

Contact Sensitivity to Preservatives in Singapore: Frequency of Sensitization to 11 Common Preservatives 2006–2011

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Background: Preservatives are indispensable agents used to prevent bacterial and fungal contamination of cosmetics, personal care products, domestic preparations, and industrial products.

Objective: We evaluated patch-test data at the National Skin Centre, Singapore, from 2006 to 2011 to identify the trends in preservative contact allergies.

Methods: All patients with suspected contact dermatitis were patch tested to 4 preservatives within the modified European standard series. Patients were also tested with 7 preservatives from our special series if clinically indicated.

Results: Three thousand one hundred seventy-seven patients were tested to preservatives in the standard series. Sensitization frequencies were all greater than 1%: parabens (2.58%), methylchloroisothiazolinone/methylisothiazolinone (1.75%), quaternium 15 (1.43%), and methyldibromoglutaronitrile (1.2%). There was no change in trends in sensitization frequencies from 2006 to 2011, with no increase in sensitization frequency to methylchloroisothiazolinone/methylisothiazolinone. The sensitization frequencies for methyldibromoglutaronitrile/phenoxyethanol and diazolidinylurea were 2.03% and 1.37%, respectively, and remained less than 1% for bronopol, imidazolidinyl urea, and 2-phenoxyethanol. A rate of 0% was seen for 1,3-dimethylol-5,5-dimethyl hydantoin and formaldehyde; 9.4% of positive patch-test results became positive only at day 7.

Conclusions: Preservatives are common causes of allergic contact dermatitis. This should be considered when introducing new preservatives into the market. Day 7 readings are important to detect late reactions.

Preservatives are added into cosmetics and household, pharmaceutical, and industrial products to prevent contamination by microorganisms and prolong the shelf life of a product. There are several epidemiology reports of patch-test reactions to preservatives including time trends over the past decade from various countries including America,¹ Europe,^{2,3} Finland,⁴ Denmark,⁵ United Kingdom,⁶ Turkey,⁷ Israel,⁸ and Asia.^{9–11} In this study, we set out to investigate the prevalence of preservative allergy in Singapore over a 6-year period.

MATERIALS AND METHODS

A retrospective analysis of data of patients who were patch tested for suspected allergic contact dermatitis at the National Skin Center, Singapore, between January 2006 and December 2011 was performed.

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All patients were tested to the baseline modified European standard series, which included the following 4 preservatives: paraben mix, methylchloroisothiazolinone/methylisothiazolinone (MCI/MI; 5-chloro-2-methyl-4-isothiazolin-3-one/2-methyl-2H-isothiazol-3-one), quaternium 15, and methyldibromoglutaronitrile (1,2-dibromo-2,4-dicyanobutane). Where clinically indicated, patients were also tested to an additional 7 preservatives present in our special series: 2-phenoxyethanol, bronopol, diazolidinylurea, methyldibromoglutaronitrile + phenoxyethanol, imidazolidinylurea, formaldehyde, and 1,3-dimethylol-5,5-dimethyl hydantoin (DMDM hydantoin). These additional preservatives are found in our cosmetic, hairdressing, oil and cooling fluid, dental and shoe series. Of note, formaldehyde was included in our standard series from January 2009. It is also important to note that quaternium 15, diazolidinylurea, imidazolidinylurea, DMDM hydantoin, and bronopol are formaldehyde-releasing preservatives.

Patch testing was performed using Finn chambers on Scanpor tape. Test materials were provided by Chemotechnique Diagnostics, Sweden. Test concentrations used are shown in Table 1.

Patch-test results were analyzed over the total period. Frequencies of sensitization (as percentage of patients tested) were calculated both as crude proportions and as proportions standardized for sex and age. Time trend analyses were also performed based on annual frequencies of sensitization standardized for sex.

TABLE 1. Patch-Test Concentrations Used (Test Materials Provided by Chemotechnique Diagnostics, Sweden)

Preservative	Concentration
Paraben mix	16% Petrolatum
MCI/MI	0.01% Aqueous
Quaternium 15	1% Petrolatum
MDBGN	0.5% Petrolatum
MDBGN + phenoxyethanol	1.5% Petrolatum
Diazolidinylurea	2% Petrolatum
Bronopol	0.25% Petrolatum
Imidazolidinylurea	2% Petrolatum
2-Phenoxyethanol	1% Petrolatum
DMDM hydantoin	2% Aqueous
Formaldehyde	1% Aqueous

MDBGN indicates methyldibromoglutaronitrile.

