

Prevalence of nickel allergy in Europe following the EU Nickel Directive – a review

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Summary

Nickel contact allergy remains a problem in EU countries, despite the EU Nickel Directive. To study the prevalence of nickel allergy in EU countries following the implementation of the EU Nickel Directive, we performed a systematic search in PubMed for studies that examined the prevalence of nickel allergy in EU countries published during 2005–2016. We identified 46 studies: 10 in the general population and 36 in patch tested dermatitis patients. A significantly lower prevalence of nickel allergy after than before the implementation of the EU Nickel Directive was found in women aged 18–35 years (11.4% versus 19.8%) ($p = 0.02$), in female dermatitis patients aged ≤ 17 years (14.3% versus 29.2%) ($p < 0.0001$), and in dermatitis patients aged 18–30 years (women: 20.2% versus 36.6%) ($p < 0.0001$) (men: 4.9% versus 6.6%) ($p < 0.0001$). Overall, the prevalence was higher in southern than in northern EU countries, and generally remained high, affecting 8–18% of the general population. A consistent pattern of decreasing prevalence of nickel allergy in some EU countries was observed, although the prevalence among young women remains high. Steps should be taken for better prevention of nickel allergy in EU countries.

Key words: allergic nickel dermatitis; contact allergy; general population; nickel; Nickel Directive; nickel regulation; prevalence; REACH.

Nickel allergy is frequent and represents a public health concern in the EU (1). To reduce the prevalence of nickel allergy and dermatitis in European citizens, the EU Nickel Directive was introduced in 1994, came into force in 2000 and into full force from 2001 onwards (2). Before this, national nickel regulations had been implemented in Denmark (1990), Sweden (1991), and Germany (1991). The Danish Nickel Regulation banned products intended to come into close contact with the skin with nickel release of $>0.5 \mu\text{g}/\text{cm}^2/\text{week}$. In Sweden, ear piercing with piercing post assemblies containing $>0.05\%$ nickel or nickel coating thicker than $0.01 \mu\text{m}$ was prohibited, and, in

Germany, nickel-containing objects had to be labelled (3). The EU Nickel Directive was included in REACH, the EU Chemicals Regulation, in 2009, and will be referred to the Nickel Restriction by REACH from that time onwards.

The Nickel Restriction by REACH prohibits marketing of metallic items with nickel release of $>0.5 \mu\text{g}/\text{cm}^2/\text{week}$ if they are intended for use in direct and prolonged contact with the skin, and of any post assemblies to be inserted into pierced holes if the release is $\geq 0.2 \mu\text{g}/\text{cm}^2/\text{week}$ (4). The intention of the original EU Nickel Directive was never to eradicate, but rather to substantially diminish, nickel allergy in the population (5). Although epidemiological studies have shown that the nickel allergy problem began to decrease in some European countries following the restriction, nickel remains the most frequent contact allergen (6). The earliest indications of a preventive effect of the restriction should be expected in the youngest age groups, who would predominantly have been exposed to nickel from metallic items sold after the

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EU Nickel Directive came into force. The older age groups may have become allergic to nickel before implementation of the restriction, and will have maintained their nickel allergy as they age (cohort effect) (7). For this reason, predominantly young age groups should be studied to gauge the success of the restriction.

The aim of this review was to evaluate whether the Nickel Restriction by REACH sufficiently protects EU citizens against developing nickel allergy. We did this by studying the published literature on the prevalence of nickel allergy in EU countries after implementation of the former EU Nickel Directive. The data presented in this study were published in a Danish EPA LOUS report (8).

Methods

PubMed was searched in December 2016 by use of the following terms: 'general population nickel' OR 'nickel allergy prevalence' OR 'nickel dermatitis'. We included original research that presented the prevalence of nickel allergy in EU countries, Norway and Switzerland (the restriction is also applicable in European Free Trade Association countries) during 2005–2016. The start time point of the search was chosen to increase the probability of including studies in which an effect of the restriction could be evaluated, and to complement earlier studies (9). The last search was performed on 31 December 2016. Studies in languages other than English and case reports were excluded. In cases of multiple publications of the same underlying data, only the study with the most comprehensive results or with the most relevant analyses of the data was included for the present review. In some cases, there was partial overlap between studies, for example partly overlapping study years; these studies were all included. All studies that presented nickel allergy prevalence in the general population were included. Studies concerning patch tested patients with dermatitis were included if they comprised >500 patients or if the prevalence of nickel allergy over time was assessed.

