

Contact sensitization to metals in Taiwan

TEH-YANG CHENG, YU-HSIAN TSENG, CHEE-CHING SUN AND CHIA-YU CHU

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

Background: Correlation of several patient factors with contact sensitization to nickel, cobalt, chromate, and other metal allergens has not been reviewed in the Taiwanese population.

Objectives: A retrospective analysis was performed to define the characteristics of patients with positive patch tests to metals in a tertiary referral medical centre between 1978 and 2003.

Patients and Methods: Patch test data of 3559 patients at a medical centre in Taiwan from 1978 to 2003 were retrospectively analysed. Contact sensitization to metals was defined as a positive reaction to at least one of the metal substances in the patch test series. Chi-squared test, Fisher's exact test, and multivariate logistic regression were used for statistical analysis.

Results: Female patients were more likely to have contact sensitization to metal allergens except chromate or mercurochrome. Patients who reacted to chromate were more likely to be male, with an occupational correlation, older age, and a site of predilection towards the extremities. Within the first and sixth decades of age, thimerosal and chromate were the leading causes of metal contact sensitization, respectively. Nickel was the major metal sensitizer among the other age groups.

Conclusions: Several patient factors were characterized related to metal sensitization in the Taiwanese population. The sources of exposure were further discussed.

Key words: ammoniated mercury; chromate; cobalt; contact sensitization; metal; nickel; thimerosal
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Metal agents are contacted inevitably in daily life and are noted to be the most common cause of allergic contact dermatitis in many countries (1–4). The rate of contact sensitization to nickel, cobalt, and chromate are similar in many countries, but the rates of sensitization to other metals differ from country to country (5–7).

Several predisposing patient factors have been shown to be characteristic of different metal agents (8–10). For example, patients who were sensitized to nickel were noted to be younger and more likely to be female (3, 9, 11). Chromate sensitization was thought to be more related to occupation, and patients were likely to be male (3, 9). The face and hands were sites of predilection for dermatitis (5, 8, 11). The relationship between atopic dermatitis and sensitization to metal appeared to be conflicting among different studies (5, 8, 9, 12, 13).

The purpose of this study was to survey the rate of sensitization to metal agents in the Taiwanese population. Also, the distribution of sex, age (by decades), occupations, sites of dermatitis, and clinical relevance are characterized with respect to each metal agent and the source of exposure.

Patients and Methods

Patient history and demographics

The National Taiwan University Hospital is a tertiary referral centre, in which our Contact Dermatitis Clinic is a referral clinic in northern Taiwan, which has Chinese-based population of more than six million people (14). The patients consisted of Taiwanese, Hakka, aborigine, and immigrants from Mainland China (15). For every patient with suspected contact dermatitis seen in

this clinic from 1978 to 2003, a questionnaire was completed, which 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.

Patch testing

Every patient with suspected contact dermatitis received a comprehensive patch test with the European standard series. Patients with specific dermatitis (i.e. pompholyx, perioral dermatitis, nummular eczema, or therapy-resistant dermatitis) received additional metals and mercurials patch test series. In addition, substances related to the patient's contactants were also administered. Patch testing followed the protocol recommended by the International Contact Dermatitis Research Group (ICDRG) with Finn Chambers[®] (Epitest Ltd Oy, Tuusula, Finland) on Scanpor[®] tapes (Norgesplaster AS, Vennesla, Norway) applied to a lesion-free area on the back. 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. The reading at D3 or D4 was considered positive if the reaction was equal to or stronger than palpable erythema, according to the guidelines of the ICDRG (14, 16).

The tested substances in the standard trays included nickel sulfate 5% petrolatum (pet.), potassium dichromate 0.5% pet., cobalt chloride 1% pet., ammoniated mercury 1% pet., and thimerosal 0.1% pet. The tested allergens in the additional metals and mercurials series included ammonium tetrachloroplatinate 0.25% pet., copper sulfate 1% aqueous solution (aq), mercury 1% pet., palladium chloride 1% pet., potassium dicyanoaurate 0.002% aq, and sodium thiosulfatoaurate 0.5% pet. (Trolab, Almiral Hermal GmbH, Reinbek, Germany) as well as mercuric chloride 0.05% aq and mercurochrome (dibromohydroxymercurifluorescein) 2% aq which were prepared by our laboratory.

