

Evaluating the Nickel Content in Metal Alloys and the Threshold for Nickel-Induced Allergic Contact Dermatitis

Many patients are currently suffering from nickel (Ni)-induced allergic contact dermatitis (ACD). There have been few Korean studies dealing with the threshold of Ni-induced ACD and quantifying the total amount of Ni in the metal alloys. The aim of this study is to evaluate the amount of Ni leached from metal alloys and Ni contents in metal alloys, and to estimate the threshold of Ni-induced ACD. All the earrings we examined leached below $0.5 \mu\text{g}/\text{cm}^2/\text{week}$, the upper limit of European Union (EU) regulation, but the other metal alloys leached a much higher amount of Ni than the limit. Likewise, all the earrings we examined contained less than 0.05% Ni ($500 \mu\text{g}/\text{g}$), the upper limit of EU regulation, but the other metal alloys exceeded this limit. Twenty Ni-sensitive subjects, who were patch-tested with various concentrations of Ni sulphate, showed positive reactions to 5% and 1% Ni sulphate, 10 subjects showed positive reactions to 0.01%, and the most sensitive subject showed reaction even to 0.0001%. The subjects in this study were more sensitive to Ni than those in the previous studies done in Europe. Taken together, strictly regulating the Ni-containing alloys that are made in Korea is needed to lower the occurrence of Ni-induced ACD.

Key Words : Dermatitis, Allergic Contact, Leaching Amount, Nickel, Threshold

Yoon Young Kim, Mi-Yeon Kim,
Young Min Park, Hyung Ok Kim,
Cjae Sook Koh*, and Hae Kwang Lee†

Department of Dermatology, Kangnam St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul; Dermapro Ltd*, Seoul; Amore Pacific R & D†, Gyeonggi-do, Korea

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Address for correspondence

Hyung Ok Kim, M.D.
Department of Dermatology, College of Medicine,
The Catholic University of Korea, 505 Banpo-dong,
Seocho-gu, Seoul 137-040, Korea
Tel : +82.2-599-9950, Fax : +82.2-590-1494
E-mail : knderma@catholic.ac.kr

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INTRODUCTION

Nickel (Ni) is the most common cause of allergic contact dermatitis (ACD) among females. Epidemiological studies conducted on the Korean general population in Korea have shown that 6.1-13.8% of the population is allergic to Ni (1). Ni sensitization frequently follows ear piercing, after which a pin containing various amounts of Ni is left in place for 4 to 6 weeks so that the wound channel may epithelize (2, 3). To prevent the occurrence of Ni-induced ACD from metal alloys such as that in earrings, the amount of bioavailable allergen in the product should be reduced below the level that elicits an allergic reaction in sensitized individuals.

In the European Union (EU), the Ni directive was passed in 1994, and this directive states that the concentration of Ni in post assemblies (used after ear piercing) may not exceed 0.05% ($500 \mu\text{g}/\text{g}$), and products that come into direct and prolonged contact with the skin (e.g. earrings, watchstrips, or zippers) should not release greater than $0.5 \mu\text{g}/\text{cm}^2/\text{week}$, and also that the Ni released from coated products should not exceed this level after 2 yr of normal use; further, in 2004, the piercing metal should not release greater than $0.2 \mu\text{g}/\text{cm}^2/\text{week}$ (4, 5). In contrast, there have not yet been any regulatory limits about the amount of leached Ni and Ni

contents in metal alloys in Korea. Recent studies have indicated a significant decline in the frequency of Ni-induced ACD after the implement of the Ni-exposure regulations in Europe (6).

Although the incidence of Ni-induced ACD is increasing in Korea, most of reports are just case reports and only a few clinical studies have been performed about metals in working fluid (7) and dental materials (8). In this study, we investigated the amount of leached Ni and Ni contents in metal alloys that are commonly used as jewelry and clothing accessories in Korea. We also determined the provocation threshold of Ni in Ni-sensitized individuals by conducting Ni-patch tests.