For each patient, a computerized data sheet was filled in at the time of patch testing and stored in the contact dermatitis database. A semiquantitative reading of the tests was done on days 3 and 7 according to the recommendation from the International Contact Dermatitis Research Group.¹² Reading of the tests results was performed by one of the dermatologists trained in this subspecialty. At day 3 and/or 7, 1+, 2+, and 3+ reading was interpreted as a positive response. To prevent overinterpretation of weak irritant reactions, doubtful results of erythema without induration and patients with angry back syndrome were excluded.

RESULTS

Three thousand one hundred seventy-seven patients, 44% men (1393) and 56% women (1784), with age range of 4 to 89 years and mean age of 38 years, were patch tested between January 2006 and December 2011. The racial distribution among Chinese, Malay, Indian, and others is shown in Table 2. Malays were underrepresented in our test population.

The frequencies of sensitization to the tested preservatives are shown in Table 3. Because of selective testing with special series, we are unable to compare the frequencies of sensitization found in preservatives of the standard series and in preservatives tested in special series directly. Sensitization frequencies for all 4 preservatives in the standard series were greater than 1% (1.2%–2.58%) and consistently higher in females. For the preservatives in the special series, sensitization frequencies were greater than 1% for diazolidinylurea (1.37%) and methyldibromoglutaronitrile/phenoxyethanol (2.03%). None of the patients reacted to formaldehyde or DMDM hydantoin. Positive reactions were also higher in females for diazolidinylurea, bronopol, imidazolidinylurea, and 2-phenoxyethanol, but lower for methyldibromoglutaronitrile/phenoxyethanol compared with males. A higher proportion of females within this test population underwent patch testing to the preservatives in special series compared with males, apart from formaldehyde. We do not have sufficient data to comment on the relevance rate of preservative contact allergy in our test population.

Time Trends

There was no change in the trend in the sensitization frequencies for the 4 preservatives in the standard series from 2006 to 2011. The frequencies seemed to have stabilized between 2010 and 2011 (Fig. 1).

Sensitization frequencies to methyldibromoglutaronitrile/phenoxyethanol, diazolidinylurea, imidazolidinylurea, bronopol, and 2-phenoxyethanol fluctuated vastly throughout the years from 2006 to 2011 (Fig. 2). Sensitization to methyldibromoglutaronitrile/phenoxyethanol was seen in 2008, 2009, and 2011 with a large spike in 2009 at 5.88%. Sensitization to diazolidinylurea was seen only in 2006 to 2009 at 1.19% to 3.03%. Sensitization to imidazolidinylurea was seen only in 2008 and 2010. Sensitization to bronopol was seen in 2007, 2009, and 2010 at 1.33% to 2.94%. Sensitization to 2-phenoxyethanol was seen only in 2007 at 2.33%.

Contact Dermatitis of the Face, Neck, and Hands

Fifty-two percent of the positive patch-test cases were associated with dermatitis on the face, neck, and/or hands, although present relevance was confirmed in only 23 cases (7.6%) (Table 4). There was a diverse range of occupations. Of all the cases with documented present relevance, toiletries and cosmetics were the predominant source of allergic contact dermatitis across the 11 preservatives.

Delayed Positive Patch-Test Results (Day 7)

The number of patients whose patch test was negative at day 3 but became positive at day 7 is shown in Table 5; 9.4% of positive patch-test reactions became positive only at day 7. This was most commonly seen for methyldibromoglutaronitrile/phenoxyethanol and diazolidinylurea sensitivity (40%). The percentage of delayed patch tests becoming positive at day 7 for the 4 standard preservatives ranged from 5% to 11%.

DISCUSSION

Sensitization rates of contact allergens are dependent not only on the inherent sensitizing capacity of the chemical, but also on the dose and type of exposure (eg, anatomical site), the amount of allergen per unit surface area of skin, the vehicle, and the

TABLE 2. Racial Distribution of Our Patch-Test Population Compared With the Singapore Resident Population

Ethnic Group	Patch-Test Population, n	Patch-Test Population, %	Singapore Residents, % (2011)*
Chinese	2526	79.5	74.1
Malay	151	4.8	13.4
Indian	280	8.8	9.2
Others	220	6.9	3.3
Total	3177	100	100

*Ministry of Health Singapore: Singapore Health Facts - Population and Vital Statistics, (<http://www.moh.gov.sg>).