Study design

This was a retrospective analysis of patch test data from 3559 patients at a medical centre in Taiwan from 1978 to 2003. Contact sensitization to metals was defined as having a positive reaction to at least one of the metal substances in the patch test series. The patients' ages were stratified into decades for each metal agent tested. The clinical relevance of a positive patch test reaction was defined as (i) present (the patch test has unmasked an allergen that is causing the current dermatitis), (ii) past (the patch test has unmasked an allergen that has caused a dermatitis in the past, but is of no present relevance), and (iii) unknown (no known exposure in the past) (17).

Table 1. Comparison between the metal-positive and the metal-negative groups*

Groups	Age	Sex (F:M ratio, %)	Atopy (personal) %	Sites 1st/2nd/3rd/4th	Occupation 1st/2nd/3rd/4th
Metal (+)				1. Upper extremities	1. Typists, secretaries, and computer workers
	33.2 ± 13.4 [†]	71.2:28.8	24.0	2. Face	2. Students
				3. Hands	3. Housewives and househusbands
				4. Lower extremities	4. Bricklayers, building workers, plumbers
Metal (–)				1. Face	1. Typists, secretaries, and computer workers
	36.2 ± 15.1 [†]	70.0:30.0	22.9	2. Upper extremities	2. Housewives and househusbands
				3. Hands	3. Students
				4. Lower extremities	4. Retired or unemployed
Metal (–) but reactive to other allergens [‡]				1. Face	1. Typists, secretaries, and computer workers
	37.1 ± 15.2 [†]	70.0:30.0	21.7	2. Upper extremities	2. Housewives and househusbands
				3. Hands	3. Students
				4. Lower extremities	4. Services industries

*The mean age of the patients who responded positively to metals was found to be significantly younger than that of the patients who did not respond to metals. In addition, the total number of patients with positive patch test reactions to allergens except metal agents collected from the same special clinic is listed here as the third group for comparison. The only significant difference between this group and the group of patients who reacted positively to metals was the mean age.

[†]Statistically significant ($P < 0.01$).

[‡]This group of patients was recruited from the database of patients receiving patch testing at the same special clinic during 1978–2003. We selected those who had reacted to at least one allergen other than metal as the control group. The total number is 830.

Table 2. Summary of various patient factors with respect to each metal agent in both sexes