MATERIALS AND METHODS

The amount of Ni leaching into artificial sweat

Since the main cause of Ni-induced ACD is the Ni-containing metals, such as jewelry, buckles, metal buttons, and hooks, we analyzed 9 pairs of earrings, 2 belt buckles, 2 metal buttons, and 1 hook for the amounts of Ni leached into artificial sweat. Because earrings of 14 K gold, earrings of 14 K gold coated with white gold, and cheap earrings of unknown

contents are most popular in Korea, each of these earrings and the earrings of other metal alloys were purchased in three very popular shops in Seoul. The artificial sweat consisted of aerated water that contained 0.5% sodium chloride, 0.1% urea, and 0.1% lactic acid and ammonia. Ammonia was used to adjust the pH to 6.5. After weighing each object and estimating the approximate surface area, each metal alloy was placed in a glass and covered with artificial sweat. The glasses were closed with para-film and stored at 30°C for 7 days. On the 7th day, the amount of Ni leached was calculated by performing atomic emission spectroscopy with an inductive couple plasma apparatus (ICP-AES, Optima 5300DV, PerkinElmer, Massachusetts, U.S.A.) at a wavelength of 231.605 nm; the results were expressed as $\mu\text{g}/\text{cm}^2/\text{week}$ and the lowest reported limit was 0.1 $\mu\text{g}/\text{cm}^2/\text{week}$.

The total amount of Ni contents in the metal alloys

To determine the total amount of Ni contents contained in the metal alloys, each metal alloy was dissolved in aqua regia (concentrated nitric acid and hydrochloric acid, 1:3 v/v) and

analyzed by ICP-AES at a wavelength of 231.605 nm. The lowest reported limit was 1 $\mu\text{g}/\text{g}$ of Ni.

Ni-Patch test

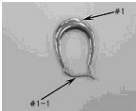
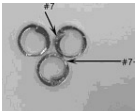
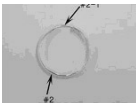
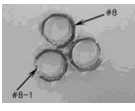

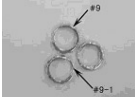





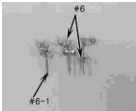

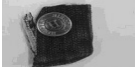
Subjects

Twenty subjects who were known to be sensitized to Ni were enrolled in this study. Ni sensitivity was confirmed in each case by a definite positive reaction 48 hr after patch testing with 5% Ni sulphate (10.4 mg/g of Ni) in petrolatum ($\text{NiSO}_4 \cdot 7\text{H}_2\text{O}$, Sigma-Aldrich Korea Ltd., Gyeonggi-do). There were 19 women and 1 man, with a mean age of 31 yr (age range, 19-48 yr). Four of the participants had a past history of atopic dermatitis (AD).

Provocation threshold for Ni

Patch testing was performed with serial dilutions of Ni sulphate at 8 sites on the upper back avoiding the midline, according to the recommendations of the International Contact Dermatitis Research Group (9). To minimize the occurrence of other skin reactions, each site was located at least 7.5 cm dis-

Table 1. Amount of leached nickel and the nickel contents from the metal alloys

Specimen No.		Amount of leached Ni ($\mu\text{g}/\text{cm}^2/\text{week}$)	Nickel contents ($\mu\text{g}/\text{g}$)	Specimen No.		Amount of leached Ni ($\mu\text{g}/\text{cm}^2/\text{week}$)	Nickel contents ($\mu\text{g}/\text{g}$)
1		Undetectable	23.1	7		Undetectable	Undetectable
1-1		Undetectable	Undetectable	7-1		Undetectable	Undetectable
2		Undetectable	Undetectable	8		Undetectable	13.4
2-1		Undetectable	Undetectable	8-1		Undetectable	13.4
3		0.25	66.2	9		Undetectable	Undetectable
4		0.33	74.1	9-1		Undetectable	Undetectable
4-1		0.43	181	10		1.36	3,830
5		0.34	86.9	11		1.41	5,150
5-1		0.42	178	12		1.38	3,130
6		Undetectable	Undetectable	13		0.44	468
6-1		Undetectable	Undetectable	14		0.38	149

Specimens: No. 1-3, cheap earrings of unknown contents; No. 4-6, earrings of 14 K gold coated with white gold; No. 7-9, earrings of 14 K gold; No. 10-11, belt buckles; No. 12, hooks; No. 13-14, metal buttons.

