

**Nickel dermatitis from earrings 15 years after EU directive
implementation: a clinical-epidemiological study and a market survey in
Rome, Italy**

Running head: Nickel dermatitis 15 years after EU directive

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ABSTRACT

Background. Nickel (Ni) dermatitis remains a highly prevalent allergic condition in Italy. There is a continuous need for clinical and epidemiological surveillance to evaluate whether or not European Ni Directive has been effective in contact allergy prevention.

Objectives. To assess the prevalence of Ni dermatitis among patch-tested patients and self-interviewed school students, and to analyze Ni release from earlobe jewelry.

Methods. Results of patch-tests performed in 2006-2007, 2015-2016, and 2017-2018 were retrieved. A questionnaire was compiled by 315 secondary school students. Ni release from earring parts was analyzed with the EN1811:2015 method.

Results. A significant time trend of decreasing Ni-positivity from 2006-2007 to 2017-2018 was observed both in the overall population (44.1% in 2006-2007, 33.0% in 2015-2016, 31.6% in 2017-2018, $p<0.0001$) and in female patients ($p<0.0001$). Conversely, change was not significant in males ($p=0.16$). Decrease was significant for all age groups, except for those aged >60 years ($p=0.51$). Among 242 students who reported earring use, 130 (54%) reported symptoms at earlobes, mostly associated with jewelry of materials other than gold and silver (59% of those with earlobe symptoms). Ni release exceeded the migration limit in 4/21 (20%) earring parts.

Conclusions. A high prevalence of Ni dermatitis and earlobe symptoms were found in Rome. A decreasing time trend was noted, with a significant decline in Ni sensitivity compared to the situation observed right after Ni Directive implementation. This most likely represents the consequence of reduced Ni content in earring parts, although a major care in the use of Ni-containing objects could contribute to explain these findings.

Keywords: Nickel, Dermatitis, Patch test, Earlobe earrings, EU directive

Introduction

Nickel (Ni) hypersensitivity, an hapten-mediated allergic contact dermatitis (ACD), is one of the most prevalent allergic conditions, both among children and adults. In 1994, in order to reduce the diffusion of Ni-induced ACD, the EU Nickel Directive set a Ni content of less than 0.05% for objects inserted into pierced parts of the body, and a Ni release $\leq 0.5 \mu\text{g}/\text{cm}^2/\text{week}$ for objects coming into direct and prolonged contact with the skin.¹ In 2004, the regulation for inserted objects changed from a maximum allowed Ni content (0.05%) to a maximum allowed release of $<0.2 \mu\text{g}/\text{cm}^2/\text{week}$, whereas it remained at $0.5 \mu\text{g}/\text{cm}^2/\text{week}$ for all other items.² Since June 2009, the EU Nickel Directive has been included in the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) regulation (item 27 of Annex XVII).

Despite the decrease in Ni dermatitis observed in some European countries since the Ni regulation was introduced, this condition remains very prevalent³⁻⁵.

The clinical patch test data obtained on 10,000 subjects from 11 European countries in 2005-2006 showed positive responses to Ni in 20.1% of the patients, with Ni ranking first place among the allergens⁶. The lowest percentage of Ni dermatitis was found in Denmark (9.7%), whereas the highest was observed in Italy (32.2%)⁶. In a previous investigation conducted by our group in 1988, before the Ni Directive came into force, we observed a positive test response to Ni in 64% of the subjects positive to at least 1 allergen of the International Contact Dermatitis Research Group (ICDRG) standard series⁷. Moreover, we observed an association between Ni dermatitis and the widespread use of cheap earrings among 735 interviewed schoolgirls⁷. In a second study conducted after the implementation of the 1994 Ni Directive, we found a persistently high prevalence of Ni dermatitis in our study group⁸. We also observed that some earlobe jewelry parts were not in compliance with Ni Directive both in terms of total content and released Ni.

We now report the results of a new survey that evaluated the effects of Ni regulation by: 1. assessing the occurrence of Ni dermatitis among patients with a suspicion of contact dermatitis 15 years after the implementation of the 1994 Ni Directive; 2. estimating the

prevalence of self-reported earlobe dermatitis in school students; 3. evaluating Ni release from earlobe jewelry parts sold on the Italian market.