TABLE 3. Preservatives Ranked by Frequency of Positive Reactions to Preservatives, Stratified by Sex Between 2006 and 2011

Preservative	Total Tested	Positive Tests	%	Male Tested	Positive Male	%	Female Tested	Positive Female	%
Paraben mix*	3177	82	2.58	1393	34	2.44	1784	48	2.69
MCI/MI*	3150	55	1.75	1382	17	1.23	1768	38	2.15
Quaternium 15*	3150	45	1.43	1382	12	0.87	1768	33	1.87
MDBGN*	3170	38	1.20	1392	15	1.08	1778	23	1.29
MDBGN + phenoxyethanol	345	7	2.03	62	2	3.23	283	5	1.77
Diazolidinylurea	366	5	1.37	137	1	0.73	229	4	1.75
Bronopol	506	4	0.79	144	1	0.69	362	3	0.83
Imidazolidinylurea	350	2	0.57	32	0	0	318	2	0.63
2-Phenoxyethanol	300	1	0.34	22	0	0	278	1	0.36
DMDM hydantoin	294	0	0	21	0	0	273	0	0
Formaldehyde†	246	0	0	129	0	0	117	0	0

*Standard series.

†Standard series from 2009.

MDBGN indicates methyldibromoglutaronitrile.

condition of the skin.² In general, a sensitivity rate of less than 1% in the patch-test populations is considered as infrequent sensitizer. If the rate exceeds 2%, it is considered a frequent sensitizer and is a cause for concern, and if the rate exceeds 3%, it indicates that a higher incidence of contact allergy is likely.³

In our clinic patch-test population, sensitization frequencies for all the preservatives in our standard series were greater than 1% but less than 3%, justifying their inclusion in the standard series. None of our patients reacted to formaldehyde, which was included in our standard series in 2009. One possible explanation is that a test concentration of 1.0% aqua for formaldehyde may be too low to detect contact allergies on our population. A recent multicenter study showed that of 3591 patients patch tested simultaneously to formaldehyde 1.0% and 2.0%, 3.4% of patients reacted to 2.0%, whereas only 1.8% of patients reacted to 1.0% ($P < 0.001$).¹³ The authors recommend that formaldehyde 2.0% aqua replace formaldehyde 1.0% in the European baseline series from 2014. Another possible explanation is that Japanese Cosmetics are popular in Asian countries. Japanese regulations ban the use of formaldehyde in

their cosmetics, and most of their cosmetics use nonformaldehyde (eg, parabens) preservatives. This could have accounted for the lack of sensitization to formaldehyde and higher prevalence of parabens sensitivity.

Regarding preservatives in our special series, sensitization frequencies of diazolidinylurea and methyldibromoglutaronitrile/phenoxyethanol were greater than 1% and 2%, respectively. Although both were tested in a targeted fashion, we may have to consider including them in our standard series. Because of the very small number of positive patch tests and also selective testing within the special testing, we are unable to make any comments on clinical relevance.

There was a higher proportion of females in our patch-test population, perhaps reflecting the more prevalent use of preservative-containing products in women in Singapore.

Table 6 shows the sensitization frequencies to preservatives in our Singapore population compared with other countries. Paraben mix sensitization frequency is much higher in Singapore compared with Europe, United Kingdom, and United States but comparable with data from Korea.

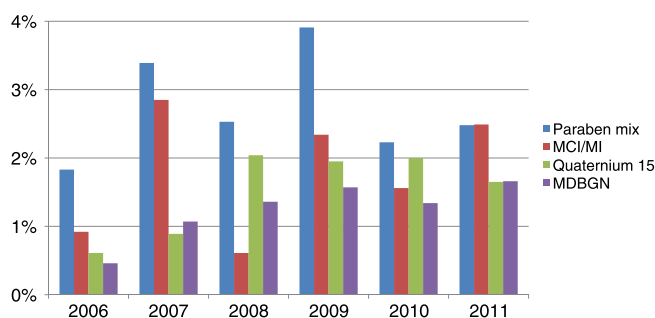
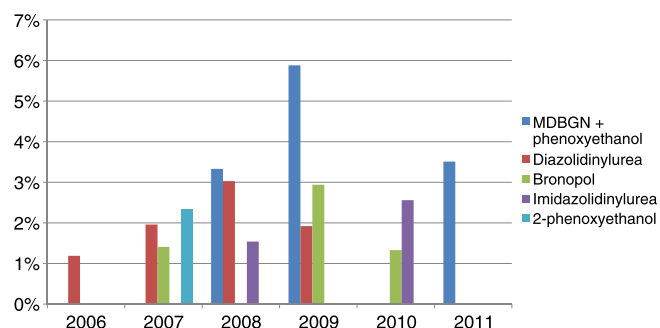
**Figure 1.** Prevalence of positive patch-test reactions to the 4 preservatives in the standard series between 2006 and 2011.**Figure 2.** Prevalence of positive patch-test reactions to the preservatives in the special series between 2006 and 2011.

