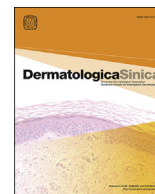


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Original Article

Contact allergy to methylisothiazolinone/methylchloroisothiazolinone: A retrospective case series in a referral center in northern Taiwan

Shu-Ling Liao, Yu-Hsian Tseng, Chia-Yu Chu*

Department of Dermatology, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, 100, Taiwan

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ABSTRACT

Background/Objective: Since 2005, there has been a significant increase in contact allergy to methylisothiazolinone (MI)/methylchloroisothiazolinone (MCI) incidences in European countries, but there has been no documented large-scale studies of such incidences in Taiwan.

Methods: From 1987 to 2015, a total of 2590 patients received patch testing in our Contact Dermatitis Clinic. Analyzed were patients with positive reactions to MI/MCI (Kathon CG) in patch testing and with suspected allergy to MI/MCI.

Results: Among the total 2590 patients, 2388 received patch testing during 1987–2005, while 202 received patch testing during 2006–2015. Because Kathon CG was not routinely patch tested for all patients from 1987 to 2005, the incidence of contact allergy to MI/MCI was thus corrected to 3/145 (2.1%) for this time period. After 2005, there were 11 patients (11/202, 5.4%) who showed positive reactions to MI/MCI. Amongst the 14 patients who showed positive reactions to MI/MCI, 12 of them were females (85.7%). The majority of the lesions was located on the hands (10 patients, 71.4%), along with the face (3 patients, 21.4%). Interestingly, 6 patients (42.9%) who showed positive reactions to MI/MCI were associated with contact allergy to essential oils, and five of them were aromatherapists.

Conclusion: According to our study, the incidence of MI/MCI contact allergy in a referral center in Taiwan was 5.4%. A trend of increasing incidence of contact allergy to MI/MCI was noted after 2005, which is consistent with the findings in Europe. Allergic contact dermatitis to MI/MCI should be suspected in patients who have eczema on the hands and face, especially those who are aromatherapists.

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Introduction

Methylisothiazolinone (MI) and methylchloroisothiazolinone (MCI) are commonly used preservatives in household and industrial products, along with cosmetics. Throughout the 1980s, an European ‘epidemic’ of contact dermatitis caused by MCI/MI occurred that showed sensitization rates increase to 5.0%.¹ Thus, the Cosmetic Ingredient Review Expert Panel of The Cosmetics Toiletry and Fragrance Association recommended the maximum concentration of MCI/MI of leave-on and rinse-off products as 7.5 and 15 ppm respectively.² In 2005, MI was permitted in cosmetic products up to a maximum 100 ppm concentration.³ In both Europe

and North America, there was a significant increase in reports of allergic contact dermatitis (ACD) to MI/MCI incidences recently.^{4–7} To exemplify, MI was Contact Allergen of the Year for 2013 in the American Contact Dermatitis Society as it was increasingly applied in cosmetics and toiletries.⁴ However, the clinical significance of ACD to MI/MCI in Taiwan has not been thoroughly investigated. Thus, we conducted a retrospective study to analyze ACD to MI/MCI incidences by a 26-year database in a referral center in northern Taiwan.

Methods

Patient history and demographics

The patient data in this study was collected in The Contact Dermatitis Clinic of The National Taiwan University Hospital, a tertiary referral center for patch testing in northern Taiwan. From

* Corresponding author. Department of Dermatology, National Taiwan University Hospital, 7 Chun-Shan South Road, Taipei, 100, Taiwan. Fax: +886 2 23934177.

E-mail address: chiayu@ntu.edu.tw (C.-Y. Chu).

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1987 to 2015, there were a total of 2590 tested patients whose backgrounds included Taiwanese, Hakka, aborigine, and Mainland Chinese immigrants.⁸ During 1987 to 2005, Kathon CG (MI/MCI) was tested in shoe series, preservative series, and cosmetic series. After 2005, it was tested in standard series. For patients tested with Kathon CG, 145 patients were tested from 1987 to 2005, along with 202 patients from 2005 to 2015. For each patient with suspected ACD observed in the clinic, a questionnaire as described elsewhere was completed.⁹ The questionnaire included a detailed history of occupation, affected sites, appearance of the skin lesions, and the possible exposure source. Personal or familial atopy diathesis was considered positive if the patients or their families had atopic dermatitis, allergic rhinitis, or asthma.¹⁰ This study followed the Declaration of Helsinki on medical protocol and ethics. Written informed consent was obtained from all participating adult subjects and from parents or legal guardians for minors or incapacitated adults.