Materials and Methods

Study groups

For the purposes of the study, two groups of subjects were analyzed: a) patch-tested individuals: patients attending the San Gallicano Dermatological Institute of Rome (Italy) in 2006-2007, 2015-2016, 2017-2018, and subjected to patch-testing because of a clinical suspicion of contact dermatitis were included. Relevant data were recorded, including age, sex, age at first symptom and type of symptom at earlobe, other body parts involved, items causing the symptoms; b) students aged 18 years or older, attending the last year of five secondary schools in Rome, were interviewed during 2015-2016 (in each school, preliminary contacts were made with the internal health care service to outline the purpose and procedural aspects of the investigation and to obtain informed consent). The ethical approval for this study was obtained from the Ethical Committee of the San Gallicano Dermatological Institute.

Patch testing

Patients were patch-tested by the European baseline series using Finn chambers (Epitest Ltd, Oy, Finland) placed on the upper back of the subjects for 48 h. Presence and intensity (from weak, +, to strong, +++) of test reaction were recorded on day 2 and 3, following the ICDRG diagnostic procedure⁹. Nickel sulfate hexahydrate (5% petrolatum) was provided by Hermal/Trolab (Reinbek, Germany).

Questionnaires

Students were asked to complete a short questionnaire, similar to the one used in our previous investigation⁷, which included the same questions about earring use and frequency of use (number of days/week), presence of earlobe piercing and age at first earlobe piercing. Moreover, students were asked about type of earrings (material and shape), type of reactions (itching, erythema or eczema) at the site of earrings and in relation to the use of other metal objects (such as necklaces, bracelets, watches, hooks on brassiere, buttons) and the presence of similar symptoms in family members.

Chemical analysis of earrings parts

The same categories of earrings (in terms of form, plating, price) selected in our previous investigation⁸ were analyzed in this study: 7 hook earrings (3, gold plated; 3, silver plated; 1 bronze), 6 lever-back earring wires (3, gold plated; 3, silver plated), 4 clips (2, gold plated; 2, silver plated), and 4 stud earrings (2, gold plated; 2, silver plated). These items were purchased in two fashion jewelry stores that sold non-precious jewelry. Samples were of low price (below 5 Euro) from unknown manufacturers with no brand name.

To determine Ni release, the EN1811:2015 method was used¹⁰. The earring components were immersed in artificial sweat which consisted of urea 0.1% (ICN Biomedicals, Inc., Aurora, USA), 0.5% NaCl (Merck, Darmstadt, Germany), and 0.1% lactic acid (Chem Service, West Chester, USA). The pH was adjusted to 6.5 with ammonium hydroxide (Merck, Darmstadt, Germany). Three samples of each type of earring part were left in a water-bath at 30 °C for 1 week. The resulting solutions were analyzed by sector field inductively coupled plasma mass spectrometry (Element 2, Thermo Finnigan, Bremen, Germany) according to a previously described method⁸. The resulting amount of Ni was divided by the exposed surface area to determine the Ni release rate ($\mu\text{g}/\text{cm}^2/\text{week}$). The surface area of earring parts was calculated manually, with Vernier calipers.

Statistical analyses

Demographic and clinical data of the patch-tested subjects, as well as the answers of the secondary school students, were entered into specifically designed databases and summarized using descriptive analysis. Comparisons between proportions in groups of interest were performed using the chi-square test. A p value <0.05 was considered as statistically significant. For sample size determination of the student group of study, a two-tailed alpha of 0.05 and power of 80% was used.

Results

Patch-test results

For the purposes of the present study, the results of 5715 patch-tests were retrieved: 1674 were performed in 2006-2007, 2100 in 2015-2016, and 1941 in 2017-2018. The mean age for the patients tested in the three study periods was 51, 35 and 36 years, respectively. Overall,

738 subjects (44.1%) resulted positive to Ni-sulfate in 5% petrolatum in the first biennial period, 693 (33.0%) in 2015-2016, and 613 (31.6%) in 2017-2018 (**Table 1**). A significant decreasing trend in Ni positivity was observed (p for trend <0.0001).

