

ORIGINAL ARTICLE

Patch test results of the European baseline series among 1309 patients in Turkey between 2013 and 2019

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Abstract

Background: Prevalence of sensitivity to contact allergens change over time as a result of variations in allergen exposure.

Objectives: The aim of the study was to describe trends in rates of sensitisation to allergens of the European baseline series in Turkey between 2013 and 2019.

Methods: The patch test results of 1309 patients with suspected allergic contact dermatitis (ACD) were analysed retrospectively, and the prevalence of contact allergies to European baseline series allergens was compared with previous data (for 1998-2005).

Results: A total of 534 (40.8%) patients exhibited one or more positive patch test reaction. The five most frequent allergens were nickel sulfate (19.6%), potassium dichromate (6.5%), cobalt chloride (6%), *Myroxylon pereirae* resin (5%), and *p*-phenylenediamine (PPD; 3.7%). Statistically significant increases in the prevalence of sensitisation to methylchloroisothiazolinone/methylisothiazolinone (MCI/MI; $P < .001$), *Myroxylon pereirae* resin ($P < .001$), PPD ($P = .008$), and fragrance mix I ($P = .036$) were observed in the 2013 to 2019 period compared with the 1998 to 2005 period. Conversely, positive reactions to neomycin sulfate ($P = .029$), clioquinol ($P = .031$), and primin ($P = .001$) decreased significantly.

Conclusion: This study provides a comprehensive profile of ACD in Turkey. The remarkable increase in the MI and MCI/MI contact allergy observed underlines the urgent need for regulatory measures to reduce exposure to MI and MCI/MI in Turkey.

KEYWORDS

allergic contact dermatitis, contact sensitivity, European baseline series, patch test, Turkey

1 | INTRODUCTION

Allergic contact dermatitis (ACD) is a common skin disorder caused by delayed hypersensitivity reaction to contact allergens. Severe and chronic contact dermatitis is known to significantly affect patients' quality of life.¹ The prevalence of contact allergy changes over time due to the introduction of new allergens and regulatory measures.^{2,3} Previous studies have estimated the prevalence of contact allergy to be between 12.5% and 40.6% in the general population.⁴ One large

cross-sectional study from Europe reported a 27% prevalence of contact sensitivity.⁵ The aetiology and epidemiology of ACD are constantly evolving along with variations in allergen exposure and the introduction of new potent allergens. Recent studies indicate an increase in the frequency of contact allergy to allergens present in cosmetics/personal care products, and topical treatments.^{6,7} By contrast, the importance of industrial allergens is decreasing in Europe with the introduction of protective and regulatory measures.^{8,9} The prevalence of contact sensitivity to allergens varies among countries

due to variations in allergen exposure, and local traditions and culture. Understanding current contact allergy trends is important for the adoption of preventive measures and to evaluate the effects of previously implemented measures.² In a study conducted at our department between 1998 and 2005 with 1038 consecutively patch tested patients, the most common allergens were nickel sulfate (17.6%), cobalt chloride (5.3%), potassium dichromate (4.6%), neomycin (2.4%), fragrance mix (2.1%), and *Myroxylon pereirae* resin (2.1%).¹⁰ The aim of this study is to evaluate the current spectrum of contact allergies in Ankara, Turkey, 15 years after our previous study, also published in this journal.

2 | METHODS

The study was approved by the Ethical Committee of the Ankara University Faculty of Medicine (no. 02-133-19). A total of 1309 consecutive patients with suspected ACD were patch tested between 2013 and 2019 at the Ankara University School of Medicine Dermatology Department. All patients were tested with the European baseline series (Chemotechnique Diagnostics, Vellinge, Sweden), supplemented with special series and patient-supplied products when indicated.

Patients' age, sex and occupation, duration and localisation of the lesions, and personal or family histories of atopy were recorded. Localisation was classified as hands, face/head/neck, leg, trunk, or generalised.

The allergens were applied with Van der Bend Chambers to the upper back. The patches were removed on Day (D) 2, and reading was performed after 30 minutes. A final reading and interpretation was performed on D4. The results were evaluated using the scoring system recommended by the ICDRG.¹¹ A reaction of + or greater with a crescendo or plateau pattern on D4 was considered as positive. Reactions with a decrescendo pattern were considered as irritant. Irritant, doubtful, and negative responses were recorded as negative.