Patch testing

Every patient with suspected ACD received a comprehensive patch test with the European standard series. As mentioned, from 1987 to 2005, Kathon CG (MI/MCI) was tested in shoe series, preservative series, and cosmetic series. After 2005, it was tested in standard series. Patch testing followed the protocol recommended by the International Contact Dermatitis Research Group (ICDRG) with Finn Chambers or IQ Chambers (Epitest Ltd Oy, Tuusula, Finland) on Scanpor tapes (Norgesplaster AS, Vennesla, Norway) applied to a lesion-free area on the back after informed consent was obtained. The Scanpor tapes were further affixed with 3M (3M, St Paul, MN, USA) tape. The patches were removed after 2 days; the sites were examined for evidence of reaction at D2 and D4 or at D3 alone. According to the ICDRG's guidelines, if the reaction was equal to or stronger than palpable erythema, the D3 or D4 readings were considered positive.^{8,9,11}

Study design

Patch test data was retrospectively analyzed. Patient history and demographics disclosed in the questionnaire were compared using

Fisher's exact test. Contact allergy to MI/MCI was defined as having a positive reaction to MI/MCI in patch test. The clinical relevance of a positive patch test reaction was defined as reported previously.¹²

Results

From 1987 to 2015, 2590 patients were patch-tested in the Contact Dermatitis Clinic. Among them, there were a total of 14 patients (0.54%) showing positive reactions to MI/MCI (Kathon CG) by patch testing (Table 1). Among these 14 patients, 9 patients (64.3%) also had positive reactions to cobalt, 5 patients (35.7%) to fragrance mix, and 4 patients (28.6%) to formaldehyde. Kathon CG was not tested in the Standard Series and was tested in shoe series, preservative series, and cosmetic series during 1987–2005. After 2005, it was routinely patch tested in the Standard Series. A total of 145 patients received patch testing for Kathon CG during 1987–2005, and 202 patients were tested with Kathon CG during 2005–2015. Three patients showed positive reactions to Kathon CG (MI/MCI) during 1987–2005 and 11 patients had positive reactions to Kathon CG (MI/MCI) during 2005–2015. All of them were confirmed to have clinical relevance to the positive patch test reaction to Kathon CG (MI/MCI). Therefore, the incidence of contact allergy to Kathon CG (MI/MCI) increased from 2.1% (3/145) to 5.4% (11/202) after 2005 ($P = 0.1665$).

Among the patients with positive reactions to Kathon CG (MI/MCI), there were 85.7% female patients ($n = 12$) and 14.3% male patients ($n = 2$). Ages ranged from 3 to 49 years old with a mean of 31 years old. There were 14.3% patients ($n = 2$) who had personal atopy history (allergic rhinitis). Hands (71.4%, $n = 10$) and face (21.4%, $n = 3$) were the most commonly affected areas (Figs 1 and 2), followed by neck (14.3%, $n = 2$), forearms (7.1%, $n = 1$), shins (7.1%, $n = 1$) and feet (7.1%, $n = 1$). All of them showed positive reactions with equal to or stronger than palpable erythema at D3 or D4 readings (Fig. 3). Most common source of MI/MCI sources were from essential oil (42.9%, $n = 6$), cosmetics (14.3%, $n = 2$) and hairdressing products (14.3%, $n = 2$) (Fig. 4). The other source of MI/MCI sources were from skin care products and wet wipes. The highest noted occupations were aromatherapist (35.7%, $n = 5$) and hairdresser (14.3%, $n = 2$). And the others were cashier, office worker, businessman, dentist assistant, sales, and electric welding worker.

Table 1 The characteristics of the patients with positive reactions to MI/MCI (Kathon CG) in patch testing.

