Cases of contact sensitization to polyaminopropyl biguanide following exposure to contact lens solution [31], wet wipes [32], foam dressing [33] and non-alcoholic hand rub [34] were reported. A case report suggests that PHMB in skin care products should be considered as a potential cause of, or contributing factor to work-related hand eczema [35].

Sukakul et al. pointed out that cases of allergic contact dermatitis due to PHMB might be missed, since PHMB is not present in baseline patch test series, and performed a retrospective analysis of 1760 patients patch tested from 2016 to 2018 at the Department of Occupational and Environmental Dermatology, Malmö, Sweden. The prevalence of positive patch test reactions to PHMB in this study was 1.1% [26].

According to our findings, the prevalence of positive reactions is much higher and approximately equal for the controls and the group of students (10.9 vs. 10.8%). A puzzling finding is the fact that no positive reactions were observed among cosmeticians. We could speculate the role of the more intensive use of disinfectants during the COVID-19 pandemic, but the sample tested by us is quite small to give a categorical statement.

Parabens are preservatives presented in different personal care products, with possible exposure through foodstuffs as well. The most commonly used parabens are methylparaben, ethylparaben, propylparaben, and butylparaben. In 2019, the American Contact Dermatitis Society chose parabens as the "*nonallergen*" of the year to draw attention to their low rate of associated allergic contact dermatitis [36]. Parabens are regulated in Europe, with a ban on isopropylparaben, isobutylparaben, phenylparaben, benzylparaben and pentylparaben since 2014 and a limit of 0,4% for single ester and 0,8% for mixtures of esters of propylparaben and butylparaben since 2021 [6].

According to a recent study of North American Contact Dermatitis Group, the overall reaction frequency to paraben mix 12% pet was 1% [14]. In Europe, positive reactions to paraben mix are also reported to be very infrequent (0.56%), so, according to some authors, this may argue for a removal from the European Baseline Series [7, 37]. Additionally, Bizjak et al. (2022) reported even lower positivity prevalence – 0.1% [13].

The obtained in the present study results indicate higher prevalence of contact sensitization to paraben mix, especially among the occupationally exposed cosmeticians (7.7%), though without significant differences between the tested groups.

CONCLUSION

This study established comparative high prevalence of contact sensitization to the selected preservatives as ingredients of cosmetic products. Formaldehyde was identified as a main contact sensitizer, with statistically significant relationship between occupational exposure (existing, even shorter as duration among the group of students as well) and prevalence of contact sensitization. Our results indicate that co-reactivity between DMDM hydantoin and imidazolidinyl urea is most likely to be observed. The group of occupationally exposed cosmeticians is at higher risk of sensitization to MCI/MI, methyldibromo glutaronitrile and paraben mix. Nevertheless, one limitation of our study is that, being a cross-sectional in nature and with a relative small number of tested individuals included, it could not be a reliable source to draw conclusions from. Further work focusing on the role of occupational exposure to cosmetics is needed in order to validate the reliability of the present findings. Proper occupational risk information, developing and disseminating of practical tools for workplace risk assessment and management, with complex programs for prevention of occupational skin diseases should be provided.

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