Several modifications were made to the European baseline series during the study period: (a) the concentration of formaldehyde was increased to 2% aq., and the concentration of methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) was raised to 0.02% aq.; (b) four new allergens were added, namely, MI 0.2% aq., textile dye mix 6.6% pet., propolis 10% pet., and 2-hydroxyethyl methacrylate (2-HEMA) 2% pet.; (c) the following allergens were removed: primin 0.01% pet. and clioquinol 5% pet. Test results with the European baseline series applicable in the study period were included in the analysis.

The Statistical Package for Social Sciences (SPSS) version 15.0 (IBM, New York, New York) was used for data analysis. Categorical variables were expressed as percentages with 95% confidence interval (CI) and associations among categorical variables were assessed using the χ^2 test, or Fisher exact test if expected values in more than one cell were lower than 5. Normally distributed continuous scale variables were expressed as mean and standard deviation. *P* values lower than .05 were considered statistically significant.

3 | RESULTS

3.1 | Patient demographics

Demographic data for our patients are displayed according to the MOAHLFAP (male, occupational, atopic, hand, leg, foot, age > 40, percent positive) index in Table 1.¹² Tests were conducted on 1309 consecutively patch tested patients: 764 (58.4%) women and 545 (41.6%) men. Patients' mean age was 40.9 (SD 16.8) years (median 41 years, range 3-87 years), and 611 (46.7%) were under 40 years of age. The largest occupational groups were housewives, office workers, and health-care personnel, and most of our patients had a medium socioeconomic status.

A total of 210 (16%) patients reported a personal history of atopy, including atopic dermatitis, allergic rhinitis, and asthma, while a family history of atopy was present in 155 patients. The hands were the most common primary site of dermatitis (49.3%), followed by the face/head/neck (22.5%), and the legs (12.4%). Mean duration of symptoms was 35.26 (SD 51.7) months (median 12, range 1-240).

3.2 | Patch test results

A total of 534 (40.8%) patients exhibited one or more positive patch test reaction; 296 patients (22.6%) were positive to only one allergen, 146 (11.2%) were positive to two, and 91 (7.0%) were positive to three or more. The five most frequently identified allergens and their respective prevalences were nickel sulfate (*n*=256, 19.6%), potassium dichromate (*n*=85, 6.5%), cobalt chloride (*n*=79, 6%), *M. pereirae* resin (*n*=65, 5%), and *p*-phenylenediamine (PPD; *n*=48, 3.7%). The distribution of reaction intensities for each European baseline series allergen tested from 2013 to 2019 is presented in Table 2.

The prevalence of contact sensitivity was 42.3% in women and 37.8% in men. There was no statistically significant association between patch test positivity and gender (*P* > .05). Contact sensitivity to potassium dichromate, thiuram mix, *M. pereirae* resin, mercaptobenzothiazole

TABLE 1 MOAHLFAP characteristics of patients

Characteristics	n (%)
Male	545 (41.6)
Occupational	71 (5.4)
Atopy	210 (16)
Hay fever ^a	133 (10.2)
Atopic dermatitis	66 (5)
Asthma ^a	53 (4)
Hand	645 (49.3)
Leg	162 (12.4)
Face	294 (22.5)
Age ≥ 40 years	698 (53.3)
Positivity share ^b	534 (40.8)

^aNot part of MOAHLFAP.

^bAt least one positive reaction to a baseline series allergen.