The rate of test-positive subjects was always higher in women than men in all the three time periods ($p<0.0001$ for each comparison, data not shown). However, whereas a significant decreasing time trend was found for women (p for trend <0.0001), this was not observed in men (p for trend=0.16, Table 1). Regarding Ni-positivity according to the age class, a significant decrease was observed for subjects in all the classes, except for those aged >60 years. In the latter group, changes in Ni-reactivity across the time periods investigated were not significant (p for trend=0.51, Table 1).

School student survey

A total of 315 secondary school students (age range: 18-21 years; 223 females, 71%) completed the questionnaire. Surveyed student responses are shown in **Table 2**, both for the overall study group and stratified according to sex. Almost all the schoolgirls (95%) reported wearing earrings, compared to 32% of the schoolboys ($p<0.0001$). The majority of the students, both girls and boys, reported a regular use of earrings (5-7 days/week). The majority of the girls and boys wearing earrings had a pierced ear (95% and 90%, respectively; $p=0.27$). Age at ear piercing was 9 and 14 years for girls and boys, respectively. Most of the students wearing earrings (44%) reported using gold and silver earrings, while earrings of other materials were infrequently used by girls and more frequently by boys (15% vs. 34%, $p=0.01$). Concerning earring shape, hook and stud earrings were used more frequently than other types of objects (47% of all respondents).

Data regarding self-reported dermatitis are shown in **Table 3**. Out of a total of 242 students that declared using earrings, 130 (54%) reported skin reactions at the earlobes. Around one third of these 130 students (35%) reported having parents with similar symptoms. Prevalence of earlobe symptoms was similar among girls and boys: 117/213 girls (55%) vs. 13/29 boys (45%), $p=0.31$ (data not shown). Erythema was the predominant symptom (55% of all students). Earrings of materials other than gold or silver were reported as the cause of symptoms more frequently than gold and silver ones (59% vs. 16%). Around half of the students declaring skin reactions at the earlobes also reported skin reactions to other metallic objects (47%), mainly facial or body piercings (28% among those who reported reactions to other items), but also necklaces and bracelets.

Quantity of Ni ions released from earrings

Table 4 shows the data on Ni release from 21 different earlobe jewelry parts and comparison with those obtained in previous years (1988 and 2005). In this study, two fashion jewelry stores were visited and the same categories of earrings sampled in previous studies were purchased. We observed that Ni release varied widely with earring type (0.015-15.2 $\mu\text{g}/\text{cm}^2/\text{week}$). Four earring parts released more than 0.2 $\mu\text{g}/\text{cm}^2/\text{week}$, and two of them, namely the clips, released much more than 0.5 $\mu\text{g}/\text{cm}^2/\text{week}$ (5.25 and 15.2 $\mu\text{g}/\text{cm}^2/\text{week}$, respectively).

Discussion

The European Ni Directive of 1994 and 2005 aimed to reduce Ni content in personal objects and associated skin reactions. A European study conducted in 2005-2006 evidenced that Italy had the highest rate of Ni patch-test positivity (32%) among European countries⁶. Here, we evaluated Ni positivity among individuals with a suspicion of contact dermatitis, who were subjected to patch-testing in one of the largest Dermatological Institutes in Italy. Three time periods were analyzed: 2006-2007 (i.e., right after the implementation of the second EU Ni Directive), 2015-2016 (i.e., 10 years after the implementation of the second EU Ni Directive), and, as a further update, 2017-2018. Notably, a significant decrease in Ni reactivity over time was observed. In fact, in 2006-2007 a positive reaction was observed in over 40% of the patients, whereas, in the following time periods, around one third of the patients were Ni-reactive. A previous study conducted by our group, which included subjects patch-tested in 1994 and 2005, evidenced Ni reactivity in ca. 54% of the patients⁸. This may be cautiously interpreted as a success of 20-years of application of Ni Directives. However, this could also represent the effect of a larger consciousness of people regarding the dermatological problem associated to Ni exposure through objects such as cheap jewelry. In fact, we observed that most of the respondents to the questionnaire that reported to use earrings declared to wear gold and silver earrings, while earrings of other cheap materials were infrequently used.