Case	Age/gender	Personal history of atopy	Primary site involved	Source of MI/MCI	Occupation	Other contact allergens
1	16F	(–)	Hands	Hair products	Hairdresser	Cobalt, nickel sulfate, paraben mix, fragrance mix, captan, captafol, phaltan, ammonium thioglycolate
2	21F	(–)	Hands	Hair products	Hairdresser	PPD, cobalt, cocamidopropylbetaine
3	3F	(–)	Foot	Skin care products*	None	–
4	20F	(+) AR	Hands, foot	Wet wipes*	Cashier	Potassium dichromate, cobalt, formaldehyde
5	40F	(+) AR	Left shin	Skin care products*	Office worker	Cobalt, nickel sulfate
6	43F	(–)	Hands	Essential oil	Aromatherapist	Benzocaine, nickel sulfate, fragrance mix, geraniol, rose oil, geranium oil bourbon
7	44F	(–)	Face	Cosmetics	Businessman	4-phenylenediamine base (PPD), cobalt, balsam of Peru, fragrance mix
8	42F	(–)	Hands	Essential oil	Aromatherapist	Paraben mix, mercapto mix, epoxy resin, formaldehyde, quaternium 15
9	28F	(–)	Face	Cosmetics	Dentist assistant	Cobalt, formaldehyde, mercury
10	32F	(–)	Neck, hands	Essential oil	Sales	Cobalt
11	49F	(–)	Face, Neck, forearms, hands	Skin care products*	Electric welding worker	Thiuram mix, cobalt, colophony, flux4% and 1% (H ₄ N ₂ , HBr)
12	35M	(–)	Hands	Essential oil	Aromatherapist	Clove oil, cinnamyl alcohol, eugenol
13	30F	(–)	Hands	Essential oil	Aromatherapist	Potassium dichromate, neomycin sulfate, cobalt, balsam of Peru, fragrance mix, clove oil, eugenol, geraniol, Clioquinol, formaldehyde, fragrance mix
14	36M	(–)	Hands	Essential oil	Aromatherapist	

ACD: allergic contact dermatitis, M: male, F: female, *: possible relevance, AR: allergic rhinitis, PPD: paraphenylenediamine dihydrochloride.

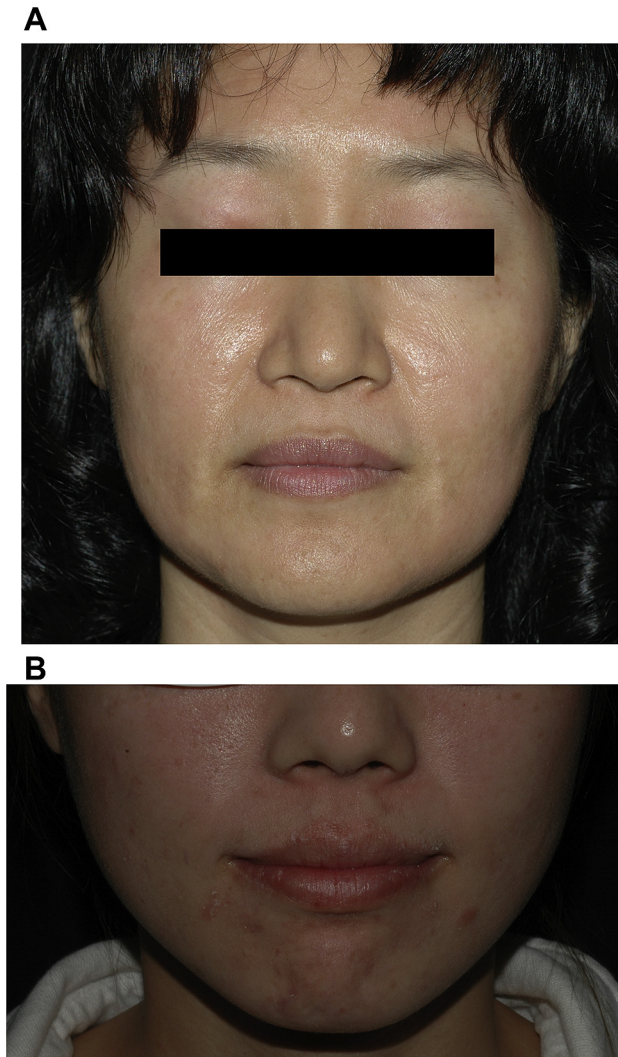


Fig. 1 (A) Patient #7. This 44-year-old female patient had some itching, infiltrated, pinkish papules and plaques on the face noted for 3 months. (B) Patient #9. This 28-year-old female patient had some itching, infiltrated, scaling, erythematous papules on the face for 1 year. Both patients received patch testing and showed positive reactions to Kathon CG.



Fig. 2 Patient #12. A 35-year-old aromatherapist had some itching scaling erythematous papules and patches on the palms and fingers for 11 months.