TABLE 2 Intensity of reactions for each European baseline series allergen

	Number of positive reactions (n)	+++ n (%)	++ n (%)	+ n (%)
Potassium dichromate	85	16 (18.8)	51 (60)	18 (21.2)
p-Phenylenediamine	48	19 (39.6)	19 (39.6)	10 (20.8)
Thiuram mix	38	11 (28.9)	16 (42.2)	11 (28.9)
Neomycin sulfate	16	—	10 (62.5)	6 (37.5)
Cobalt chloride	79	15 (19)	41 (51.9)	23 (29.1)
Benzocaine	10	—	8 (80)	2 (20)
Nickel sulfate	256	74 (28.9)	151 (60)	31 (12.1)
Clioquinol	3	—	3 (100)	—
Colophonium	24	4 (16.7)	16 (66.7)	3 (12.5)
Paraben mix	10	2 (20)	6 (60)	2 (20)
N-isopropyl-N'-phenyl-p-phenylenediamine	7	—	5 (71.4)	2 (28.6)
Lanolin alcohol	8	—	5 (62.5)	3 (37.5)
Mercapto mix	8	1 (12.5)	4 (50)	3 (37.5)
Epoxy resin	10	1 (10)	8 (80)	1 (10)
Myroxylon pereirae resin	65	2 (3.1)	40 (61.5)	23 (35.4)
p-tert-Butylphenol formaldehyde resin	14	1 (7.1)	9 (64.3)	4 (28.6)
2-Mercaptobenzothiazole	7	2 (28.6)	2 (28.6)	3 (42.8)
Formaldehyde	15	2 (13.3)	8 (53.3)	5 (33.4)
Fragrance mix I	47	2 (4.3)	32 (68)	13 (27.7)
Sesquiterpene lactone mix	6	—	6 (100)	—
Quaternium-15	5	—	3 (60)	2 (40)
Primin	3	—	2 (66.6)	1 (33.4)
Methylchloroisothiazolinone/methylisothiazolinone	40	6 (15)	22 (55)	12 (30)
Budesonide	7	1 (14.3)	6 (85.7)	—
Tixocortol-21-pivalate	2	—	2 (100)	—
Methyldibromo glutaronitrile	41	2 (4.8)	22 (53.7)	17 (41.5)
Fragrance mix II	28	2 (7.1)	21 (75)	5 (17.9)
Hydroxyisohexyl 3-cyclohexene carboxaldehyde	12	1 (8.4)	8 (66.6)	3 (25)
Methylisothiazolinone	23	4 (17.4)	11 (47.8)	8 (34.8)
Textile dye mix	20	7 (35)	8 (40)	5 (25)
2-Hydroxyethyl methacrylate	4	—	3 (75)	1 (25)
Propolis	0	—	—	—

(MBT), and formaldehyde was significantly more frequent in male patients ($P < .05$). However, women exhibited significantly more frequent contact sensitivity to nickel sulfate ($P < .001$).

Contact sensitivity to allergens was observed in 38.3% ($n = 267$) of the patients over 40 years of age and in 42.9% ($n = 262$) of those under 40 years of age. No statistically significant difference was observed between patch test positivity in terms of age groups ($P > .05$). Sensitisation to potassium dichromate, *M. pereirae* resin, MBT, formaldehyde, fragrance mix I, and methyldibromo glutaronitrile (MDBGN) was significantly more common in patients over 40 years of age ($P < .05$), whereas sensitivity to PPD, cobalt chloride, nickel

sulfate, and textile dye mix was significantly higher in patients under 40 years of age ($P < .05$).

A positive reaction to one or more allergens was detected in 42.4% ($n = 89$) of the patients with a personal history of atopy and 30.3% ($n = 20$) of patients with atopic dermatitis. There was no statistically significant relationship between patch test positivity and atopy/atopic dermatitis ($P > .05$). There was also no statistically significant relationship between the reaction to major allergen groups (metals, fragrances, preservatives, rubber additives, topical treatments) and atopy/atopic dermatitis. The most common positive allergens in patients with atopic dermatitis were nickel sulfate, MCI/MI, *M.*

TABLE 3 Distribution of positive patch test reactions in terms of gender, age, and atopy