The literature search resulted in 874 non-duplicate studies. One study, published in 2002, was additionally included because it compared the prevalence of nickel allergy in schoolgirls of different ages, and was therefore considered to be relevant for a correct evaluation of the EU Nickel Directive (10); accordingly, 875 studies were initially considered. After review of the titles and abstracts, 801 studies were excluded; an additional 28 studies were excluded after full-text review. One study that did not meet the criterion on number of patients (11) was nevertheless included, as it contained data on very young children and was therefore regarded as important. In total, 46 studies were included in the review, of

which 10 studies presented data from the general population (Appendix S1), and 36 studies presented data on patch tested dermatitis patients (patient studies), with and without age stratification (Appendices S2 and S3). The patch test concentration of nickel is stated in the appendices only when it differed from 5% or 0.20 mg/cm² for the TRUE Test®. Important comments about the individual studies are marked and explained in the appendices. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram is presented as Fig. 1.

Results

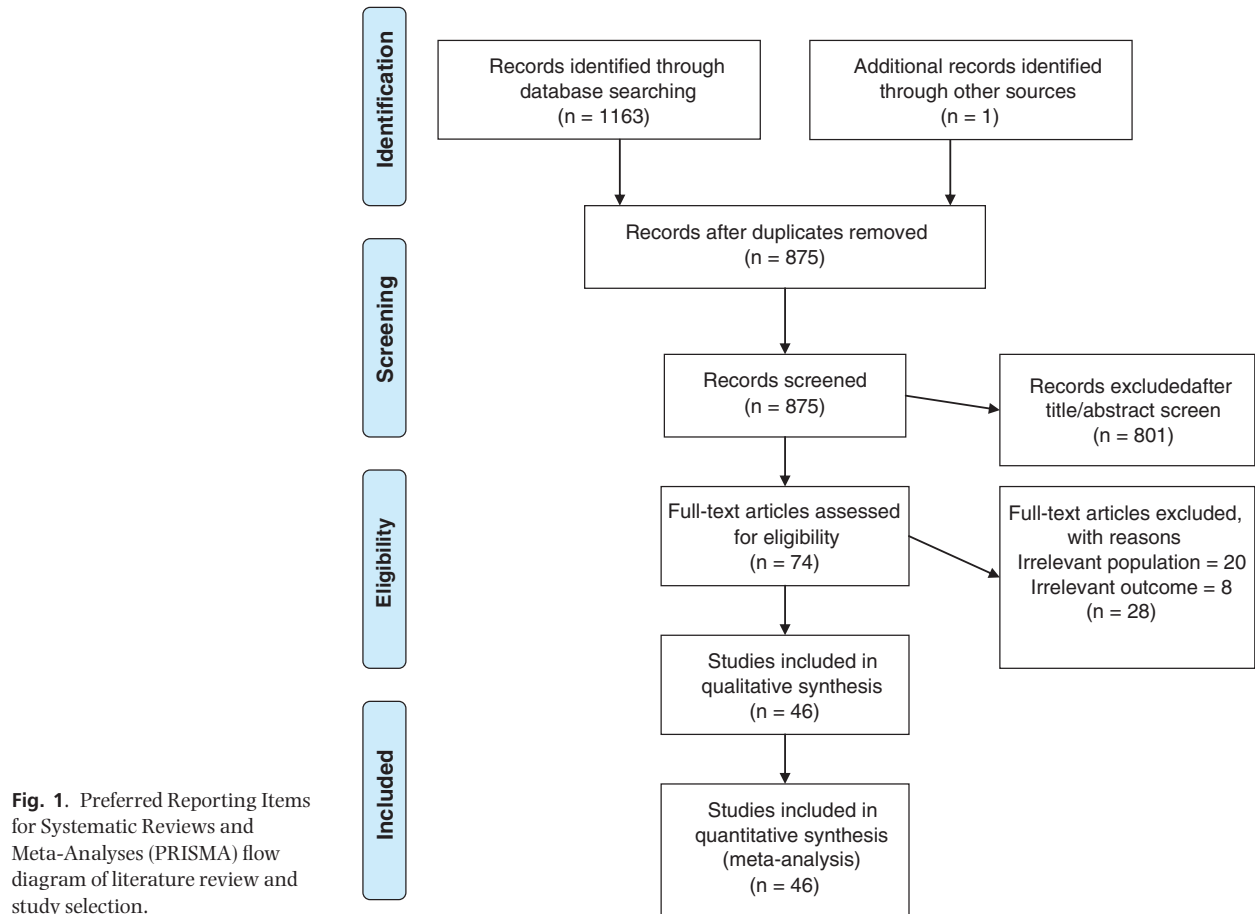
Study characteristics

The studies were cross-sectional or longitudinal, and data on men and women of all ages were collected retrospectively or prospectively. The 10 general population studies included 19 396 individuals [2080 (10.7%) with nickel allergy] from eight countries. The 36 patient studies included 519 951 patients [92 373 (17.8%) with nickel allergy] from 17 countries in total. Most of the patients were patch tested because of suspicion of allergic contact dermatitis (ACD). Nickel allergy was the most common contact allergy in both the general population and in the patient studies, and the prevalence was higher in women than in men.

General population studies

There were 10 studies concerning the prevalence of nickel allergy in the general population (Appendix S1). Three of the studies were Danish, three were Swedish, two were Norwegian and one Polish; one concerned five EU countries, namely Germany, Italy, The Netherlands, Portugal, and Sweden.

