

Changing trends of contact allergens in Thailand: A 12-year retrospective study

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Abstract

Background: Contact allergen prevalences often change. Continual surveillance is necessary to detect trends in sensitization rates and emerging allergens.

Objective: To identify the prevalence of, and trends in, the positive reactions to each allergen in the baseline series during a 12-year period in Thailand.

Methods: The medical records of 2803 patients who underwent patch testing at the Contact Dermatitis Clinic, Siriraj Hospital, between 2006 and 2018, were retrospectively reviewed. The baseline series used by the clinic was adapted from the European and the International baseline series. The patch testing results were subdivided into 2-year blocks in order to compare the prevalences of each allergen.

Results: The prevalences of positive reactions to nickel, fragrance mixes I and II, dichromate, cobalt, carba mix, methyldibromo glutaronitrile, paraben mix, neomycin sulfate, methylisothiazolinone (MI), epoxy resin, *N*-isopropyl-*N*-phenyl-4-phenylenediamine and the corticosteroids significantly decreased. Methylchloroisothiazolinone (MCI)/MI was the only allergen associated with a significant increase of positive reactions, from 2.4% to 10.7%. However, the proportion of positive reactions to MCI/MI decreased in the final 2-year period.

Conclusions: Approximately half of the substances in the screening patch test series showed a decline in the number of positive reactions, whereas MCI/MI showed an increasing prevalence.

KEYWORDS

allergic contact dermatitis, epidemiology, patch test

1 | INTRODUCTION

The field of contact dermatitis is continuously evolving. Environmental exposure changes over time, and allergens may differ from country to country. Continual surveillance of contact allergens is necessary to detect trends in sensitization rates, and identify obsolete and emerging allergens, both of which are important for preventive intervention in allergic contact dermatitis (ACD), and the management of ACD.¹ To identify the allergens causing ACD, patch testing is essential. For all

patients undergoing testing for contact allergy, the use of screening baseline allergens in the initial series is recommended. Additional series may be added to the initial test, or used subsequently, on the basis of the patient's exposure history and the clinical appearance of the dermatitis.² The screening or baseline series includes common core allergens responsible for ACD worldwide, and the allergens are adjusted to suit each population. For example, the International baseline series contains 32 allergens,³ whereas the European baseline series contains 30.⁴ The North American Contact Dermatitis Group

has agreed on a baseline set of 70 allergens.⁵ The series of allergens used for baseline testing by the North American Contact Dermatitis Group has been amended almost every year, in accordance with alterations in the prevalence of contact allergies and variations in the patch test reactions among populations.⁶ Moreover, much useful information about the sources of contact allergens has been published over the recent decade, and this has helped to avoid allergen exposure and reduce sensitization rates. The objectives of this study were to identify the prevalence of, and trends in, the positive reactions to each allergen in the baseline series during a 12-year period in Thailand.

2 | MATERIALS AND METHODS

2.1 | Study population

The medical records of 2803 patients who underwent patch testing at the Contact Dermatitis Clinic, Faculty of Medicine, Siriraj Hospital between 1 July 2006 and 30 June 2018 were retrospectively reviewed and analysed. All patients suspected of having allergic contact dermatitis were referred to that clinic for patch testing, without further selection. Patients referred to the clinic had been evaluated by dermatologists using uniform inclusion criteria before referral. They were patch tested with our baseline series and, depending on the individual patients' clinical histories, with additional suspected allergens. Our baseline series had been adapted from the European and the International baseline series, but with the exclusion of primin.⁷ All allergens included in the baseline series are listed in Table 2. A history of atopic tendency was defined as having at least one atopic marker (a history of atopic eczema, asthma, or hay fever). This study was approved by the Siriraj Institutional Review Board (Si083/2017).

2.2 | Interpretation of patch test results

Patch testing was performed in accordance with the guidelines of the ICDRG.⁸ The allergens (Chemotechnique Diagnostics, Vellinge, Sweden) were loaded in aluminium Finn Chambers (SmartPractice, Phoenix, Arizona) and placed on unaffected skin on the upper back for 48 hours. The reactions were interpreted on day (D) 2 and D4, and patients were asked to visit the clinic on D7 for reading, according to patients' availability and suspicion of delayed reactions to individual allergens.⁸ The patch test results and patient data were collected by chart review.