	Gender			Age			Atopy		
	Male (N = 545), n (%)	Female (N = 764), n (%)	P-value	<40 years (N = 611), n (%)	≥40 years (N = 698), n (%)	P-value	Atopic patients (N = 210), n (%)	Nonatopics (N = 1099), n (%)	P-value
Potassium dichromate	56 (10.3)	29 (3.8)	<.001	29 (4.7)	56 (8.0)	.016	10 (4.8)	75 (6.8)	.27
p-Phenylenediamine	21 (3.9)	27 (3.5)	.76	33 (5.4)	15 (2.1)	.002	8 (3.8)	40 (3.6)	.90
Thiuram mix	29 (5.3)	9 (1.2)	<.001	13 (2.1)	25 (3.6)	.12	3 (1.4)	35 (3.2)	.17
Neomycin sulfate	7 (1.3)	9 (1.2)	.89	7 (1.1)	9 (1.3)	.81	2 (1.0)	14 (1.3)	.70
Cobalt chloride	30 (5.5)	49 (6.4)	.50	48 (7.9)	31 (4.4)	.010	16 (7.6)	63 (5.7)	.29
Benzocaine	5 (0.9)	5 (0.7)	.59	6 (1.0)	4 (0.6)	.40	1 (0.5)	9 (0.8)	.601
Nickel sulfate	52 (9.5)	204 (26.7)	<.001	148 (24.2)	108 (15.5)	<.001	51 (24.3)	205 (18.7)	.059
Clioquinol	1 (0.2)	2 (0.3)	>.99	0 (0)	3 (0.4)	.25	0 (0)	3 (0.3)	>.99
Colophonium	14 (2.6)	10 (1.3)	.094	10 (1.6)	14 (2.0)	.62	3 (1.4)	21 (1.9)	.63
Paraben mix	4 (0.7)	6 (0.8)	.92	5 (0.8)	5 (0.7)	.83	3 (1.4)	7 (0.69)	.23
N-isopropyl-N'-phenyl- p-phenylenediamine	4 (0.7)	3 (0.4)	.46	5 (0.8)	2 (0.3)	.19	1 (0.5)	6 (0.5)	.90
Lanolin alcohol	3 (0.6)	5 (0.7)	.81	2 (0.3)	6 (0.9)	.30	1 (0.5)	7 (0.6)	.78
Mercapto mix	6 (1.1)	2 (0.3)	.073	3 (0.5)	5 (0.7)	.73	1 (0.5)	7 (0.6)	.78
Epoxy resin	5 (0.9)	5 (0.7)	.59	4 (0.7)	6 (0.9)	.67	0 (0)	10 (0.9)	.17
Myroxylon pereirae resin	42 (7.7)	23 (3.0)	<.001	15 (2.5)	50 (7.2)	<.001	14 (6.7)	51 (4.6)	.22
p-tert-Butylphenol formaldehyde resin	4 (0.7)	10 (1.3)	0.32	6 (1.0)	8 (1.1)	.77	5 (2.4)	9 (0.8)	.044
2-Mercaptobenzothiazole	6 (1.1)	1 (0.1)	.023	0 (0)	7 (1.0)	.017	1 (0.5)	6 (0.5)	.90
Formaldehyde	10 (1.8)	5 (0.7)	.048	3 (0.5)	12 (1.7)	.037	1 (0.5)	14 (1.3)	.32
Fragrance mix I	25 (4.6)	22 (2.9)	.10	14 (2.3)	33 (4.7)	.018	12 (5.7)	35 (3.2)	.071
Sesquiterpene lactone mix	2 (0.4)	4 (0.5)	>.99	1 (0.2)	5 (0.7)	.22	1 (0.5)	5 (0.5)	.97
Quaternium-15	4 (0.7)	1 (0.1)	.17	1 (0.2)	4 (0.6)	.38	0 (0)	5 (0.5)	>.99
Primin	2 (0.4)	1 (0.1)	.57	0 (0)	3 (0.4)	.25	0 (0)	3 (0.3)	>.99
Methylchloroisothiazolinone/ methylisothiazolinone	19 (3.5)	21 (2.7)	.45	22 (3.6)	18 (2.6)	.28	11 (5.2)	29 (2.6)	.045
Budesonide	3 (0.6)	4 (0.5)	>.99	3 (0.5)	4 (0.6)	>.99	4 (1.9)	3 (0.3)	.003
Tixocortol-21-pivalate	2 (0.4)	0 (0)	.17	1 (0.2)	1 (0.1)	>.99	0 (0)	2 (0.2)	>.99
Methyldibromo glutaronitrile	22 (4.0)	19 (2.5)	.11	12 (2.0)	29 (4.2)	.023	5 (2.4)	36 (3.3)	.50
Fragrance mix II	16 (2.9)	12 (1.6)	.092	9 (1.5)	19 (2.7)	.12	4 (1.9)	24 (2.2)	.79
Hydroxyisohexyl 3-cyclohexene carboxaldehyde	8 (1.5)	4 (0.5)	.077	6 (1.0)	6 (0.9)	.82	2 (1.0)	10 (0.9)	.95
Methylisothiazolinone	12 (3.6)	11 (2.4)	.30	12 (3.2)	11 (2.6)	.60	7 (5.1)	16 (2.4)	.086
Textile dye mix	12 (4.6)	8 (2.3)	.12	15 (5.3)	5 (1.5)	.009	17 (3.4)	3 (2.8)	.78
2-Hydroxyethyl methacrylate	2 (7.1)	2 (5.9)	.84	1 (2.8)	3 (11.5)	.17	2 (4.7)	2 (2.5)	.39
Propolis	—	—	—	—	—	—	—	—	—

Note: Significant results ($P < .05$) are shown in bold.

pereirae resin, and fragrance mix I. Distributions of positive patch test reactions in terms of gender, age, and atopy are shown in Table 3.