TABLE 4. Relationship Between Positive Patch Tests and Contact Dermatitis of the Face, Neck, and Hands

Preservative (Concentration)	Total No. Tested	(a) Positive Tests	Data Available on Sites Affected*	Sites Affected			(b) Total	No. (%) Present Relevance	Percentage of Positive Patch Tests Associated With Dermatitis of the Face, Neck, and/or Hands (b/a)
				Face and Neck Only	Hands Only	Face, Neck and Hands			
Paraben mix†	3177	82	55	31	10	1	42	2 (4.7)	51%
MCI/MI†	3150	55	49	14	27	0	41	12 (29)	75%
Quaternium 15†	3150	45	35	12	16	1	29	3 (10)	64%
MDBGN†	3170	38	27	22	7	1	30	3 (10)	79%
MDBGN + phenoxyethanol	345	7	7	5	0	1	6	0	86%
Diazolidinylurea	366	5	5	5	0	0	5	2 (40)	100%
Bronopol	506	4	4	3	1	0	4	1 (25)	100%
Imidazolidinylurea	350	2	2	2	0	0	2	0	100%
2-Phenoxyethanol	300	1	1	0	0	0	0	0	—
DMDM hydantoin	294	0	0	0	0	0	0	0	—
Formaldehyde‡	246	0	0	0	0	0	0	0	—
Total	15,054	302	185	94	61	4	159	23 (7.6)	52%

*The contact clinic database had incomplete data on sites affected for 117 positive patch tests.

†Standard series.

‡Standard series from 2009.

MDBGN indicates methylidibromoglutaronitrile.

Of the positive patch-test cases, 52% were associated with dermatitis on the face, neck, and/or hands, although present relevance was confirmed in 7.6% (23) of these cases. Toiletries and cosmetics were the predominant source of allergic contact dermatitis across the 11 preservatives. These personal care products are often applied using the hands onto the face and neck.

In recent years, there has been an outbreak in contact allergy to MI in Europe and the United Kingdom. According to the Information Network of Departments of Dermatology (IVDK),¹⁴ the frequency of sensitization to MCI/MI was constantly around 2.1% from 1998 to 2009. After that, it increased to 3.9% in 2011, paralleled by an increase in the frequency of allergic reactions to MI 0.05% aqua from 1.9% in 2009 to 4.4% in 2011. Data from the United Kingdom¹⁵ revealed increasing sensitization frequency to MCI/MI from 0.9% in 2008 to 4.9% in 2011 to 2012, paralleled by an increase in the frequency of allergic reactions to MI 0.02% aqua from 0.6% in 2009 to 2.5% in 2012. In the past, MI was used only in combination with MCI, with MI concentrations of 4 parts per million (ppm). A few years ago, MI was introduced into the market as a stand-alone preservative at up to 100 ppm as a preservative in cosmetics and skin care products. More widespread consumer exposure in these countries has most likely led to the increase in primary sensitization to MI and subsequently to a rise in MCI/MI reactions resulting from immunological cross-reactions. In Korea,¹⁰ MCI/MI had the third highest patch-test positivity (5.47%). Although the increased sensitivity rate is similar to results from Europe, it occurred later in Korea, perhaps due to a delay in the import of new cosmetic products into Korea. However, this is

not the case in the United States¹ (2.3% in 2001–2002; 2.5% in 2009–2010) and in our population. The reason for this remains unclear.

Our study also illustrates the need for a second patch-test reading at day 7. Failure to do so may result in about 1 in 10 cases of contact allergy to be missed.