	Ni	Co	Cr	NH ₄ Hg	Thim	Hg	MC	HgCl ₂	Cu	ThAu	Metal (+)	Metal (–)	Total
Sex													
Female	500 (79.4%)	162 (64.0%)	54 (32.9%)	140 (75.7%)	109 (72.2%)	1 (100%)	17 (51.5%)	21 (77.8%)	6 (66.7%)	1 (100%)	768 (71.2%)	1736 (70.0%)	2504 (70.4%)
Male	130 (20.6%)	91 (36.0%)	110 (67.1%)	45 (24.3%)	42 (27.8%)	0	16 (48.5%)	6 (22.2%)	3 (33.3%)	0	311 (28.8%)	744 (30.0%)	1055 (29.6%)
Age group (years)													
0–10	7 (1.1%)	5 (2.0%)	2 (1.2%)	0	8 (5.3%)	0	1 (3.0%)	2 (7.4%)	1 (11.1%)	0	20 (1.9%)	53 (2.1%)	98 (2.0%)
11–20	106 (16.8%)	34 (13.4%)	4 (2.4%)	11 (5.9%)	25 (16.6%)	0	3 (9.1%)	6 (22.0%)	1 (11.1%)	0	136 (12.6%)	238 (9.6%)	555 (11.2%)
21–30	257 (40.8%)	84 (33.2%)	36 (22.0%)	62 (33.5%)	66 (43.7%)	0	14 (42.4%)	8 (29.6%)	2 (22.2%)	1 (100%)	399 (37.0%)	787 (31.8%)	1695 (34.2%)
31–40	129 (20.5%)	53 (20.9%)	45 (27.4%)	50 (27.0%)	26 (17.2%)	0	5 (15.0%)	5 (19.0%)	2 (22.2%)	0	238 (22.1%)	506 (20.4%)	1049 (21.2%)
41–50	74 (11.7%)	38 (15.0%)	34 (20.7%)	29 (15.7%)	12 (7.9%)	1 (100%)	2 (6.0%)	3 (11.1%)	2 (22.2%)	0	147 (13.6%)	428 (17.3%)	766 (15.5%)
51–60	31 (4.9%)	22 (8.7%)	33 (20.1%)	25 (13.5%)	9 (6.0%)	0	4 (12.1%)	3 (11.1%)	1 (11.1%)	0	92 (8.5%)	269 (10.9%)	483 (9.8%)
61–70	19 (3.0%)	13 (5.1%)	9 (5.5%)	7 (3.8%)	4 (2.6%)	0	3 (9.0%)	0	0	0	38 (3.5%)	150 (6.1%)	240 (4.8%)
>71	7 (1.1%)	4 (1.6%)	1 (0.6%)	1 (0.5%)	1 (0.7%)	0	1 (3.0%)	0	0	0	9 (0.8%)	44 (1.8%)	67 (1.4%)
Sites of Dermatitis													
First	Face* 37.6%	Upper extremities 39.8%	Upper extremities* 53.3%	Face 45.9%	Upper extremities 38.5%						Upper extremities* 38.9%	Face 36.3%	
Second	Upper extremities* 36.6%	Face 33.7%	Hands* 47.5%	Upper extremities* 30.6%	Face 32.1%						Face 33.7%	Upper extremities 32.4%	
Third	Hands* 17.9%	Hands 28.9%	Lower extremities* 22.1%	Hands 25.2%	Hands 25.6%						Hands 24.7%	Hands 24.5%	
Occupation													
First	Typist, secretary, and computer worker 30.4%	Typist, secretary, and computer worker 21.7%	Bricklayer, building worker, and plumber 39.2%	Typist, secretary, and computer worker 29.2%	Student 31.4%						Typist, secretary, and computer worker 26.4%	Typist, secretary, and computer worker 25.0%	
Second	Student 17.7%	Bricklayer, building worker, and plumber 20.8%	Typist, secretary, and computer worker 9.8%	Housewife and husband 26.6%	Typist, secretary, and computer worker 22.9%						Student 15.3%	Housewife and husband 14.0%	
Third	Housewife and husband 9.6%	Student 8.5%	Housewife and husband 9.8%	Electronic and engineering industry 8.0%	Housewife and husband 11.4%						Housewife and husband 11.3%	Student 12.6%	
Total	630	253	164	185	151	1	33	27	9	1	1079	2480	3559

Co, cobalt; Cr, chromate; Cu, copper sulfate; Hg, metallic mercury; HgCl₂, mercuric chloride; MC, mercurochrome; Ni, nickel; ThAu, sodium thiosulfate; Thim, thimerosal.

*Statistically significant ($P < 0.05$).

Statistics

The prevalence of contact sensitization to each metal agent within our tested population was calculated. The mean age, sex, atopy diathesis, site of dermatitis, and occupations were compared between the metal-positive and metal-negative groups by the chi-squared test. A one-tailed *P* value of 0.05 or less was considered to be significant. The sex, age distribution, site of dermatitis, occupation, atopy diathesis, and clinical relevance were analysed by the chi-squared test or by the Fisher's exact tests if the cell frequencies were lower than five. The reference groups for these comparisons comprised those in which patients reacted to metal agents other than the tested one. Furthermore, multivariate logistic regression was used to analyse various factors (age, sex, site of dermatitis, and occupation) and the positive patch test reactions versus the non-positive reactions to nickel, cobalt, chromate, ammoniated mercury, or thimerosal. All the analyses were performed using SAS software (version 8.02; SAS Institute, Cary, NC, USA).