In line with our findings, a significant decrease in Ni dermatitis was observed from 1985 and 2002 to 2010 in Danish, German and Italian women¹¹. Conversely, an increase of Ni dermatitis was observed in the USA (up to 66.3%) as well as in Thailand and Korea, where the markets have remained unregulated¹²⁻¹⁴. Nevertheless, the prevalence of Ni dermatitis in

Italy remains among the highest compared to northern Europe countries (Denmark, Germany and UK: 14.2–18.8%)¹¹, while it is similar to southern Europe countries. In Spain, 36.3% of females aged 20–40 years positively reacted to Ni¹⁵, and in Greece the prevalence of Ni dermatitis in female children ranged between 24.1 and 31.4% in 1994–2007¹⁶. These data show that in southern regions of Europe, including Italy, the prevalence of Ni dermatitis remains a more relevant public health problem than in northern Europe countries where the market has been regulated since 1990¹⁷.

In the present study, Ni reactivity was significantly more common among females than males, and this was observed in all the three time periods, in line with our previous studies⁷. Interestingly, Ni reactivity significantly decreased over time only for women, whereas no significant change was observed in men. Among male patients, Ni reactivity was around 20% in all the study periods. These findings suggest a strong association of Ni allergy with use of earrings. Indeed, reactions in females were mostly observed at earlobes. Instead, occupational Ni exposure may explain Ni reactivity in males, together with a wider use of piercings than in previous years. Moreover, reactions to buttons, mobile phones, and coins should be considered.

We also observed that Ni sensitivity significantly decreased across the time periods analyzed for all age classes, except for the patients aged >60 years. This finding suggests that older groups were probably exposed to nickel and sensitized at younger age, before the implementation of the Ni regulation.

Data from the secondary school-based survey evidenced that half of the students who reported using earrings had symptoms at the earlobe, erythema being the most frequent one. Both erythema and eczema, the latter reported by a lower proportion of respondents (15%), represent markers of Ni contact dermatitis¹⁸. Skin symptoms at earlobe were reported more frequently by schoolgirls (55%) than schoolboys (45%). Earlobe dermatitis was mostly attributed to the use of earrings of materials other than gold or silver (59% vs. 16%). Several studies found earrings as the major cause of Ni sensitization^{3, 19}. In fact, it is well known that earrings for the earlobe pose a special risk for Ni sensitization as the skin is broken and the metal bypasses the normal skin barrier²⁰. A relevant proportion of the students with symptoms at earlobes (47%) reported reactions also to other metallic items, which were, in order of frequency, facial or body piercings, necklaces and bracelets, watches, and others

(buttons, belt and hook brassiere). Comparing the present questionnaire data with those registered in the investigation we conducted in 1988 on 735 school girls, some differences may be noted⁷. The occurrence of self-reported earlobe dermatitis is lower than that in 1988 survey (54% vs. 67%, $p=0.0003$). This decrease in the prevalence of earlobe dermatitis is likely attributable to the benefits of the Ni Directive; the same was observed in Germany where the positive effect of the 1994 EU regulation was observed in 2003.²¹

While the main type of reaction at earlobes was erythema in this survey (55% vs. 27% in 1988, $p<0.0001$) and itching in 1988 (44% vs. 28% in this study, $p=0.0011$), the items causing skin reactions more frequently remain earrings of materials other than gold or silver both today and in the past. Differently, reactions due to gold and silver earrings were reported more frequently in the present survey than in 1988 (16% vs. 3%, $p<0.0001$). Furthermore, in this survey, facial and body piercings were reported as a new cause of reactions. Piercing of other parts of the body besides the earlobes has in fact become very common nowadays and can be a cause of skin damaging conditions^{22, 23}. This result is relevant because metallic items which are inserted into other parts of the human body are also included in the Ni Directive. Interestingly, a study showed that Ni sensitivity increased with the number of body piercings²⁰.

To investigate whether or not the Ni Directive had an effect on the Ni content of jewelry, analysis of the Ni released from cheap jewelry sold on the Italian market was performed. Ni release from the items analyzed in this study was much lower than from the earrings sampled in 1988, and also from those assayed in 2005, which, however, already showed a decreased release compared to 1988. Fifteen years after the Ni Directive came into force, we thus found that the Ni content of earrings was finally reduced, with the exception of clips. On the other hand, this kind of earring is rarely used among young people (in this study less than 1% among the students that declared wearing earrings). Importantly, four earring parts (20% of samples) exceeded the requirement of $0.2 \mu\text{g}/\text{cm}^2/\text{week}$, and two of them (i.e., the clips) released much more than $0.5 \mu\text{g}/\text{cm}^2/\text{week}$. In other studies, Ni release from various objects including jewelry parts exceeded the migration limit. In Germany, data from 2002 to 2009 showed that Ni allergy was still frequent, possibly due to insufficient protection from Ni jewelry items; in fact, about 10% of several hundred parts taken from 187 jewelry items released Ni between 0.2 and $2 \mu\text{g}/\text{cm}^2/\text{week}$ for posts and between 0.5 and $5 \mu\text{g}/\text{cm}^2/\text{week}$ for