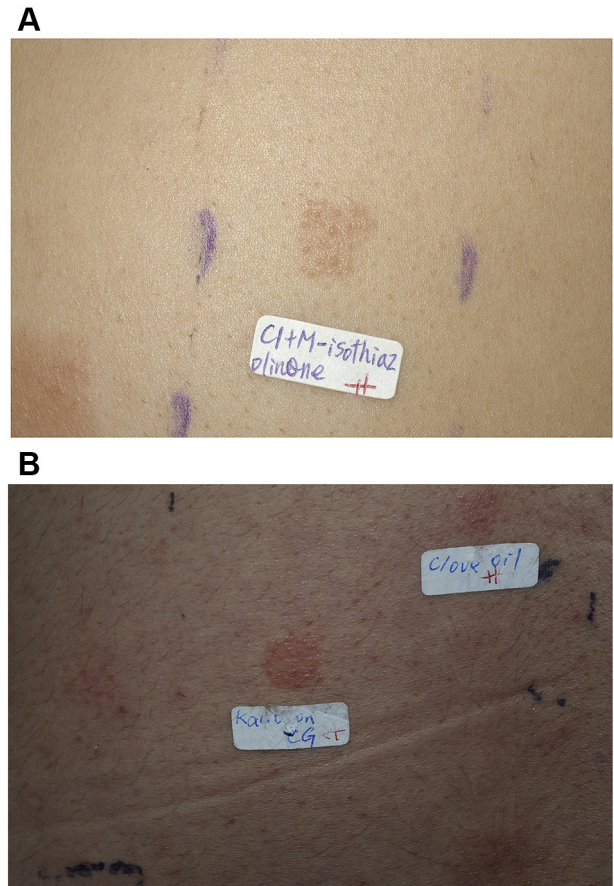


Fig. 3 (A) Patient #7 and (B) Patient #12 both had positive results presenting as well-defined, palpable erythema with tiny vesicles at the MI/MCI tested sites at day-3 reading.



Fig. 4 The associated sources for MI/MCI. The most common sources were essential oil, hair dressing products and cosmetics. The other associated sources included skin care products and wet wipes.

Discussion

In this study, we found the incidence of contact allergy to MI/MCI increased from 2.1% to 5.4% after 2005. Although there was no significant difference ($P = 0.1665$, Table 2) between the incidence before and after 2005, there was a trend of two-fold increase, which was compatible with those from European countries. The incidences of contact allergy to MI/MCI were around 4.5–4.9% in Belgium, France, and United Kingdom.^{5–7}

Kathon CG, the trade name for a 3:1 combination of MCI/MI produced by Dow Chemical Company, has been used as a preservative since the 1980s in the United States.¹³ There has been a striking increased incidence of ACD to MI/MCI reported in European countries and North America in recent years.^{4–7} The possible sources of MI/MCI that cause ACD includes cosmetic products, like makeup, hair products, sunscreen, and moisturizing creams; common pediatric skin care products⁵; occupational products, like paints, glues, lacquers, and cutting oils; household products, like dishwasher soap, washing powder, laundry detergents, fabric softeners, and product of wood protection.⁵ In this study, the most commonly associated sources of MI/MCI exposure were essential oil (42.9%), cosmetics (14.3%) and hairdressing (14.3%) (Fig. 4).

We found the most commonly associated source of MI/MCI might be essential oil, which has never been reported to be a common source of exposure to MI/MCI. In our previous report, people who were diagnosed as having ACD to essential oils also frequently had positive reactions to fragrance mix (77.8%).¹⁴ Among the patients with contact allergy to MI/MCI, those with associated source of essential oil ($n = 6$), 83.3% ($n = 5$) had worked as aromatherapists and they all claimed frequent exposure to cosmetic products. Most of the aromatherapists in Taiwan are also hairdressers.¹⁴ Therefore, we surmise that patients frequently exposed to essential oil or fragrance may also contact to cosmetic products, soap, and shampoo, which are all common sources of MI/MCI. However, there has been no report on the association between ACD to fragrance mix and contact allergy to MI/MCI before. Because of the variable concentration of multiple components and also the complex interactions, which was known as the quenching effect, it was difficult to determine the sensitizing agent responsible for skin reactions associated with essential oils.¹⁴ Besides, the second and third most commonly associated sources of MI/MCI were hair dressing products and cosmetics respectively. Although parphenylenediamine (PPD) is the most important allergen of ACD in hair dressers,¹⁵ there are some reports showing the incidences of ACD to MI/MCI were around 2.1–5.1% in this profession.^{16,17} In addition, patients with ACD to PPD were also frequently allergic to fragrance mixture (9.8–14.3%), which were also the most common allergen in patients who had contact allergy to essential oils.¹⁸ In this study, 5 patients (35.7%) had contact allergy to fragrance mix. This indicates that MI/MCI might be used in essential oil ingredient.

