# Decrease in nickel allergy in women after the second EU nickel directive

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After the first EU nickel directive had been adopted by the Council and the European Parliament in 1994 (EU Communities Directive 94/27/EC) (1), we noted a significant decrease in the frequency of nickel allergy in female patients under the age of 31 years in 2001 (2). However, a further analysis of data from 2002 to

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2009 showed no further significant decline, which was explained by insufficient protection from nickel-releasing objects, as a considerable number of objects were found to exceed the nickel migration limit set by the directive (3). Two main reasons may account for these observations: (i) inconsistencies in the original nickel directive (e.g. application of a factor 'adjusting' the actual measured values resulting in unacceptable levels in reality); and (ii) non-compliance with the directive (4).

In 2004, the directive for post assemblies changed from a maximum allowed nickel content (0.05%) to a maximum allowed release, which was set at $< 0.2\ \mu g/cm^2/week$ (Commission Directive 2004/96/EC) (5), while it remained at $0.5\ \mu g/cm^2/week$ for all other items.

We wondered whether this reinforcement of the nickel directive is reflected in the subsequent epidemiology of nickel allergy.

In this study, we analysed the age-stratified time trend of nickel allergy from 2005 to 2012, with a focus on the subgroups of female patients aged 1–17 and 18–30 years, using the clinical data of the Information Network of Departments of Dermatology (IVDK).

## Methods and Results

The IVDK is a network dedicated to the clinical surveillance of contact allergy, and has been described elsewhere (6). During the study period (2005–2012), 74 854 patients were patch tested with nickel sulfate 5% pet. Reactions on the third day after application or, where these were unavailable, on the fourth day were considered as the outcome, aggregated into positive (+ to +++) versus non-positive (negative, irritant reaction, ?) for the analyses. For data management and analysis, SAS™ software (version 9.2; SAS Institute, Cary, NC, USA) and R statistical software, version 2.14, were used (http://www.r-project.org), following the pertinent guidelines (7).

The total number of patients tested was 74 854 (46 550 females and 28 304 males). These subgroups were further stratified for age (Table 1), with a special focus on women and on the age intervals 1–17, 18–30 and 31–44 years. Allergy frequencies per 2 years per subgroup are shown in Table 1, and, to better illustrate the trend, in Fig. 1 (women). Considering the whole period (2005–2012), significant decreases in nickel allergy were seen in women aged 1–17, 18–30 and 31–44 years (Fig. 1), whereas, in women aged 45–60 years, allergy to nickel increased significantly (Table 1). Similar increases have been observed previously (2, 8, 9), and were explained by a cohort effect (individuals had probably been exposed to 'unregulated' nickel when they were younger, before the first directive of 1994). In women aged > 60 years, no trend was discernible. In contrast, during the period 2005–2012, there was no trend in men (all age groups) (data not shown, findings not further discussed).

## Discussion

In our study, we found a significant decrease in nickel allergy in three age groups of women, namely 1–17, 18–30 and 31–44 years (Fig. 1), and a significant increase in the older age group (45–60 years) (for explanation, see above), between 2005 and 2012. This may be cautiously interpreted as a success of the second nickel directive of 2004. In addition, the first nickel directive of 1994 may also have contributed to these observations, as was discernible particularly in the older age groups (Fig. 1), both directives resulting in reduced exposure to nickel. However, the age subgroups had different exposure to nickel over time: in the period 2005–2006, the vast majority of the nickel-allergic young women (1–17 years) had their piercings before the second nickel directive of 2004, whereas in the period 2011–2012, the youngest group (1–12 years) would have benefited from the new directive. Nickel exposure of the remainder (13–17 years) may theoretically have taken place before 2005, when they were aged ≤ 9 years. However, according to a recent questionnaire study of 5000 patients (from dental and dermatological practices) in Germany, 52.8% had obtained their first piercing when aged < 18 years, the vast majority (about 90%) of them between the ages of 11 and 17 years (10), meaning that, in the period 2011–2012, the subgroup aged 1–17 years consisted mainly of individuals protected by the second directive. However, the frequency of nickel allergy is still high. One reason may be that the European Committee of Standardization (CEN) only recently, in January 2011, adopted a new amendment (EN 1811:2011) to compensate for interlaboratory variation by the use of 'uncertainty intervals' instead of using the 'adjustment factor' of 0.1. (11), and this only officially came into force on 1 April 2013 (12). A further reason may be violation of the directive (3, 13–15). Many nickel-releasing earrings have been detected on the market, for example in East Asia (16). Jewellery might be imported to the EU, particularly from East Asia. In a study of Chinese and Thai earrings using the dimethylglyoxime (DMG) test, 31.5% of Chinese earrings and 29.2% of Thai earrings were DMG test-positive (16). In addition, other exposures may exist that lead to dermatitis, including modern sources such as laptops (17) and mobile phones (18, 19); the former are not yet covered by the nickel directive, and the latter have only recently been covered