clasps and ornamental parts²⁴. The same authors observed a new decrement in Ni allergy prevalence in Germany from 2005 to 2012, after the advent of the second EU Directive of the year 2004.²⁵

In Denmark, 22% of 354 metallic pieces of jewelry and accessories released an excessive amount of Ni with the highest proportion of positive samples in earrings purchased from two street vendors and from immigrant clothing stores²⁶. In 2002-2003, in Stockholm, 8% of 786 metallic items released a quantity of Ni above the level established in the Directive²⁷, a significant decrease compared to the rate found in 1999 (25%), prior to the implementation of the Directive²⁸. The problem of imported jewelry remains relevant, considering that 31.5% of Chinese earrings and 29.2% of Thai earrings were Ni positive in a previous study²⁹. A recent US study reported release of Ni from 82.3% (0.01-98 $\mu\text{g}/\text{cm}^2/\text{week}$), of cobalt from 36.4% (0.02-0.5 $\mu\text{g}/\text{cm}^2/\text{week}$), and of lead from 38.5% of the samples tested (0.03-2718 $\mu\text{g}/\text{cm}^2/\text{week}$). The frequent co-existence of Ni and other allergic metals such as cobalt and chromium in some jewelry manufacturing (e.g. in gold jewelry to alter the gold colour and in cobalt–chrome jewellery) may also play a role in allergic contact dermatitis.³⁰

A few study limitations have to be acknowledged. Firstly, students that participated in the survey were not patch-tested. Patch-testing is needed to estimate the true prevalence of Ni allergy, since previous studies showed that self-reported skin reactions generally overestimate the true prevalence of Ni allergy.³¹⁻³³ Nonetheless, a recent large population-based study on 16 year-old adolescents reported a significant association between self-reported body piercing, self-reported skin symptoms after contact with metal items and nickel allergy explored by patch-testing.³⁴ Secondly, this is a single-center study, we cannot generalize our findings to the rest of the population in our country.

Conclusions

Our data showed a lower Ni release from inexpensive earring parts sampled in Rome, Italy, with respect to those tested in not regulated countries. These observations suggest a success of the Ni Directive in Italy. Nevertheless, 20% of earring parts analyzed still contained more Ni than the migration limit of the Ni Directive and the problem of Ni dermatitis remains higher in Rome than in other European cities, where the Ni Directive was applied earlier than in our country.

The decrease observed in patch-test positive responses to Ni from 2006 to 2018, as well as in self-reported earlobe dermatitis, are also in line with a possible effect of the Ni Directive. The decline in Ni exposure might be also due to the greater awareness of people regarding the dermatological complications of Ni exposure and the broader knowledge on the association between use of inexpensive jewelry and allergenic risks.

The frequency of both patch-test Ni sensitivity and self-reported earlobe dermatitis was higher in women, but relevant also in men. Earrings remain one of the most important objects causing Ni dermatitis, with symptoms mostly correlated with the use of earrings made of non-precious metals rather than gold and silver. Some new sources of Ni dermatitis should be considered, such as body or face piercings, which were less relevant in the past.