Occupation-related dermatitis was detected in 5.4% ($n = 71$) of patients. The occupations most commonly associated with occupational contact dermatitis were construction work ($n = 25$, 1.9%), hair-dressing ($n = 13$, 0.9%), and health care ($n = 7$, 0.5%). The allergens statistically significantly associated with occupational dermatitis were potassium dichromate, PPD, thiuram mix, cobalt chloride,

colophonium, mercapto mix, epoxy resin, and MBT ($P < .001$). Occupational contact dermatitis was detected in 2.7% of female patients and in 9.2% of male patients, the difference being statistically significant ($P < .001$). No significant difference was observed in occupational dermatitis shares between the age groups (5.9% in patients under 40 years of age, and 5% in those ≥ 40 ; $P > .05$). The hands were statistically significantly the most frequent localisation in patients with occupational contact dermatitis ($P < .001$).

TABLE 4 Comparison of the frequencies of positive patch test reactions to the European baseline series allergens in the periods from 1998 to 2005 and from 2013 to 2019

Allergen	Vehicle	Number of positive reactions/total number of tested patients 2013-2019	2013-2019 prevalence, % (95% CI)	Number of positive reactions/total number of tested patients 1998-2005	1998-2005 prevalence, % (95% CI)	P value
Potassium dichromate	0.5% pet.	85/1309	6.5 (5.2-8.0)	48/1038	4.6 (3.4-6.0)	.052
p-Phenylenediamine	1.0% pet.	48/1309	3.7 (2.7-4.8)	19/1038	1.8 (1.1-2.8)	.008
Thiuram mix	1.0% pet.	38/1309	2.9 (2.1-4.0)	21/1038	2.0 (1.2-3.0)	.18
Neomycin sulfate	20.0% pet.	16/1309	1.2 (0.7-2.0)	25/1038	2.4 (1.5-3.5)	.029
Cobalt chloride	1.0% pet.	79/1309	6 (4.8-7.5)	56/1038	5.3 (4.1-6.9)	.51
Benzocaine ^a	10.0% pet.	10/1309	0.8 (0.4-1.4)	8/1038	0.7 (0.3-1.5)	.99
Nickel sulfate	5.0% pet.	256/1309	19.6 (17.4-21.8)	183/1038	17.6 (15.3-20.0)	.23
Clioquinol	5.0% pet.	3/1247	0.2 (0-0.7)	9/1038	0.8 (0.3-1.6)	.031
Colophonium	20.0% pet.	24/1309	1.8 (1.2-2.7)	11/1038	1.0 (0.5-1.8)	.13
Paraben mix	16.0% pet.	10/1309	0.8 (0.4-1.4)	3/1038	0.2 (0.5-0.8)	.12
N-isopropyl-N-phenyl-4-phenylenediamine	0.1% pet.	7/1309	0.5 (0.2-1.1)	8/1038	0.7 (0.3-1.5)	.48
Lanolin alcohol	30.0% pet.	8/1309	0.6 (0.3-1.2)	5/1038	0.4 (0.1-1.1)	.68
Mercapto mix	2.0% pet.	8/1309	0.6 (0.3-1.2)	3/1038	0.2 (0.5-0.8)	.26
Epoxy resin	1.0% pet.	10/1309	0.8 (0.4-1.4)	7/1038	0.6 (0.2-1.3)	.37
Myroxylon pereiarae resin	25.0% pet.	65/1309	5 (3.9-6.3)	22/1038	2.1 (1.3-3.1)	<.001
p-tert-Butylphenol formaldehyde resin	1.0% pet.	14/1309	1.1 (0.6-1.8)	14/1038	1.3 (0.7-2.2)	.54
2-Mercaptobenzothiazole	2.0% pet.	7/1309	0.5 (0.2-1.1)	8/1038	0.7 (0.3-1.5)	.48
Formaldehyde ^a	2.0% aq.	15/1309	1.1 (0.6-1.9)	13/1038	1.2 (0.6-2.1)	.81
Fragrance mix I	8.0% pet.	47/1309	3.6 (2.6-4.7)	22/1038	2.1 (1.3-3.1)	.036
Sesquiterpene lactone mix	0.1% pet.	6/1309	0.5 (0.2-1.0)	—	—	—
Quaternium-15	1.0% pet.	5/1309	0.4 (0.1-0.9)	9/1038	0.8 (0.3-1.6)	.13
Primin	0.01% pet.	3/1247	0.2 (0-0.7)	15/1038	1.4 (0.8-2.3)	.001
Methylchloroisothiazolinone/methylisothiazolinone (MCI/MI) ^a	0.02% aq.	40/1309	3.1 (2.2-4.1)	1/1038	0.09 (0-0.5)	<.001
Budesonide	0.01% pet.	7/1309	0.5 (0.2-1.1)	—	—	—
Tixocortol-21-pivalate	0.1% pet.	2/1309	0.2 (0-0.6)	—	—	—
Methyldibromo glutaronitrile	0.5% pet.	41/1309	3.1 (2.3-4.2)	—	—	—
Fragrance mix II	14.0% pet.	28/1309	2.1 (1.4-3.1)	—	—	—
Hydroxyisohexyl 3-cyclohexene carboxaldehyde	5.0% pet.	12/1309	0.9 (0.5-1.6)	—	—	—
Methylisothiazolinone	0.1% aq.	23/800	2.9 (1.8-4.3)	—	—	—
Textile dye mix	6.6% pet.	20/610	3.3 (2.0-5.0)	—	—	—
2-Hydroxyethyl methacrylate	2.0% pet.	4/62	6.5 (1.8-15.7)	—	—	—
Propolis	10.0% pet.	0/62	0 (0-0)	—	—	—