Jensen et al. compared two groups of schoolgirls of different ages (305 primary school girls and 275 high-school girls) in 1999–2000 in Denmark (10). A significantly lower prevalence of nickel allergy was found in younger girls than in older girls (3.9% versus 17.1%) ($p=0.004$), indicating an effect of the Danish Nickel Regulation, and possibly differences in nickel exposure. The same pattern was reflected in a study that compared the prevalence in a Danish population at two time points (274 women in 1990–1991, and 1843 women in 2006–2008) (12). A significantly lower prevalence of nickel allergy was seen among the youngest women (18–35 years) in 2006 than in 1990 (11.4% versus 19.8%) ($p=0.02$). Among middle-aged women (36–55 years), there was a significant increase in prevalence over time (6.5% versus 13%) ($p=0.03$), and a



non-significant increasing trend was observed in older women (56–69 years) (2.3% versus 5.1%) ($p=0.4$). In the same study, there was a declining trend for men of all ages. It is possible that the prevalence of nickel allergy was underestimated in this study, because patch test reading was performed only on day 2.

There were two follow-up (longitudinal) studies of schoolchildren in Sweden and Denmark (13, 14). Josefson et al. found that 24.4% of 369 girls aged 8–15 years in 1982 had developed nickel allergy when they were retested in 2006–2007. Positive patch test reactions were seen in 9% of the girls, and in 30.1% in the same individuals who had become 30–40 year old women. The Swedish Nickel Regulation and, later, the EU Nickel Directive came into force in Sweden during the follow-up period. In this study, only 39% of the initially recruited girls were followed up (13). In a similar Danish study, Mortz et al. found new cases of allergy to nickel in 7% of a cohort of adolescents in the time period 1995–2010: a period during which nickel release was regulated in Denmark. In 1995, 1146 adolescents (54.1% girls) aged 12–16 years were patch tested, and 8.6% (13.7% of girls;

1.9% of boys) were found to be positive. In 2010, 403 of the same individuals (63.5% women) and 39 from the original cohort who had not previously been patch tested were patch tested (age 28–30 years). In total, 11.8% reacted positively to nickel (18.3% of women; 1.2% of men) (14).