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Table 1. Patch-test results overall, and stratified according to sex and age groups for the three time periods

	Ni positive, n/N (%)			p trend
	2006-2007	2015-2016	2017-2018	
Overall	738/1674 (44.1)	693/2100 (33.0)	613/1941 (31.6)	<0.0001
Sex				
Female	630/1222 (51.6)	541/1365 (39.6)	490/1300 (37.7)	<0.0001
Male	108/452 (23.9)	152/735 (20.7)	123/641 (19.2)	0.16
Age class, years				
≤20	28/55 (50.9)	48/226 (21.2)	62/284 (21.8)	<0.0001
21-30	54/102 (52.9)	161/572 (28.1)	175/590 (29.7)	<0.0001
31-40	98/204 (48.0)	233/588 (39.6)	165/490 (36.7)	0.019
41-50	159/305 (52.1)	115/341 (33.7)	78/235 (33.2)	<0.0001
51-60	154/385 (40.0)	73/199 (36.7)	50/180 (27.8)	0.018
>60	245/623 (39.3)	63/174 (36.2)	83/202 (41.1)	0.51

Table 2. Use of earrings by 18 to 21-year-old high-school students: frequency and characteristics of used jewelry

Variables	Total (N=315) n (%)	Females (N=223) n (%)	Males (N=92) n (%)
Use of earrings			
Yes	242 (77)	213 (95)	29 (32)
No	73 (23)	10 (5)	63 (68)
Frequency of use§			
Regularly	175 (72)	160 (75)	15 (52)
Occasionally	45 (19)	43 (20)	2 (7)
In the past	22 (9)	10 (5)	12 (41)
Pierced ear§			
Yes	229 (95)	203 (95)	26 (90)
No	13 (5)	10 (5)	3 (10)
Earring material§			
Gold and silver	105 (44)	94 (44)	11 (38)
Cheap jewelry	42 (17)	32 (15)	10 (34)
Mix	85 (35)	81 (38)	4 (14)
Nr	10 (4)	6 (3)	4 (14)
Earring shape§			
Hook and stud	113 (47)	104 (49)	9 (31)
Clip	2 (1)	2 (1)	0 (0)
Piercing	36 (15)	27 (13)	9 (31)
Mix	55 (22)	54 (25)	1 (3)
not reported	36 (15)	26 (12)	10 (35)

§percentages calculated among those who reported using earrings

Table 3. Survey data on self-reported dermatitis among the 242 secondary school students who reported using earrings

Variables	Students (N=242) n (%)
Occurrence of symptoms at earlobe	
Yes	130 (54)
No	109 (45)
not reported	3 (1)
Family members with similar symptoms§	
Yes	46 (35)
No	84 (65)
Earlobe symptoms§	
Itching	37 (28)
Erythema	72 (55)
Eczema/Dermatitis	19 (15)
not reported	2 (2)
Earring material causing symptoms§	
Gold and silver	20 (16)
Other	77 (59)
Mixed	16 (12)
not reported	17 (13)
Shape of earring causing symptoms§	
Hook and stud	59 (45)
Piercing	14 (11)
Mixed	13 (10)
Clips	0 (0)
not reported	44 (34)
Symptoms related to other metallic items§	
Yes	61 (47)
No	69 (53)
Other metallic items causing symptoms ^	
Necklaces	11 (18)
Bracelets	9 (15)
Necklaces and bracelets	11 (18)
Watches	5 (8)
Hook brassiere	3 (5)
Buttons	3 (5)
Facial or body piercing	17 (28)
Other (i.e., belt)	2 (3)

§percentages calculated among the 130 students who reported having symptoms at earlobe

^percentages calculated among the 61 students who reported symptoms related to other items

Table 4. Nickel release form earring parts

Earring type	Plating	Ni release ($\mu\text{g}/\text{cm}^2/\text{week}$)		
		1988	2005	2015-2016 (this study)
Fish hook earring wire	Gold	321	0.154 $\pm$ 0.011	0.135 $\pm$ 0.015
Fish hook earring wire	Silver		4.62 $\pm$ 0.25	0.48 $\pm$ 0.22
Fish hook earring wire	Bronze		0.194 $\pm$ 0.015	0.35 $\pm$ 0.032
Lever-Back earring wire	Gold	700	0.021 $\pm$ 0.001	0.015 $\pm$ 0.010
Lever-Back earring wire	Silver		0.088 $\pm$ 0.005	0.12 $\pm$ 0.011
Clips	Gold	300	225 $\pm$ 14	15.2 $\pm$ 0.5
Clips	Silver		10.9 $\pm$ 0.3	5.25 $\pm$ 0.1
Stud earring	Silver		0.031 $\pm$ 0.002	0.044 $\pm$ 0.011
Stud earring	Gold		0.058 $\pm$ 0.003	0.065 $\pm$ 0.018