TABLE 5. Number of Patch Tests Which Only Became Positive at Day 7

Preservative	Positive Tests	Only 2nd Patch Test Positive	%
Paraben mix*	86	9	10
MCI/MI*	55	6	11
Quaternium 15*	46	3	7
MDBGN*	38	2	5
MDBGN + phenoxyethanol	7	0	0
Diazolidinylurea	5	2	40
Bronopol	4	1	25
Imidazolidinylurea	2	0	0
2-Phenoxyethanol	1	0	0
DMDM hydantoin	0	0	0
Formaldehyde†	0	0	0
Total	244	23	9.4

*Standard series.

†Standard series from 2009.

MDBGN indicates methylidibromoglutaronitrile.

TABLE 6. Sensitization Frequencies (%) to Preservatives in Our Singapore Population Compared With Europe, United Kingdom, United States, and the Middle East

Preservative	Singapore		Europe				United Kingdom ⁶		Turkey ⁷		Israel ⁸		United States ¹			Asia		
	Europe ²		IVDK ³	Finland ⁴		Denmark ⁵	2004–2005		2000–2004		2002–2004		2007–2009		2009–2010	Thailand ⁹	Korea ¹⁰	China ¹¹
	2006–2011	2008		1996–2009	2000–2002		2004–2005	2004–2005	2000–2004	2002–2004	2007–2009							
Paraben mix*	2.58	0.5	1.33	0.2	0.5	0.8	0.8	0.6	—	—	—	1.1	0.8	0.5	9.2	3.1	—	
MCI/MI*	1.75	2.6	2.22†	1.3	1.8	2.0†	2.0†	0.3	3.7	3.7	3.7	3.6	2.5	—	4.3	5.5	—	
Quaternium 15*	1.43	1.0	0.66	0.8	1.0	1.9	1.9	0.6	—	—	—	8.6	5.8	—	1.5	3.3	—	
MDBGN*	1.20	3.1	4.5	1.5	3.7	1.2	1.2	—	2	2	2	—	—	—	5.6	1.5	—	
MDBGN + phenoxethanol	2.03	—	3.89	—	—	—	—	0.9	1.7	1.7	1.7	5.5	3.8	—	—	4.3	—	
Diazolidinylurea	1.37	0.8	0.71	0.9	1.6	1.1	1.1	0.3	—	—	—	3.1	2.2	—	3.6	1.4	—	
Bronopol	0.79	—	1.25	0.2	0.6	1.3	1.3	—	—	—	—	3.1	1.0	—	—	3.3	1.0	
Imidazolidinylurea	0.57	0.6	0.6	0.8	0.8	0.9	0.9	—	—	—	—	—	—	—	—	—	—	
	0.3	—	2.4	—	—	—	—	—	—	—	—	—	—	—	—	—	—	
	2.2	1.7	2.9	2.0	—	—	—	—	—	—	—	—	—	—	—	—	—	
2-Phenoxyethanol	0.34	—	0.24	—	—	—	—	—	—	—	0	—	—	—	—	1.7	—	
DMDM hydantoin	0	—	0.49	—	0.7	—	—	0.6	1.6	1.6	1.6	2.7	1.0	—	3.5	1.7	—	
Formaldehyde§	0	2.4	1.54	2.5	3.1	2.0	2.0	1.3	1	1	1	7.7	5.8	—	3.5	—	1.3	

Note that sensitization frequency to MC/MI increased in Europe (IVDK¹²) to 3.9% in 2011 and in the United Kingdom¹³ to 4.96% in 2011–2012. This was paralleled by an increase in sensitization frequency to MI from 1.9% in 2009 to 4.4% in 2011 (IVDK¹²) and from 0.6% in 2009 to 2.5% in 2012 in the United Kingdom.¹³ In Korea, MC/MI had the third highest patch-test positivity (5.47%). Although the increased sensitivity rate is similar to results from Europe, it occurred later in Korea, perhaps due to a delay in the import of new cosmetic products into Korea.

*Standard series.

§Standard series from 2009.

MDBGN indicates methylisobromoglutaronitrile.

CONCLUSIONS

Preservatives are important causes of nonoccupational (cosmetics and household products) and occupational (pharmaceutical and industrial products) contact dermatitis. This should be taken into consideration when introducing new preservatives into the market. Preservative contact allergy was seen more frequently in Singaporean females. A second patch-test reading at day 7 is important so as not to miss late reactions to contact allergens.

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