Detection limit of the amount of leached Ni from metal alloys: $<0.1 \mu\text{g}/\text{cm}^2/\text{week}$. Detection limit of the Ni contents in metal alloys: 1 $\mu\text{g}/\text{g}$.

tant from each other, and the test was performed at least 2 weeks after the preliminary diagnostic patch test reaction was no longer visible. The dilutions we used were 1% (2.1 mg/g of Ni), 0.5%, 0.1%, 0.01%, 0.001%, 0.0005%, 0.0001%, and 0.00005% of Ni sulphate. The patches were applied on single polypropylene-coated aluminum patch test Finn Chambers that were premounted on Scanpor tape (Norgesplaster, Oslo, Norway). Various concentrations of Ni sulphate in petrolatum were applied directly into the 7-mm inner diameter Finn Chamber, in an 8-mm long strip, so as to fill half of the chamber (mean amount: 23 mg petrolatum-based allergen). After application, the tape was fixed by pressing it firmly against the skin, and the top of each chamber was gently pressed to ensure even distribution of the Ni sulphate against the skin. The patches were removed 48 hr after application, and a definitive reading of the patch test was done 96 hr after applying the patch; the readings were rated as follows: +, papular erythema without vesicles; ++, vesicular reaction; +++, extreme (spreading, bullous, and ulcerative) reaction; ?, doubtful reaction (erythema only); -, negative reaction.

RESULTS

The amount of Ni leaching in the artificial sweat

The results of analyzing the amount of Ni leaching from

14 different metal alloys into artificial sweat are summarized in Table 1. All the metal alloys were analyzed twice, and the average is shown as the results. Six pairs of earrings (2 pairs of the cheap earrings of unknown contents, one pair of 14 K gold earrings coated with the white gold, and 3 pairs of 14 K gold earrings) leached Ni below the lowest detectable limit (<0.1 µg/cm²/week), and the other three pairs of earrings leached 0.25-0.43 µg/cm²/week of Ni. One pair of the three 14 K gold earrings coated with white gold leached the highest amount of Ni among all the earrings, which was 0.43 µg/cm²/week. The amount of Ni released from the 2 belt buckles, 1 hook, and 2 metal buttons were 1.36 and 1.41 µg/cm²/week, 1.38 µg/cm²/week, and 0.38 and 0.44 µg/cm²/week, respectively.

The total amounts of Ni content in the metal alloys

The total amounts of Ni contents in the metal alloys are also shown in Table 1. Five earrings contained an undetectable amount (<1 µg/g) of Ni, and the other earrings contained 13.4 to 181 µg/g of Ni. One pair of the three 14 K gold earrings coated with white gold contained 181 µg/g of Ni, which was the highest amount of Ni content among all the earrings. The other metal alloys, including the belt buckles, metal buttons, and hook, contained various amounts of Ni in the range of 149 to 3,830 µg/g.

Table 2. Results of patch testing with serial dilutions of nickel sulphate in petrolatum in 20 subjects after 96 hr

Ni con.	5%	1%	0.5%	0.1%	0.01%	0.001%	0.0005%	0.0001%	0.00005%
Subject									
1	++	++	+	-	-	-	-	-	-
2	++	++	++	+	-	-	-	-	-
3	++	+	-	-	-	-	-	-	-
4	+++	+++	++	++	++	+	-	-	-
5	++	++	+	+	-	-	-	-	-
6	++	++	++	+	-	-	-	-	-
7	++	++	++	++	+	-	-	-	-
8	++	++	++	+	-	-	-	-	-
9	++	++	++	+	-	-	-	-	-
10	+++	++	++	++	+	-	-	-	-
11	++	++	++	+	-	-	-	-	-
12	+++	+++	++	++	++	+	-	-	-
13	+++	+++	++	+	+	+	+	?	-
14	++	++	+	-	-	-	-	-	-
15	+++	++	++	++	+	+	+	+	-
16	++	++	++	+	+	+	-	-	-
17	+++	++	++	+	+	+	-	?	-
18	++	++	++	+	-	-	-	-	-
19	++	++	++	+	+	-	-	-	-
20	+++	++	++	+	+	+	-	-	-
Total No. of positive subjects with reactions	20	20	19	17	10	7	2	1	0

5% (10.4 mg/g of Ni), 1% (2.1 mg/g of Ni), 0.5% (1.04 mg/g of Ni), 0.1% (0.21 mg/g of Ni), 0.01% (0.021 mg/g of Ni), 0.001% (0.0021 mg/g of Ni), 0.0005% (0.00104 mg/g of Ni), 0.0001% (0.00021 mg/g of Ni), and 0.00005% (0.000104 mg/g of Ni). Subjects with atopic dermatitis: No 2, 4, 12, and 20.