Results

Of the investigated individuals, 1079 (30.3%) patients showed positive patch test reactions to at least one metal agent. The female to male ratios were not significantly different between the metal-reactive and the metal-non-reactive groups (Table 1). The mean age was 33.2 years in the metal-reactive group, which was significantly younger than that of the metal-non-reactive group (36.2).

All metal agents

The first three leading causes of metal contact sensitization were nickel, cobalt, and ammoniated mercury in female patients and nickel, chromate, and cobalt in male patients. The female patients had higher percentages of sensitization to all metal agents except chromate (Table 2).

Nickel, cobalt, and chromate

As shown in Figure 1, 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, and the male cobalt-sensitized individuals were more often co-sensitized to chromate.

Organic mercury, mercury metal, and mercury salts

Patients were more commonly sensitized by ammoniated mercury or thimerosal than the other tested mercurials. Co-sensitization of ammoniated mercury and thimerosal was found to be significant with a *P* value less than 0.01 (Table 3).

Stratification by age

After stratifying the patients into decades of age, nickel was noted to be the most common cause of contact sensitization in most age groups (Fig. 2a and 2b). The chromate-sensitized patients were distributed evenly in age from their 20s to 50s (Fig. 2a). In addition, more patients in their 30s to 50s were sensitized to ammoniated mercury than among the other age groups.

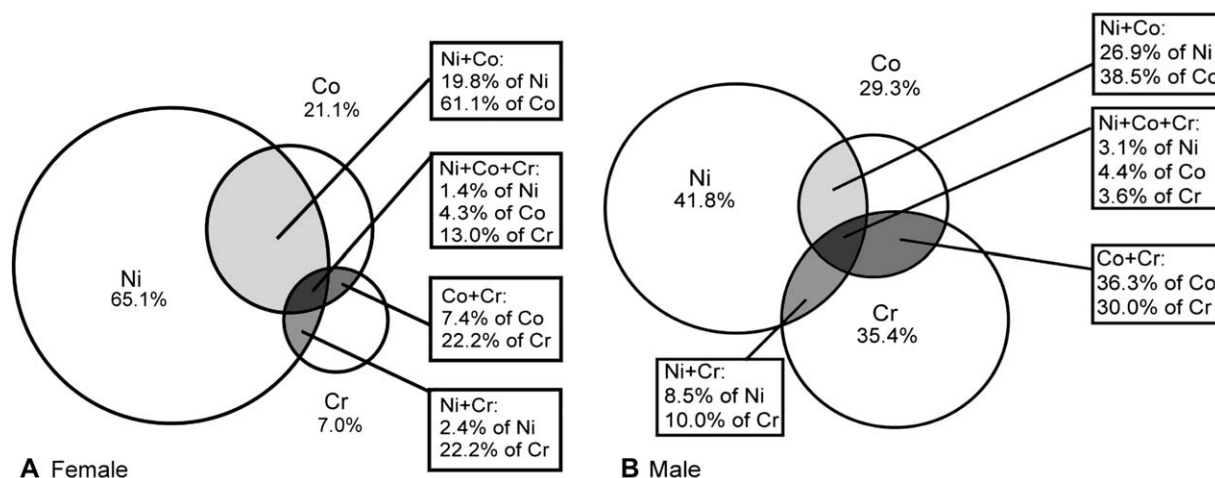


Fig. 1. The percentages of co-sensitization to nickel, cobalt, and chromate in female (a) and in male (b) patients. The percentages outside the boxes represent the percentage of patients with positive reactions to the indicated metal allergens among all metal-reactive patients of the same gender. Co, cobalt; Cr, chromate; Ni, nickel.