The prevalence of nickel allergy has been studied in two large groups of adolescents in Sweden (15, 16). In the most recent study of 2236 adolescents aged 16–19 years, 7.5% reacted positively to nickel in 2011–2013 (9.8% of girls; 4.9% of boys) (15). In 2000–2004, a total of 4376 individuals aged 14.9–23.4 years were patch tested, and 9.9% reacted positively (13.3% of girls; 2.5% of boys). This translated into 11.8% of girls and 1.6% of boys when the many dropouts were considered (16). The prevalence was very similar to that found in schoolgirls in Denmark in 1995 (13.7%) and in schoolgirls in Sweden during 1982–1983 (9%) (13, 14). The prevalence of nickel allergy among women aged <40 years in all included studies of the general population is shown in Fig. 2.

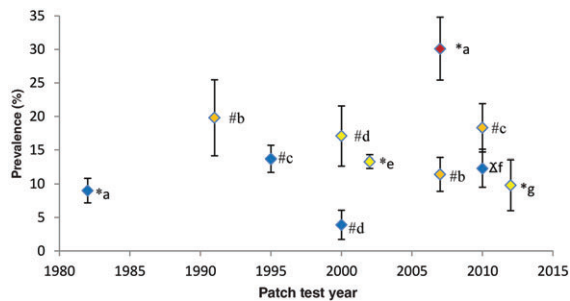


Fig. 2. Studies from the general population reporting data on the prevalence of nickel allergy in young females. Country symbols: #, Denmark; *, Sweden; X, Poland. Age groups: blue – majority ≤ 15 years; yellow – majority between 16 and 20 years; orange – majority between 21 and 30 years; red – majority > 30 years. The lower-case characters refer to references in Appendix S1: (a) is reference 6; (b) is reference 5; (c) is reference 3; (d) is reference 10; (e) is reference 7; (f) is reference 4; and (g) is reference 2. See Appendix S1 for detailed information about studies. The error bars represent the 95% confidence intervals of the mean prevalence in the study, and were calculated for this study.

Ear piercing has long been reported as the leading cause of nickel allergy (2, 17–19). In three of the aforementioned studies, the prevalence of nickel allergy was also studied in those ear-pierced after and those ear-pierced before the Danish Nickel Regulation came into force. A statistically significantly lower prevalence of nickel allergy was reported in all three studies in women ear-pierced after 1990–1992 (Jensen: 7.7% versus 24.6%) ($p = 0.003$) (Thyssen: 6.9% versus 15.6%) ($p = 0.004$) (Mortz: 14% versus 29%) ($p < 0.005$) (10, 14, 20). In the study by Thyssen et al., the pattern was especially pronounced among the younger women (18–35 years) (8.3% versus 22.1%) ($p = 0.002$). Moreover, the prevalence of nickel allergy was significantly higher among women ear-pierced during 1990–2006 than among those who had never been ear-pierced (6.9% versus 3.0%) ($p = 0.03$) (20).

The two Norwegian studies showed a very high prevalence of nickel allergy, namely 17–19%, in the years 1994–1995 in adults from the general population. However, no regulatory effect can be expected at this early time point in Norway.

Only two studies were from outside Scandinavia. The largest of these compared the prevalence of contact allergies among 3119 individuals during 2008–2011 in five EU member states. Nickel allergy was found in 14.5% of all those tested, with a statistically significant higher prevalence in women than in men (22.2% versus 5.2%) ($p < 0.01$). A statistically significant difference in the prevalence between the countries was also found: the lowest age-standardized prevalence of nickel allergy

was found in Sweden (8.3%), and the highest in Portugal (18.5%) ($p < 0.01$) (21).

In Poland, the prevalence of nickel allergy among 528 adolescents aged 15 years was found to be 7.8% (12.3% in girls; 1.4% in boys) (22).

Studies of patients with suspected ACD

Thirty-six studies that included patch tested patients were identified. In 16 of these studies, patients were stratified by age. These studies are summarized in Appendix S3. The remaining 20 studies are summarized in Appendix S2. The following results are based on nine studies from two major European networks that collect data from patients patch tested for suspected ACD, namely the European Surveillance System on Contact Allergies (ESSCA) and the Information Network of Departments of Dermatology (IVDK). These networks were selected because they contain, by far, the largest amount of data and cover many countries.