Diagnostic patch testing with Ni sulphate in petrolatum for determining the provocation threshold

All 20 subjects had positive results on the preliminary diagnostic patch testing with 5% Ni sulphate in petrolatum (10.4 mg/g of Ni). The results of the tests with serial dilutions of Ni sulphate in petrolatum are shown in Table 2. All the subjects had positive reactions with 1% Ni sulphate in petrolatum (2.1 mg/g of Ni). Ten of the 20 subjects showed a positive reaction to 0.01% Ni sulphate. The lowest concentration of Ni sulphate eliciting a positive reaction varied considerably from person to person, ranging from 1% to 0.0001%.

DISCUSSION

In this study, all of earrings we examined leached Ni below the regulation limit of Ni, according to the directive by the EU. Although they contained Ni below the regulation limit, the 14 K gold earrings coated with white gold leached Ni in the artificial sweat unexpectedly. These results indicated that even gold plating cannot prevent Ni from being released. It is interesting that 2 of the 3 pairs of cheap earrings of unknown contents leached less than 0.1 $\mu\text{g}/\text{cm}^2/\text{week}$ of Ni, whereas 2 of the 3 pairs of 14 K gold earrings coated with the white gold leached 0.33 and 0.43 $\mu\text{g}/\text{cm}^2/\text{week}$ of Ni, respectively.

The dimethylglyoxime (DMG) test is widely used to check whether Ni is contained in the metal alloys, and we performed this test in our study. The results showed that the belt buckles, hook, and metal buttons were all positive, whereas only one pair of earring was positive and the other earrings were all negative (data not shown). This range of reactivity illustrates a potential limitation of the DMG test, that is, the test is only positive upon release of more than 10 μg of Ni (10). For this reason, we analyzed the amount of Ni contained in the metal alloys by using aqua regia instead of the DMG test. All of the 6 pairs of earrings that leached undetectable amounts of Ni contained undetectable amounts of Ni. The other 3 pairs of earrings contained a variable amount of Ni in the range of 13.4 to 181 $\mu\text{g}/\text{g}$. The other metal alloys contained much higher amounts of Ni, from 149 to as high as 5,150 $\mu\text{g}/\text{g}$. Thus, 6 pairs of earrings contained Ni below the limit of Ni, according to the regulations of the EU, but the other 3 pairs of earrings and the other metal alloys exceeded this limit. Overall, there is a close relation between the amount of Ni leached in the artificial sweat and the total content of Ni in the metal alloys, except for a few earrings. To our knowledge, this is the first study about the relation between the leaching amount of Ni and the total content of Ni in the metal alloys.

Next, to further examine the clinical relevance of the EU regulations for limiting Ni, we performed the Ni-patch test for the Korean patients who were sensitive to Ni because it is the most valuable clinical method used to define the thresh-

olds for eliciting ACD. Various studies have proposed the optimum vehicle for Ni-patch test, but the results are controversial (11, 12). In a recent study, the results of patch testing using petrolatum or water as vehicle were broadly comparable, but more volunteers reacted to a lower Ni concentration when petrolatum was used as a vehicle (13). Therefore, in our study, Ni-patch testing was done with petrolatum as the vehicle to determine the lowest concentration of Ni that induced ACD.

In our study, 50% of the participants reacted to 0.01% Ni sulphate (0.976 $\mu\text{g}/\text{cm}^2$), 10% reacted to 0.0005% Ni sulphate (0.0488 $\mu\text{g}/\text{cm}^2$), and the most sensitive person reacted even to 0.0001% Ni sulphate (0.0097 $\mu\text{g}/\text{cm}^2$). In other studies, the average concentration to which only a very limited number of sensitized persons will react is between 0.0002-0.004% (0.019-0.39 $\mu\text{g}/\text{cm}^2$), and 50% will react to 0.02-0.35% (1.95-34 $\mu\text{g}/\text{cm}^2$), which are higher concentrations than in our results (13-20). Although patch tests were performed on only 20 subjects in this study, our subjects were more sensitive to Ni than those of other studies.

It is well known that subjects with atopic dermatitis (AD) are more sensitized to hydrophilic agent such as nickel, food, and flower, but less sensitized to hydrophilic or lipophilic agents such as urushiol. In this study, 4 subjects (20%) had AD and one of them showed Ni-ACD even to 0.01% of Ni. Larger studies are needed to investigate the relationship of AD and Ni-induced ACD.