Table 3. The relationships among the tested mercurials*

Frequency %	NHHg			Thim			Hg			MC			HgCl ₂		
	All	Only	All	All	Only	All	All	Only	All	All	Only	All	All	Only	All
Female	140	97	109	14.2%	12.6%	18.2%	1	77	1	0	17	1	21	2	30 [†]
	(75.7%)	(78.9%)	(72.2%)	10.0%	74.8%	10.0%	0.1%	10.0%	0.1%	2.2%	0.1%	2.7%	0.3%	0.3%	3.9%
Male	45	26	42	13.5%	8.4%	14.5%	0	26	0	16	0	6	3	13 [†]	13 [†]
	(24.3%)	(21.1%)	(27.8%)	25.2%	25.2%	25.2%	0%	25.2%	0%	5.1%	0%	1.9%	1.0%	1.0%	4.8%
Total	185	123	151	14.0%	11.4%	17.1%	1	103	1	33	0	27	5	43 [†]	43 [†]
	(74.0%)	(74.0%)	(74.0%)	9.5%	9.5%	9.5%	0.1%	9.5%	0.1%	3.1%	0%	2.5%	0.5%	0.5%	4.2%

Hg, metallic mercury; HgCl₂, mercuric chloride; MC, mercurochrome; NHHg, ammoniated mercury; Thim, thimerosal.

*Ammoniated mercury and thimerosal were significantly co-sensitized, but the other combinations among the mercurials were not. The group of 'all' consisted of those with positive reactions to that agent with or without positive reactions to other metal allergens. The groups of 'only' consisted of those with positive results to that metal agent alone without positive reactions to other metal allergens. The percentage in the second row of each sex represented the percentage of positive reactions to each metal agent in the same sex group. The percentage in the parenthesis represented the percentage of each sex in the same group who responded positively to metals.

[†]Statistically significant ($P < 0.01$).

Sites of predilection

Among the metal-sensitized individuals, the upper extremities, face, and hands were the common sites of dermatitis, listed in decreasing order (Table 2). Upper extremities were more commonly involved among individuals who were sensitized to chromate (53.3%) than the other groups. The percentage of facial involvement was higher in those who were sensitized to ammoniated mercury (45.9%) than in those who reacted to at least one metal allergen (33.7%).

Atopy diathesis

The percentages of patients with a personal history of atopy were not found to be significantly different among the metal-reactive (24.0%) and the metal-non-reactive (22.9%) groups.

Occupations

Typist, secretary, and computer worker were the leading occupations in most groups, just as they were in the general population. However, bricklayer, building worker, and plumber were the leading occupations for patients who reacted positively to chromate and the second most common occupations for those who reacted positively to cobalt. Student was the most common occupation in the group who responded positively to thimerosal with a percentage of 31.4%, which was higher than the average (15.3%). A similar finding was noted for the occupations of housewife and househusband, who represented 11.3% of the metal-reactive group, but 26.6% of the ammoniated mercury-reactive group.

Clinical relevance

Nickel-, cobalt-, chromate-, ammoniated mercury-, and thimerosal-positive reactions had present relevance rates of 76.6%, 70.0%, 81.5%, 26.7%, and 20.9%, respectively. Sensitization to ammoniated mercury had a past relevance rate of 18.6% (nickel 12.3%, cobalt 10.1%, chromate 1.9%, and thimerosal 3.6%).

Discussion

The prevalence of sensitization to each metal agent in the investigated population was nickel sulfate 17.7%, cobalt chloride 7.1%, potassium dichromate 4.6%, ammoniated mercury 5.2%, thimerosal 4.2%, mercurochrome 0.9%, and mercuric chloride 0.8%. For nickel, cobalt, and chromate, our data were similar to those found in Singapore (1), Germany (2), Turkey (3), and the