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**Table 1.** Frequencies of allergy to nickel (5%) in female patients tested between 2005 and 2012 (n = 46 550) stratified for age groups; trend from 2005 to 2012

| Age group (years) | 2005–2006 | 2007–2008 | 2009–2010 | 2011–2012 | Total no. | Trend | *p*-value |
|---|---|---|---|---|---|---|---|
| 1–17 | | | | | | | |
| % positive | 17.27 | 15.06 | 14.05 | 11.58 | | ↓ | < 0.05 |
| No. tested | 278 | 239 | 306 | 328 | 1151 | | |
| 18–30 | | | | | | | |
| % positive | 26.41 | 23.97 | 19.97 | 19.75 | | ↓ | < 0.001 |
| No. tested | 1386 | 1547 | 1908 | 2046 | 6887 | | |
| 31–44 | | | | | | | |
| % positive | 36.17 | 34.81 | 30.03 | 31.14 | | ↓ | < 0.001 |
| No. tested | 1844 | 1902 | 2251 | 2373 | 8370 | | |
| 45–60 | | | | | | | |
| % positive | 20.48 | 21.60 | 21.16 | 23.88 | | ↑ | < 0.01 |
| No. tested | 2793 | 3129 | 4140 | 4467 | 14 529 | | |
| 61–99 | | | | | | | |
| % positive | 9.48 | 8.74 | 7.69 | 8.98 | | → | 0.2827 |
| No. tested | 3237 | 3603 | 4292 | 4481 | 15 613 | | |

→, no significant trend.
Cochran–Armitage trend test, two-sided; downward arrows indicate a significant decrease in the prevalence of allergy, and upward arrows indicate a significant increase in the prevalence of allergy.

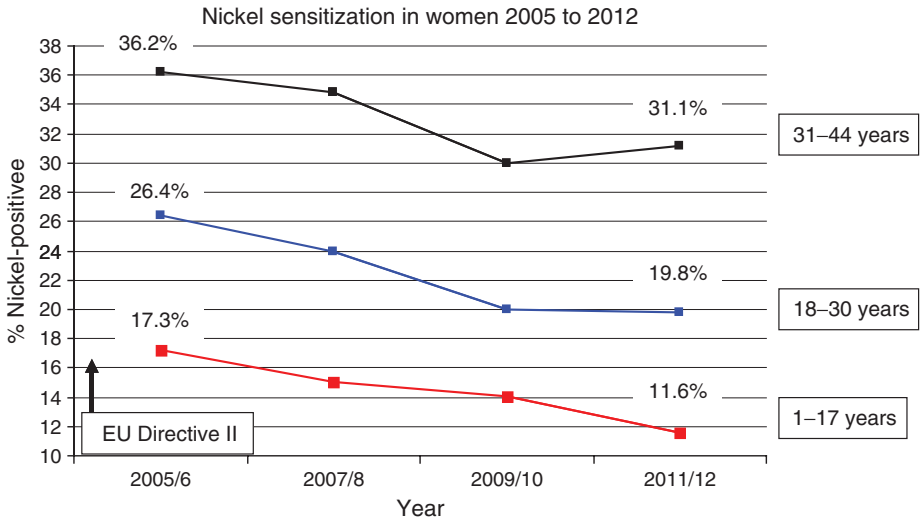


**Fig. 1.** Nickel allergy in women (aged 1–17, 18–30 and 31–44 years); data from the Information Network of Departments of Dermatology 2005–2012; 46 550 patients tested. The decreasing trends were significant (Cochrane–Armitage trend tests: for *p*-values, see Table 1). Nickel Directive II (2004) (5).

(20). By contrast, unregulated occupational exposure to nickel, which may have a certain impact on nickel allergy in some occupations (21–23), is probably irrelevant for the subgroup studied (young females, the majority being school students).

Regarding the decrease in nickel allergy over time, one should be aware that the decrease is probably not (or only partly) attributable to decreasing exposure (as in Sweden (14), but rather to a gradual change in the profiles of groups in different time periods: in the first period (2005–2006), they mainly consisted of individuals not yet protected by the new directive, and in the last period (2011–2012), they consisted of individuals who were almost totally protected. This indicates a first (modest) success of the directive, especially as the subgroups were 'contaminated' to a certain extent with 'unprotected' individuals. From an epidemiological point of view, this scenario is certainly not optimal. A complete 'wash-out' phase would have been desirable – as, for example, in young hairdresser apprentices showing no sensitization at all after the removal of acid permanent wave (glyceryl mono thioglycolate) (24). However, deviation from the

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optimum may be justified, as nickel allergy is very important and proof of efficacious regulation is needed. Efforts should now focus on the control of compliance with the directive, the new EN 1811-2011 included. Meanwhile, continuous epidemiological surveillance is indispensable, as the current 0.5 µg/cm$^2$/week limit set by the nickel directive may still be too high (25).

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