2.3 | Statistical analysis

The data were analysed with PASW STATISTICS for Windows, version 18.0 (SPSS, Chicago, Illinois). Descriptive statistics are presented as frequency and percentage, or mean $\pm$ SD. The patch test results for each period were compared by use of the χ^2 test with Yates' continuity correction or Fisher's exact test, as appropriate. The *P*-values were adjusted with the Bonferroni method to correct for 30 statistical tests; hence, a *P*-value of <0.0017 indicates statistical significance.

Regarding the use of "prevalence" vs "incidence" in this study, the numbers of positive reactions in the study might not represent new cases of ACD. Thus, the word "prevalence" is preferable to the word "incidence."

3 | RESULTS

During 2006 to 2018, 2803 patients were patch tested with our baseline series. The 2135 females (76.2%) and 668 males (23.8%) tested had a mean age of 42.4 ± 15.5 years. The mean duration of the presenting symptoms was 34.0 ± 55.0 months. In total, 1850 (66.0%) patients had at least one positive patch test reaction, and 1226 (66.3%) had clinically relevant reactions (Table 1). Of the 1850 patients with positive patch test reactions, 781 (42.2%) had a personal history of atopy, and 631 (34.1%) had a family history of atopy. A personal history of atopy was not associated with the results of patch testing (*P* = 0.69).

Nickel was the most frequent allergen, with 24.0% patch test positivity over the 12-year study period. Its clinical relevance (CR) was reported for 84.7% of patients. The next most frequent culprit allergens were methylisothiazolinone (MI) (14.6%, CR = 73.1%), dichromate (13.1%, CR = 40.2%), fragrance mix I (12.6%, CR = 47.8%), methylchloroisothiazolinone (MCI)/MI (11.2%, CR = 60.5%), and cobalt (10.5%, CR = 43.6%). Table 2 shows the prevalences of the positive patch test reactions during the study period. The rate of positive reactions significantly decreased for many allergens, including nickel sulfate, fragrance mix I, potassium dichromate, cobalt(II) chloride, carba mix, fragrance mix II, methyldibromo glutaronitrile, paraben mix, neomycin sulfate, MI (starting 2012, when first introduced), budesonide, epoxy resin, *N*-isopropyl-*N*-phenyl-4-phenylenediamine, and hydrocortisone-17-butyrate. MCI/MI was the only allergen to show an increasing share of positive reactions (*P* < 0.0001) over the 12-year period. The highest prevalence of MCI/MI allergy was found between 2014 and 2016, but the figure subsequently fell in the final 2-year period. From 2012 to 2018, since MI at the concentration of

TABLE 1 Demographic data of the patients

Demographic data	Total patients (N = 2803)
Age (years), mean (SD)	42.4 (15.5)
Duration (months), mean (SD)	34.0 (55.0)
Sex, n (%)	
Male	668 (23.8)
Female	2135 (76.2)
Atopy history, n (%)	1176 (42.0)
Atopic family history, n (%)	985 (35.1)
History of metal allergy, n (%)	1087 (38.8)
History of cosmetic allergy, n (%)	397 (14.2)
History of drug allergy, n (%)	488 (17.4)
Positive for at least one allergen, n (%)	1850 (66.0)
Of these: clinical relevance, n (%)	1226 (66.3)