In the five studies from the ESSCA, the overall prevalence of nickel contact allergy was almost unchanged in the period 2002–2012 (23–27). In the first study, covering 2002–2003, 17.3% of subjects had positive patch test reactions to nickel; the lowest prevalence was found in Denmark and the highest in Italy (8.1% versus 31.7%) (23). This pattern was replicated in all studies up to 2012 (23–27) (Fig. 3). In 2004, a high prevalence of nickel allergy was observed in clinics in which patients were tested because of suspicion of occupational dermatitis (27). In the study from 2005 to 2006, the EU countries were divided by region. A higher proportion of positive test reactions was observed in the southern EU (Italy and Spain) than in the central EU (The Netherlands, Switzerland, Austria, and Germany) (24.4% versus 19.7%) (26). In the most recent study, from 2009 to 2012, the prevalence remained highest in Spain and Italy, and lowest in Germany and Denmark (26.4%/26.2% versus 11.9%/12.6%) (Fig. 3) (23).

Belloni Fortina et al. found a decrease in the prevalence of nickel allergy during 2002–2010 in a study of 6583 children aged 1–16 years of both sexes from ESSCA centres (28). In total, 16.7% had positive test reactions, and the highest prevalence (26.7%) was found among the youngest children, aged 1–5 years. No reason for the high prevalence could be found, but it was hypothesized that this could be attributable to stricter selection criteria or false-positive results in very young patients. The lowest prevalence was found in children from the western EU (United Kingdom), and the highest in very young children from the southern EU (Spain, Italy, and Slovenia) (5.3% of 6–12-year-old children from the western

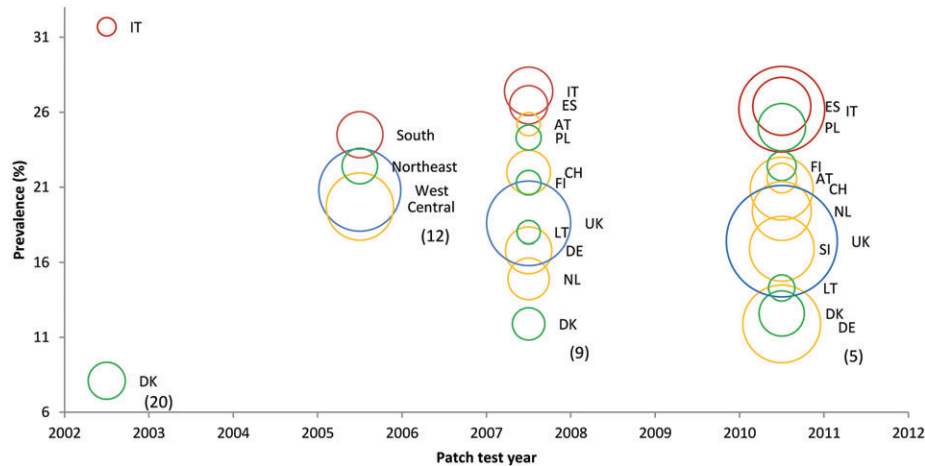


Fig. 3. Prevalence of nickel allergy in dermatitis patients by country or region, patch tested in the European Surveillance System on Contact Allergies network 2002–2003 (reference 20, Appendix S2), 2005–2006 (reference 12, Appendix S2), 2007–2008 (reference 9, Appendix S2), and 2009–2012 (reference 5, Appendix S2). For 2002–2003, results from only two departments are presented: Padova in Italy (IT) and Gentofte in Denmark (DK). For 2005–2006, the countries were clustered into regions, as follows. South (red): Italy (IT) and Spain (ES). Northeast (green): Finland (FI), Lithuania (LT), and Poland (PL). West (blue): United Kingdom (UK). Central (yellow): The Netherlands (NL), Switzerland (CH), Austria (AT), and Germany (DE). For the other two test periods, the prevalence was specified per country: Denmark (DK) and Slovenia (SI). The sizes of the circles indicate the numbers of patients patch tested by contributing clinics in a country.

EU versus 30.2% of 1–5-year-old children from the southern EU).