In summary, it was demonstrated that all of the earrings leached below 0.5 $\mu\text{g}/\text{cm}^2/\text{week}$ of Ni, the level the EU has regulated, but the other metal alloys leached above this level. Although we performed patch testing on 20 subjects, the results suggest that the Ni-sensitive subjects in our study were more sensitive to Ni than the Ni-sensitive subjects in other studies, which were mostly done in Europe. Based on these results, stricter regulation about Ni containing metal alloys will be needed in Korea in the near future. Such revised regulations would be able to help preventing sensitization and elicitation of Ni-induced ACD and ultimately reduce the frequency of Ni-induced ACD in Koreans.

REFERENCES

1. Eun HC. *Epidemiological and clinical review of contact dermatitis in Korea*. *Korean J Dermatol* 1995; 33: 209-24.
2. McDonagh AJ, Wright AL, Cork MJ, Gawkrödger DJ. *Nickel sensitivity: the influence of ear piercing and atopy*. *Br J Dermatol* 1992; 126: 16-8.
3. Larsson-Stymne B, Widstrom L. *Ear piercing-a cause of nickel allergy in schoolgirls?* *Contact Dermatitis* 1985; 13: 289-93.
4. European Parliament and Council Directive 94/27/EC of 30 June 1994. *Official Journal of the European Communities*, 22 July 1994, No. L188/1-2, *The 12th amendment to Directive 76/769/EEC (Nickel)*.
5. Commission Directive 2004/96/EC of 27 September 2004 amending Council Directive 76/769/EEC as regards restrictions on the market-

- ing and use of nickel for piercing post assemblies for the purpose of adapting its Annex I to technical progress. *Official Journal of the European Union* 28 September 2004: L301/51.
6. Jensen CS, Lisby S, Baadsgaard O, Vølund A, Menné T. *Decrease in nickel sensitization in a Danish schoolgirl population with ears pierced after implementation of a nickel-exposure regulation. Br J Dermatol* 2002; 146: 636-42.
 7. Lee JY, Ko IJ, Kim YH, Kim HO, Kim CW. *Contact dermatitis from metal working fluid. Korean J Dermatol* 1990; 28: 283-7.
 8. Lee JY, Yoo JM, Cho BK, Kim HO. *Contact dermatitis in Korean dental technicians. Contact Dermatitis* 2001; 45: 13-6.
 9. Fregert S. *Manual of Contact Dermatitis. 2nd ed. Copenhagen: Munksgaard. 1981.*
 10. Fischer T, Fregert S, Gruvberger B, Rystedt I. *Nickel release from ear piercing kits and earrings. Contact Dermatitis* 1984; 10: 39-41.
 11. Cronin E. *Nickel. Contact Dermatitis. London: Churchill Livingstone, 1980.*
 12. Wahlberg JE. *Petrolatum-a reliable vehicle for metal allergens? Contact Dermatitis* 1980; 6: 134-5.
 13. Emmett EA, Risby TH, Jiang L, Ng SK, Feinman S. *Allergic contact dermatitis to nickel: bioavailability from consumer products and provocation threshold. J Am Acad Dermatol* 1988; 19: 314-22.
 14. Hindsén M, Bruze M, Christensen OB. *Individual variation in nickel patch test reactivity. Am J Contact Dermat* 1999; 10: 62-7.
 15. Nielsen NH, Menné T, Kristiansen J, Christensen JM, Borg L, Poulsen LK. *Effects of repeated skin exposure to low nickel concentrations: a model for allergic contact dermatitis to nickel on the hands. Br J Dermatol* 1999; 141: 676-82.
 16. Hindsén M, Bruze M. *The significance of previous contact dermatitis for elicitation of contact allergy to nickel. Acta Derm Venereol* 1998; 78: 367-70.
 17. Hindsén M, Bruze M, Christensen OB. *The significance of previous allergic contact dermatitis for elicitation of delayed hypersensitivity to nickel. Contact Dermatitis* 1997; 37: 101-6.
 18. Allenby CF, Goodwin BF. *Influence of detergent washing powders on minimal eliciting patch test concentrations of nickel and chromium. Contact Dermatitis* 1983; 9: 491-9.
 19. Rystedt I, Fischer T. *Relationship between nickel and cobalt sensitization in hard metal workers. Contact Dermatitis* 1983; 9: 195-200.
 20. Wahlberg JE, Skog E. *Nickel allergy and atopy. Threshold of nickel sensitivity and immunoglobulin E determinations. Br J Dermatol* 1971; 85: 97-104.