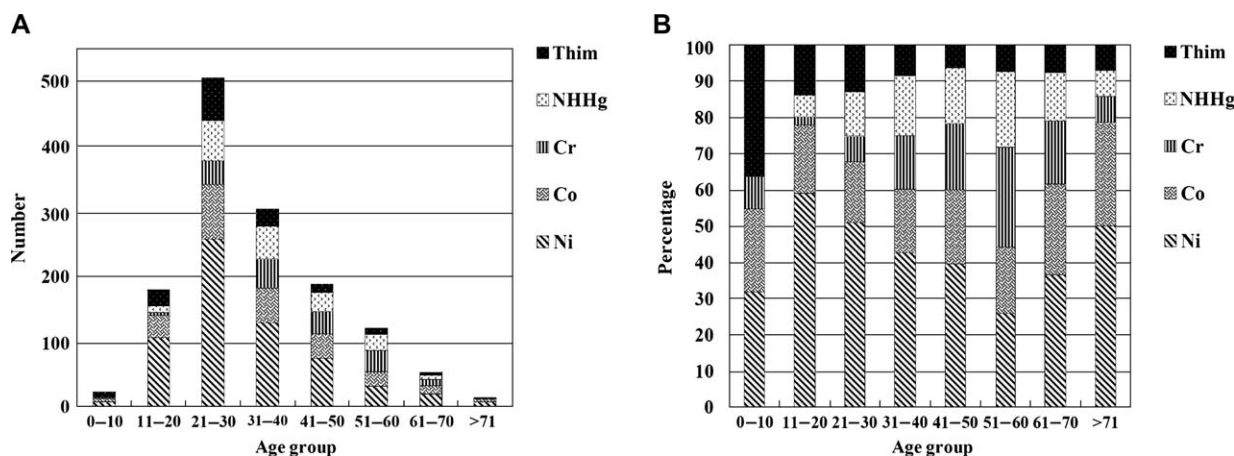


Fig. 2. The age distribution of patients who were sensitized to metals. The number of patients sensitized to nickel, cobalt, chromate, ammoniated mercury, or thimerosal in each age group (a). The percentages of patients with positive reactions to each metal agent in each age group (b). Co, cobalt; Cr, chromate; Ni, nickel; NHHg, ammoniated mercury; Thim, thimerosal.

USA (8). But for mercurials, it varied from country to country (4, 18–21). A multivariate logistic regression was used to analyse the various patient factors and the results are shown in Table 4.

The most common sources of exposure to nickel were eyeglass frames and the belt buckles in students' uniforms. The reason for this might be that nickel-releasing alloys were widely used in the manufacture of eyeglass frames, ornaments, buckles, buttons, and zippers in the past. We found that the prevalence of nickel-sensitized individuals increased from 14.3% in 1978–1990 to 23.0% in 1991–2003, which was different from the decreasing trends in Germany (15.5% in 1992–2000 to 11.05% in 1995–2002) and Denmark (24.8% in 1985–1986 to 9.2% in 1997–1998) (9, 22, 23). This might be in part related to the following factors: ear piercing and wearing of ornaments have become gradually more popular and are considered as important sources of exposure nowadays; the accuracy of diagnosis of allergic contact dermatitis has increased, and more stringent criteria have been adopted for performing

patch tests since the 1990s. As material science improved over the time, the population was encouraged to avoid using nickel-releasing eyeglass frames and ornaments.

In this study, the second most common metal agents were cobalt and chromate in female and male patients, respectively. Only one third of cobalt-sensitized individuals were not co-sensitized to nickel or chromate as has been found in other studies (1, 8). This might contribute to the slightly increased prevalence of cobalt sensitization over time (6.1% in 1978–1990 to 8.7% in 1991–2003). In addition, the most important source of chromate exposure was cement in our studies (Tables 2 and 4). There are about 846,000 construction workers in Taiwan (about 12% of all labourers), and this was the first and second most common occupation of the individuals who were sensitized to chromate and cobalt, respectively. In fact, 21% of construction workers have experienced occupational dermatitis (24). The prevalence of chromate-sensitized individuals has not changed much over time (4.7% in 1978–1990 to 4.4% in 1991–2003).

Table 4. Multivariate logistic regression analysis of various factors*

Variants/metals	Ni	Co	Cr	NHHg	Thim
Age >35 years	0.547 (0.453–0.661)	0.829 (0.633–1.085)	1.378 (0.955–1.988)	1.220 (0.903–1.648)	0.401 (0.273–0.588)
Female	1.529 (1.230–1.900)	0.895 (0.663–1.208)	0.505 (0.337–0.757)	1.300 (0.901–1.877)	0.919 (0.626–1.348)
Upper extremities	1.611 (1.327–1.956)	1.655 (1.244–2.201)	1.586 (1.075–2.341)	1.142 (0.818–1.593)	1.242 (0.865–1.785)
Face	1.275 (1.049–1.549)	1.207 (0.901–1.617)	0.600 (0.382–0.942)	1.333 (0.960–1.852)	1.367 (0.951–1.965)
Bricklayers, building workers, and plumbers	0.175 (0.055–0.559)	3.240 (1.930–5.439)	22.599 (14.038–36.382)	0.967 (0.374–2.504)	0.754 (0.228–2.498)

Co, cobalt; Cr, chromate; NHHg, ammoniated mercury; Ni, nickel; Thim, thimerosal.