TABLE 2 Positive patch test (PT) reactions between 2006 and 2018

Allergens	Tested concentration (%)	Total positive PT reactions, n (%)	Percentage of positive PT reactions								P-value
			2006-2008 (n = 212)	2008-2010 (n = 254)	2010-2012 (n = 360)	2012-2014 (n = 513)	2014-2016 (n = 612)	2016-2018 (n = 852)			
I. Metals											
Nickel sulfate	2.5	1002 (35.7)	54.2	48.0	31.7	32.6	36.3	30.8	<0.0001*		
Potassium dichromate	0.5	672 (24.0)	30.2	28.3	19.7	22.4	28.1	20.9	<0.001		
Cobalt(II) chloride	1.0	367 (13.1)	26.4	17.7	11.9	12.3	11.3	10.7	<0.0001*		
		294 (10.5)	19.3	17.7	12.2	8.4	8.0	8.5	<0.0001*		
II. Cosmetic-related											
Fragrances		1097 (39.1)	40.1	48.0	43.9	37.2	41.5	33.7	<0.0001*		
Fragrance mix I	8.0	558 (19.9)	21.7	24.0	26.9	20.5	20.3	14.7	<0.0001*		
Fragrance mix II	14.0	354 (12.6)	16.0	15.7	17.8	11.9	13.2	8.7	<0.0001*		
Myroxylon perirae resin (balsam of Peru)	25.0	206 (8.1)	18.2	13.1	10.8	9.6	7.7	5.3	0.001*		
Compositae mix II	5.0	197 (7.0)	9.4	6.7	8.6	7.6	6.4	6.0	0.37		
Preservatives		11 (0.7)				1.9	1.0	0.5	0.32		
Methylisothiazolinone	0.2 aq.	626 (22.3)	19.8	33.1	22.5	18.9	27.6	18.0	<0.0001*		
Methylisothiazolinone/methylchlorisothiazolinone	0.02 aq.	220 (14.6)				25.0	18.5	11.2	<0.0001*		
Methyldibromo glutaronitrile	0.3	315 (11.2)	2.4	10.6	8.9	11.1	16.8	10.7	<0.0001*		
Paraben mix	16.0	133 (4.8)	4.8	12.3	9.7	3.7	2.9	2.3	<0.0001*		
Formaldehyde	2.0 aq.	122 (4.3)	10.8	11.8	3.9	4.1	2.6	2.1	<0.0001*		
Diazolidinyl urea	2.0	66 (2.4)	3.8	2.8	2.8	1.4	3.1	1.8	0.20		
Quaternium 15	2.0	21 (1.4)				1.8	2.0	0.9	0.25		
Imidazolidinyl urea	2.0 aq.	34 (1.2)	0.9	0.8	0.8	0.8	2.5	0.8	0.052		
Other cosmetics		27 (1.0)	1.9	2.0	0.8	0.6	1.0	0.7	0.30		
p-Phenylenediamine	1.0	224 (8.0)	13.7	8.7	5.6	8.2	7.0	7.9	0.021		
Lanolin alcohol	30.0	168 (6.0)	8.5	6.3	3.9	5.8	5.7	6.5	0.34		
III. Resins		59 (2.1)	5.7	3.2	1.7	2.5	1.3	1.4	0.002		
Colophonium	20.0	235 (8.4)	13.7	10.6	9.2	8.2	8.5	6.1	0.008		
4-tert-Butylphenol formaldehyde resin	1.0	169 (6.0)	8.0	5.5	6.4	6.4	6.8	4.7	0.39		
Epoxy resin	1.0	48 (1.7)	5.2	2.4	1.7	1.0	1.3	1.4	0.002		
IV. Medications		31 (1.1)	2.8	3.1	1.7	1.0	0.5	0.4	<0.0001*		
Neomycin sulfate	20.0	171 (6.1)	17.0	9.8	6.9	5.8	2.8	4.5	<0.0001*		
Corticosteroids		134 (4.8)	10.8	7.9	4.4	5.3	2.1	4.1	<0.0001*		
Budesonide	0.01	47 (1.7)	7.5	2.4	3.1	0.6	0.8	0.7	<0.0001*		
Tixocortol-21-pivalate	0.1	29 (1.0)	5.2	1.6	2.8	0.4	0.2	0.1	<0.0001*		
Hydrocortisone-17-butyrate	1.0	19 (0.7)	2.8	0.8	0.3	0.2	0.7	0.6	0.004		
		2 (0.1)				3.7	0	0	<0.0001*		

TABLE 2 (Continued)

Allergens	Tested concentration (%)	Total positive PT reactions, n (%)	Percentage of positive PT reactions								P-value
			2006-2008 (n = 212)	2008-2010 (n = 254)	2010-2012 (n = 360)	2012-2014 (n = 513)	2014-2016 (n = 612)	2016-2018 (n = 852)			
V. Rubber additives		372 (13.3)	23.1	13.4	18.3	14.4	12.4	8.6	<0.0001*		
Carba mix	3.0	262 (9.4)	11.0	9.2	13.9	11.5	9.5	5.8	<0.0001*		
Thiuram mix	1.0	92 (3.3)	6.6	3.9	4.7	2.3	3.9	1.8	0.002		
Mercaptobenzothiazole	2.0	45 (1.6)	3.3	2.0	2.5	1.8	1.5	0.7	0.064		
Mercapto mix	2.0	34 (1.2)	2.8	2.0	1.1	1.8	0.5	0.8	0.053		
Black rubber mix	0.6	11 (0.8)				1.8	1.0	0.6	0.53		
N-isopropyl-N-phenyl-4-phenylenediamine	0.1	20 (0.7)	3.3	0.8	0.6	0.6	0.3	0.5	0.001*		

*A P-value of <0.0017 indicates statistical significance.