The third most commonly associated source of MI/MCI was cosmetics in this study. There are several previous reports showing that the most common allergens of ACD to cosmetics were fragrances and preservatives.¹⁹ MI/MCI was increasingly used as a preservative since 2005 to substitute the use of methylidibromo glutaronitrile (which also includes phenoxyethanol) due to the recognition of methylidibromo glutaronitrile as an important sensitizer and irritant in Europe.¹⁹ In Food and Drug

Administration's database in Taiwan, there are 77 documented products (e.g. hair products and cosmetics) that contain MI/MCI as preservatives. However, the database only documents “cosmeceutical products” but not all the “cosmetics”. Lundov et al. founded that the frequency of MI usage in cosmetics is low (around 1.5%) in the United Kingdom.²⁰ However, patients may not only contact to cosmetics but also hair or household products.

In this study, common concomitant positive allergens in patients with contact allergy to MI/MCI were cobalt (9 patients, 64.3%), fragrance mix (5 patients, 35.7%), and formaldehyde (4 patients, 28.6%). Cobalt is the second common metal allergen, next to nickel.²¹ There was an increasing frequency of cobalt allergy in females due to chromium-tanned leather.²¹ In the past, cobalt exposure was frequently seen in metal, glass and pottery workers.²¹ The evidence of association between cobalt and MI/MCI allergy was limited in the literature, which may need further survey. However, it's well known that nickel/cobalt allergy is more common in women, which also reflects more frequent ear piercing and wearing of ornaments in women.⁹ Our previous study also revealed the degree of nickel and cobalt co-sensitization was higher than that of the other combinations. In addition, the female cobalt-sensitized individuals were more often co-sensitized to nickel.⁹ Among the 9 patients sensitized to cobalt, 5 also co-sensitized to other metals; in those with isolated metal allergy to cobalt, most of them had other co-sensitized agents like hair products, fragrance, or rubber chemicals (Table 1).

The frequency of contact allergy to fragrance mix was around 4.7–13.3% in Denmark, United Kingdom, Singapore, Germany, Netherlands, and Hungary, while the incidence was 8.4% in Taiwan.²² Maio P. et al. showed that among the patients who had positive reaction to MCI/MI, 20% and 13% of them had positive reactions to fragrance mix and chromium, respectively.²³

In this study, most (85.7%) of the patients with contact allergy to MI/MCI were female. In accordance with previous large scale studies, which showed a female-gender-prevalence in most of patients with ACD, especially in ACD to essential oil, hair dressing products, and cosmetics.^{15–23} Due to the increased use of MI/MCI as a preservative in cosmetics and that a high prevalence of cosmetic and hairdressing practices in the female population, these phenomena may explain the female predominance noted in this study. The mean age of the patients with contact allergy to MI/MCI was 31 years old, which is significantly younger than the total patients receiving patch testing (36.4 years old) in the same period. The above results are consistent with previous studies showing that ACD is more common in younger population, while geriatric patients are prone to have irritant contact dermatitis.^{14,24}

We found hands (71.4%, $n = 10$) and face (21.4%, $n = 3$) were the most affected areas. All of the patients who had contact allergy to MI/MCI with associated sources such as essential oil, hair dressing and cosmetics presented skin lesions on the face and/or hands. Aromatherapist and hair dresser were the first two common associated occupations, and the associated sources of these two groups were essential oil and hair products. In the previous literature,^{14,17} face and hands were also the most common involved sites in patients diagnosed as having occupational contact dermatitis due to hair care products and essential oil. In this study, there was a 3-year-old girl diagnosed as having foot eczema. It has been reported that baby toilet tissue or other pediatric skin care products could be the sources of MI/MCI.^{25,26} Even though the patient's mother did not frequently use wet wipes on the lesion sites, the patient did expose to some pediatric skin care products before. The other possible sources of exposure might be washing powder, laundry detergents, or fabric softeners during washing the shoes.

Although it did not reach statistical significance, a trend of increasing incidence of contact allergy to MI/MCI from 2.1% to 5.9%

Table 2 Differences in the MCI/MI positive reactions during the studied periods.

Period	N	Positive reaction	Percentage	P-value ^a
1987–2005	145	3	2.1%	0.1665
2006–2015	202	11	5.4%	

^a Fisher's exact test.

after 2005 was noted in a tertiary referral center for patch testing in northern Taiwan. Most of the patients were female. The commonly associated sources of MI/MCI were essential oil, hair dressing products and cosmetics. Face and hands were the most affected locations. For dermatologists, contact allergy to MI/MCI should be considered in managing female patients with facial or hand eczema, especially those who work as an aromatherapist or hair-dresser. We also revealed a possible link between exposure to essential oil and contact allergy to MI/MCI. Further studies are needed to disclose whether this is due to exposure to other cosmetic/hair products or concomitant sensitization to MI/MCI in the ingredients of essential oil.

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Conflict of interest disclosures

The authors declare that they have no financial or non-financial conflicts of interest related to the subject matter or materials discussed in this article.

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