Note: Significant results ($P < .05$) are shown in bold.

Abbreviations: aq., aqueous; CI, confidence interval; pet., petrolatum.

^aBenzocaine 5.0% pet., formaldehyde 1.0% aq., and MCI/MI 0.01% aq. were tested in the 1998 to 2005 period.

3.3 | Comparison of prevalences for allergens between 2013-2019 and 1998-2005

A comparison of the frequencies of positive patch test reactions to the European baseline series allergens in the period from 1998 to 2005 and 2013 to 2019 is shown in Table 4. Statistically significant

increases in the prevalence rates of sensitisation to MCI/MI ($P < .001$), *M. pereiarae* resin ($P < .001$), PPD ($P = .008$), and fragrance mix I ($P = .036$) were observed in the period from 2013 to 2019 compared with 1998 to 2005. By contrast, positive reactions to neomycin sulfate ($P = .029$), clioquinol ($P = .031$), and primin ($P = .001$) decreased significantly.

Nine new allergens were added to the European baseline series after the 1998 to 2005 period. The share of positive reactions to the new allergens, in descending order of frequency, were textile dye mix (3.2%), MDBGN (3.1%), MI (2.9%), fragrance mix II (2.1%), hydroxyisohexyl 3-cyclohexene carboxaldehyde (0.9%), budesonide (0.5%), and tixocortol-21-pivalate (0.2%). Although tested on only 62 patients, 2-HEMA exhibited a 6.5% positivity rate, whereas no positive reactions were observed to propolis. The prevalence of occupational dermatitis was similar between the 2013 to 2019 and 1998 to 2005 periods (5.4% vs 5.6%, respectively).

4 | DISCUSSION

The present study reports the results of 1309 patients consecutively patch tested with the European baseline series at our department between 2013 and 2019, and the results are compared with those of a previous study conducted in our department involving 1038 patients between 1998 and 2005.

Nickel sulfate was the most commonly identified positive allergen in both periods, with similar prevalences (19.6% in 2013-2019 vs 17.6% in 1998-2005). The increase of nickel contact allergy over recent decades has mainly been explained by ear piercing in combination with the use of imitation jewellery and the frequent wearing of blue jeans with metal buttons and zippers.^{13,14} Nickel sensitivity can also be acquired by occupational exposure. Employment in occupations such as nickel plating, hard metal work, and mining may also be a risk factor for nickel sensitivity in male patients. Legislation was passed in the European Union (EU) in 2000 that aimed at reducing nickel release in consumer products.^{15,16} Despite a slightly downward trend, nickel is still the most common cause of contact allergy among both children and adults in the general population.¹⁷ Because during the study period there were still no regulations in Turkey limiting the levels of leachable nickel in items that have prolonged skin contact, nickel sulfate has retained its position as the most common positive allergen in the European baseline series, with an even higher prevalence (19.6%). In this study, and also in the period from 1998 to 2005, nickel sensitivity was statistically significantly more common in women and in patients under 40 years of age. These results may be attributed to the custom of ear piercing in girls at very young ages in Turkey.