0.2% aq. was introduced into our baseline series, 1512 patients were patch tested with both MCI/MI (0.02% aq.) and MI (0.2% aq.). Of all patients in this group, 169 (11.2%) reacted to both MCI/MI and MI, 50 (3.3%) reacted only to MI without simultaneous contact allergy to MCI/MI, and 35 (2.3%) reacted only to MCI/MI.

The allergens were divided into five categories: cosmetic-related, resins, medications, metals, and rubbers. The cosmetic-related allergens showed the highest prevalence of positive patch test reactions (39.1%). Except for the resins, the positive results for all of the groups decreased significantly.

4 | DISCUSSION

When compared with the results of an earlier study in Thailand in 2000 to 2009, the number of patients with positive allergic reactions in the current study had fallen from 81.2% (in 2000-2009) to 66.0%, and the share of clinical relevance had increased from 56.5% to 66.3%.⁹ These falling prevalences might be attributable to decreasing exposures to sensitizers as a result of recent concerns about contact allergies. Moreover, people can easily receive more data about contact allergen avoidance in this information age, and many substitutes are used instead of common allergens. The findings also suggest that the baseline series in use in Thailand needs to be updated to better comply with current exposures. Although another possible explanation for the decrease in the rate of positive reactions might be the growing number of patients who were able to more easily access the clinic than in the past based on patients' requests, the number of cases with clinical relevance had increased. Our results show the concordance of the prevalence of contact allergens in Europe, the United States, and Asia. The most common allergens in this study were very similar to those found by previous studies from many regions around the world, especially nickel, which was found to be the most common sensitizer during the past decade.⁹⁻¹²

The prevalence of contact allergy to metals (nickel sulfate, cobalt [II] chloride, and potassium dichromate) significantly decreased during the 12 years of the present study. As nickel has been well known as a common allergen for decades, nickel-free items have become increasingly common worldwide; for example, the use of rhodium or platinum instead of nickel in jewellery has contributed to the reduced prevalence of nickel contact allergy. In Thailand, for instance, exposure to nickel-containing jewellery is higher than reported in European countries, because nickel is unregulated in our market.¹³ Furthermore, the rate of cobalt contact allergy significantly decreased concomitantly with that of nickel. Since cobalt detection tests have become more commonly used, the element has been found in many sources other than metallic objects, resulting in people avoiding exposure to cobalt.¹⁴ Interestingly, the relevance of cobalt allergy in this study was mostly attributable to jewellery. The relevance of cobalt allergy from our study is much higher than finding in Denmark.¹⁵ This difference correlated with the positive cobalt spot test reactions, which were reported for 37.4% of jewellery on the Thai market but only 2% of jewellery in Europe.^{13,15} A decline in the prevalence of chromium

allergy has also been reported in the United States and Europe.^{5,16} In the past, cases of chromium sensitization were predominantly found among construction workers.¹⁷ The decline in chromium allergy is consistent with a decrease in worker exposure to chromium(VI), which is traditionally found in cement, thanks to the addition of ferrous sulfate.¹⁸ Major cement companies in Thailand have also announced that chromium(VI) will be reduced by the industry. A recent Swedish study suggested that there has been a shift of chromium exposure to metallic dyes and tanned leather.¹⁹ However, leather clothing is not suitable for the warm-to-hot climate in Thailand, and, in any case, is no longer in fashion. Nowadays, synthetic leather has become more popular and needs no tanning process; this has contributed to the significant decline in the prevalence of chromium allergy in this study.

Regarding cosmetic allergens, the reduced prevalences of fragrance mix I allergy and fragrance mix II allergy have most probably resulted from the replacement of those fragrances with the numerous alternatives that are now available for use in cosmetics that do not have to be labelled.^{20,21} Thus, fragrance mixes I and II might no longer be sufficient for screening for fragrance contact allergy in patients, and new substances may need to be added to baseline series. Conversely, the prevalence of *Myroxylon pereirae* resin allergy did not significantly change in the current study period. This could be because, first, the resin is in common use in Thailand, and, second, it might cross-react with many herbal products that are widely used in Asian food and local cosmetic products.