*Five variants were analysed here: age (over 35 years old versus less than 35 years old), sex (female versus male), site of dermatitis (upper extremities and face as two variants), and occupation (bricklayers, building workers, and plumbers). The control group for each metal agent comprised those who reacted to a metal other than the tested one. For example, the control group for the nickel-sensitized group comprised individuals who reacted to metals other than nickel. The cells with bold type characters have reached statistically significant level of $P < 0.05$.

A series of studies has been performed since 1995 to reduce the concentration of hexavalent chromate in the cement. Ferrous sulfate was added while manufacturing the cement, and it, indeed, reduced the concentration of the hexavalent chromate (24, 25). However, the effective storage period was noted to be shortened, which was thought to be related to the hot and humid environment in Taiwan. Thus, some researchers suggested that adding ferrous sulfate immediately before use might strengthen its reducing effect (24, 25).

Ammoniated mercury was widely used as the active ingredient in facial whitening agents in the past (in about 42% of the tested cosmetics in the 1980s) (7). The prevalence did not change much over time (4.9% in 1978–1990 to 5.6% in 1991–2003). However, the present relevance rate decreased from 39.8% in 1978–1990 to 9.5% in 1991–2003. This might be related to the limitation of ammoniate mercury to be used in cosmetics by the government since 1983. Unfortunately, ammoniated mercury was still found in some of the poorly labelled cosmetics nowadays. Sensitization to thimerosal has been found to be clinically irrelevant in some reports (10, 20, 26–28), but not in others (21). In our study, thimerosal was found to have a present relevance rate of 20.9%, which may have been caused by the wide use of thimerosal and mercurochrome for surgical disinfection and wound care in Taiwan in the past. The prevalent rate of sensitization to thimerosal increased from 2.8% in 1978–1990 to 6.5% in 1991–2003. However, the present relevance rate decreased from 33.3% to 12.9% between these two periods of time. This might be the result of the restrictions for using thimerosal and mercurochrome since the 1980s. However, thimerosal was still found in some contact lens cleansers, eye-drops, poorly labelled cosmetics, and vaccines. Students, the most common occupation in this group, might have had a higher probability of receiving ophthalmic medications, vaccinations, and of using contact lens cleansers or cosmetics of low quality (21). In addition, obvious cross-reaction was noted among the mercurials except metallic mercury (7).

This study was limited by its retrospective nature and the selection of patients in a specialized clinic. Thus, the prevalence of sensitization to each metal agent only represented the patients receiving patch testing from this clinic. Furthermore, mercurochrome and mercuric chloride were routinely tested in patients only during 1980–1987 (7). Besides, additional metal and mercurial series were not performed routinely for each patient. Thus, the prevalence rate of sensitization to metal

agents other than nickel, cobalt, chromate, ammoniated mercury, or thimerosal might be underestimated. In addition, the rate of sensitization to gold salts was low in our study. This might be attributed to the fact that in the 1970s–1990s, when Taiwan was still in developing status, Most people used to keep their valuables (including gold or platinum) in their safe deposit boxes instead of wearing them. The Taiwanese people now wear more stainless steel, silver, platinum, and titanium ornaments, but gold ornaments remain less popular than those made of other metals. In addition, only a small proportion of the study population worked in chemical industries (1.7% in the metal-reactive group and 2.5% in the metal-non-reactive group). Silver was not tested in our series.

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Address:

Chia-Yu Chu, MD, PhD
 Department of Dermatology
 National Taiwan University Hospital
 National Taiwan University College of Medicine
 7, Chung-Shan South Road
 Taipei 100
 Taiwan
 Tel: +886 2 2356 2141
 Fax: +886 2 2393 4177
 e-mail: chiayu.chu@gmail.com