Cobalt was the second most common positive allergen in our patients. Cobalt sensitivity frequently accompanies nickel sensitivity in women and chromate sensitivity in men.¹⁸ In this study, 49 patients (3.7%) exhibited concomitant sensitivity to nickel sulfate and cobalt, and 22 (1.6%) exhibited concomitant sensitivity to potassium dichromate and cobalt chloride. The prevalence of chromium sensitisation increases with age, and may be related to cement or leather exposure.^{19,20} In this study, chromate sensitivity was statistically significantly associated with male gender ($P = .35$) and occupational dermatitis ($P < .001$). Recent studies have revealed a decrease in the rate of contact sensitivity to chromium in EU countries following the implementation of EU regulations on the release of chromium(VI) from both cement and leather products.²¹ However, due to the

absence of regulations in the study period, chromate maintained its importance as a major occupational antigen, and chromate sensitivity seems to have become more common in recent years (6.5% in 2013-2019 vs 4.6% in 1998-2005). In Turkey, according to Regulation of Chemicals (published on 23 June 2017) nickel release is restricted to 0.5 $\mu\text{g}/\text{cm}^2/\text{week}$ in products intended to come into direct contact with the skin. The chromium content of cement is limited to 2 ppm and the content of chromium in leather products that come into contact with the skin is limited to <3 ppm.²² The regulation will enter full force at the end of 2021 and the positive effects on the prevalence of metal sensitivity will be seen in the years to come.

Fragrances constitute the second most frequent cause of ACD.²³ The estimated prevalences of contact allergy to fragrance substances are 6% to 14% in patients with contact dermatitis, and 1.7% to 4.1% in the general population.²⁴⁻²⁷ Fragrance allergy tends to occur earlier in women compared with men because of a higher use of cosmetic products, and the prevalence increases at older ages due to age-related poor skin barrier function and increased use of topical medications and emollients.²⁸⁻³⁰ Prevalences of contact allergy to fragrance allergens in this study were 5% for *M. pereirae* resin, 3.6% for fragrance mix I, 2.1% for fragrance mix II, and lower than 1% for hydroxyisohexyl 3-cyclohexene carboxaldehyde. We observed marked increases in contact sensitivity to fragrance allergens between 2013 and 2019 compared with the period from 1998 to 2005 (5% vs 2.1% for *M. pereirae* resin, and 3.6% vs 2.1% for fragrance mix I). Sensitivity rates of *M. pereirae* resin and fragrance mix I were statistically more common in patients over 40 years of age.

PPD is a colouring agent often used in hair dyes and body painting, such as black henna tattoos. It is also a well-known cause of occupational contact dermatitis in hairdressers and beauticians. In this study, PPD was the fifth most common allergen, with a 3.7% sensitisation prevalence, and also an important cause of occupational dermatitis. In addition to occupational exposure, the application of temporary tattoos containing higher concentrations of PPD is a major cause of sensitivity in children and adolescents. Our results reveal a 2-fold increase in PPD contact allergy, from 1.8% in the 1998 to 2005 period to 3.7% in 2013 to 2019, and the sensitivity rate was significantly higher in patients under 40 years of age. Textile dye mix is a new allergen in the European baseline series, with the reported frequency of contact allergy varying from 2.1% to 6.9% in different centres in Europe.³¹ A total of 20 (3.2%) patients in this study exhibited contact sensitivity to textile dye mix, and simultaneous reactivity to PPD was observed in 75% of textile dye mix-positive patients. A high share of positive reactions to textile dye mix may be due to cross-reactivity to PPD.

Preservatives are well-known skin sensitisers and represent one of the main causes of contact allergy. Isothiazolinones are currently the most common cause of contact allergy to preservatives. Reported prevalence rates of sensitisation to MI and MCI/MI in Europe are 4.5% and 4.1%, respectively. In the United States, sensitisation prevalence has increased to 6.4% to MI and 10.9% to MCI/MI.^{32,33} MI began to be added to cosmetic products in 2005, and started to be tested in the European baseline series in the 2013 to 2014 cycle.

Along with the increased use of MI in lieu of MDBGN, formaldehyde-releasing preservatives, and parabens, the prevalence of contact allergy to MI has increased alarmingly in Europe and North America.⁹ MI is regarded as the most important preservative in terms of sensitisation in this century, and was also awarded the title of “contact allergen of the year” in 2013 by the American Contact Dermatitis Society.³⁴ In a previous study conducted at our department between 1998 and 2005, MCI/MI sensitivity was observed in only one patient (0.09%), and the sensitivity rates of other preservatives (paraben mix, formaldehyde, and quaternium-15) were all lower than 1%.¹⁰ The results of another study from Turkey involving 1256 patients between 1996 and 2006 also revealed low sensitisation prevalence rates for preservatives. The prevalence of positive reaction to MDBGN was 1%, and the sensitisation rates of formaldehyde, formaldehyde releasers, and MCI/MI were all below 1%.³⁵