Regarding preservatives, MCI/MI was the only allergen in this study to show a significantly higher prevalence of positive patch test reactions. The highest prevalence of MI (alone) contact allergy was observed from 2012 to 2014, which was also when it was first used in our baseline series. This study found that an increase of a few more percentage points of MI allergy occurred after MI (0.2% aq.) had been introduced as a baseline series allergen in addition to MCI/MI (0.02% aq.). After MI 2000 ppm had been recommended to be patch tested in consecutive patients to avoid MI allergy cases being missed, 32.7% of patients with MI contact allergy were detected without reactions to MCI/MI in a multicentre study.²² Compared with our results, 50 of 254 patients (19.7%) had positive reactions to only MI, which is a lower prevalence than reported. Nevertheless, MI (0.2% aq.) should still be included in the baseline series to detect MI-allergic patients, although the trend of MI allergy has decreased. In Thailand, MCI/MI and MI are generally found in many leave-on and rinse-off products, and domestic manufacturers make widespread use of MCI/MI and MI as preservatives in leave-on cosmetic products.²³ Although MCI/MI could be found in paints, industrial oils, and fluids, our isothiazolinone-allergic patients had clinically relevant reactions mainly to cosmetics. The numbers of patients with ACD caused by MCI/MI and MI alone have also been increasing in many other countries.²⁴⁻²⁶ The current study showed a much higher share of positive reactions (14.6%) to MI in Thailand than in European countries (1.5%-4.6%).²⁴ Interestingly, the prevalences of allergies to MCI/MI and MI alone decreased during the final 2-year period examined by the present study. This might be a result of recent local restrictions on the use of MCI/MI and MI alone in cosmetic products: the ASEAN Harmonized Cosmetic Regulatory

Scheme and the Thai FDA regulated the use of MCI/MI and MI alone with effect from 2016.^{27,28} In comparison, the prevalence of contact allergy caused by parabens as a preservative decreased significantly from 10.8% to 2.1%. This decrease could be linked to concerns that parabens might cause breast cancer; in response, the European Commission banned the use of parabens in cosmetic products,^{10,29} which affected the global cosmetic industry. Similarly, the prevalence of methylidibromo glutaronitrile-positive patch test reactions also declined, because its use was prohibited in many products. On the other hand, the prevalences of formaldehyde and formaldehyde-releaser (quaternium-15, imidazolidinyl urea, and diazolidinyl urea) allergies were nearly unchanged during the 12-year study period. Statistically insignificant, decreasing trends of formaldehyde and formaldehyde-releaser allergies have been reported in Europe.³⁰ A minor proportion of consumer products in the Thai market contain formaldehyde releaser preservatives,²³ which may have caused the limited changes in their contact allergy prevalence. These changes might also be explained by a number of consumer products possibly containing formaldehyde despite its presence not being identified on the product labelling.³¹

Moreover, trends in sensitization to medication allergens (neomycin, budesonide, and tixocortol-21-pivalate) significantly decreased. Our results were similar to those of a study from Belgium.³² Neomycin was the most common topical antimicrobial drug causing ACD in the current study, because it was one of the most common over-the-counter topical antibiotics sold in Thailand. The prescription of neomycin has diminished; therefore, the prevalence of contact allergy to neomycin has fallen over the last 12 years. Of all of the allergens in the rubber group, carba mix had the highest share of positive patch test reactions, similarly to the findings of a study in Europe.³³ The prevalence of rubber allergy significantly decreased. Over the last two decades, rubber and rubber accelerators have become widely known as potent contact sensitizers. This has resulted in a change in primary prevention efforts in work environments and the replacement of rubbers with other substances, such as silicone or polyvinyl chloride; the combined effect is the declining trend of rubber allergy.

In conclusion, the prevalence trends of contact allergens have changed over the last 12 years in Thailand, and mostly in concordance with global patterns. The prevalences of positive patch test reactions to the contact allergens in the baseline series used in Thailand have mostly decreased. Regular surveillance of the prevalences of allergens in baseline patch test series is important in order to keep them relevant to ACD patients in individual countries and regions. The periodic updating of baseline series will enhance the detection of emerging and obsolete contact allergens, which could improve the care of our patients.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to report.

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