This study shows a marked increase in the prevalence of sensitisation to MCI/MI, rising to 3.1% over a period of 10 years. The prevalences of sensitivity to MDBGN and MI, which were not tested in our previous study, were 3.1% and 2.9% respectively. In total, 12 of 23 patients who reacted to MI also reacted to MCI/MI. Another study conducted in Turkey between 2016 and 2018 reported a much higher share of sensitivity to MCI/MI (6.1%) and MI (8%).³⁶ Parabens are some of the most commonly used preservatives in personal care products, and are known to be far less sensitising than most of the newer preservatives.³⁷ The prevalences of contact allergy to paraben mix and quaternium-15, respectively, have remained stable over the years in our patients, with < 1% in both study periods. The prevalence of formaldehyde sensitivity has also not changed, with a sensitisation frequency of approximately 1%. The most remarkable finding of our study is the significantly higher shares of sensitivity to MCI/MI, MI, and MDBGN. The marked increase in the rate of MCI/MI sensitivity from 2013 to 2019 indicates that in parallel with the worldwide epidemic, sensitivity to MCI/MI is currently also a major public health problem in Turkey. The change of the MCI/MI test concentration from 0.01% aq. between 1998 and 2005 to 0.02% aq. between 2103 and 2019 could have also contributed to the increase in sensitivity, either as a more sensitive diagnostic instrument or due to more false-positive reactions. Following the MDBGN contact allergy epidemic, the EU initiated a ban on MDBGN in leave-on products in 2004, and in rinse-off products in 2008. However, according to recent studies, the sensitisation frequency to MDBGN in Europe is still approximately 2.5%–2.8%.³⁸ Turkish cosmetics regulation allows the use of MCI/MI in rinse-off products with a maximum concentration of 15 ppm and MI is allowed to be used in concentrations up to 100 ppm. MDBGN is not allowed to be used as a preservative in cosmetics. MDBGN has been banned from cosmetics since 2015. Although MDBGN is no longer present in cosmetics, MCI/MI and MI are found in the majority of rinse-off personal care products, such as liquid soaps, shampoos, conditioners, and body washes.³⁹ The high rate of MDBGN sensitivity in this study may be due to previous contact with MDBGN as well as the 0.5% test concentration of MDBGN which may cause false-positive reactions.

Sensitivity prevalences for rubber antigens (thiuram mix, mercapto mix, and MBT) in this study were not significantly different from those between 1998 and 2005. Occupational thiuram allergy may well develop due to rubber glove use, and allergic reactions to thiuram mix were most commonly seen in health-care personnel and construction workers in this study. As much as 19 (22.4%) of the 85 patients with chromate sensitivity also exhibited concomitant thiuram mix patch test positivity, and 89.4% of these patients were construction workers. Wearing rubber gloves on eczematous skin may cause secondary sensitisation to thiurams due to increased penetration of rubber antigens.

Neomycin is a stable, water-soluble antibiotic widely used in topical formulations to prevent or treat superficial infections. Although it was once one of the most important allergens, sensitivity prevalences have decreased in recent years.^{40–42} Our results indicate that, in parallel with the decrease of sensitivity in Europe and North America, neomycin sensitivity has also been decreasing in Turkey (1.2% in 2013–2019 vs 2.4% in 1998–2005). This decreasing trend was most likely influenced by increased use of topical antibiotics containing fusidic acid or mupirocin.

Acrylates have long been known as occupational allergens for dental technicians. However, the importance of HEMA as a contact allergen has increased considerably in recent years due to its use in nail cosmetics. Acrylate sensitivity is currently both an occupational problem in beauticians/nail technicians and also a consumer problem.^{43–45} 2-HEMA was only recently added to the European baseline series. Although it was tested in only 62 patients in this study, its share of contact allergy was 6.5%. Of the four 2-HEMA-sensitive patients, three were cosmeticians and one was a dental technician. The sensitivities were occupationally related and clinically relevant in all cases.

In conclusion, comparison between 2013 to 2019 and 1998 to 2005 revealed a significant increase in the frequency of sensitisation to fragrance allergens and preservatives over the years. The remarkable rise in the frequency of MI and MCI/MI contact allergies in particular emphasises the need for regulatory measures to be adopted in Turkey.

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AUTHOR CONTRIBUTIONS

Ayse Boyvat: Conceptualization; methodology; project administration; supervision; writing-review and editing. **Incilay Kalay Yildizhan:** Data curation; investigation; writing-original draft; writing-review and editing.

CONFLICTS OF INTEREST

None declared.

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