In the following, we describe two studies from the IVDK, covering patients from Germany, Austria, and the German-speaking parts of Switzerland, and one further study based on data from Denmark, Germany, the United Kingdom, and Italy. A statistically significant decrease in the proportion of positive patch test reactions to nickel among girls aged 1–17 years was found in a large study comprising almost 75 000 patients from the IVDK, in the period 2005–2012 (17.3% versus 11.6%) ($p < 0.05$) (29). There were differences in reported piercing over time in the different groups. In 2005–2006, the majority of girls aged 1–17 years had been pierced before 2004, whereas in 2011–2012 most had been pierced after 2004. Women in the age groups 18–30 and 31–44 years had a statistically significant decrease in nickel allergy during 2005–2012 ($p < 0.001$), whereas in women aged 45–60 years a statistically significant increase was seen ($p < 0.01$). The same pattern was seen in a large study of 180 000 patients in Denmark (1985–2010), Germany (1995–2010), Italy (1997–2010), and the United Kingdom (2004–2010) (6). Thus, a statistically significant decrease in the prevalence of nickel allergy in the observed time period was seen in women aged < 30 years in all countries ($p < 0.01$). In contrast, in women aged > 30 years, a statistically significant increase was seen in all countries. The increase is probably explained by a cohort effect.

In another study of IVDK patients, the prevalence was 14.3% in girls aged 1–17 years in 2009 (1). During 1994–2009, there was a statistically significant decrease in the prevalence of nickel allergy in girls aged 1–17 years, in women aged 18–30 years, and in boys aged 18–30 years (all $p < 0.0001$). However, during 2000–2009, no further decrease was observed in the youngest group (1–17 years). In women aged > 30 years, an increase in the prevalence of nickel allergy during the period was seen, probably because of a cohort effect. There was some overlap with patients from the previously mentioned IVDK study in the time period 2005–2009 (29).

Discussion

In this review, we found that the prevalence of nickel allergy in some EU countries was substantially reduced after the former EU Nickel Directive and later the Nickel Restriction by REACH had been fully implemented. The decreasing prevalence was most prominent in the northern EU countries. In the studies reviewed, a significantly lower prevalence of nickel allergy was found among young Danish women after compared with before implementation of the Danish Nickel Regulation (aged 18–35 years) (11.4% versus 19.8%) ($p = 0.02$). A lower prevalence was also found among Danish women ear-pierced after than those ear-pierced before implementation of the Danish Nickel Regulation (e.g. 6.9% for those ear-pierced between 1990–2006, and 15.6%

for those ear-pierced before 1990) ($p = 0.004$) (10, 12, 14, 20). After implementation of the EU Nickel Directive, a considerable decrease in the prevalence of nickel allergy among dermatitis patients aged 1–16 years was seen in several EU countries (28). Additionally, the prevalence was significantly decreased among female dermatitis patients aged ≤ 17 years and among female and male dermatitis patients aged 18–30 years in Germany, Switzerland, and Austria. There was a clear, consistent pattern of statistically significant decreases in the prevalence of nickel allergy over time up to the year 2010 in female eczema patients aged < 30 years of age in Denmark, United Kingdom, Italy, and Germany (6). However, the prevalence of nickel allergy in the population was $> 10\%$ among young women in some EU countries, and a relatively high incidence among Danish women was observed even after the Danish Nickel Regulation came into force. This means that, despite the Nickel Restriction by REACH having a major impact on the prevalence and incidence of nickel allergy in the population, a substantial problem still exists, especially among young women.

Because the Nickel Restriction by REACH is very similar to the original Danish Nickel Regulation, early Danish studies have been used in this review as a part of the evaluation of the effect of the Nickel Restriction by REACH. Jensen et al. and Thyssen et al. published the only population-based studies in which the prevalence of nickel allergy was assessed in subgroups of different individuals both before and after the Danish Nickel Regulation came into force (9, 10). Their results indicate a protective effect of the Danish Nickel Regulation. After selection of those women ear-pierced before and those ear-pierced after the regulation came into force in Denmark, the decreasing prevalence of nickel allergy remained statistically significant (10, 20). In the two studies following the prevalence of nickel allergy in the same individuals at different time points, it was shown that a substantial number of new cases of nickel allergy occurred over time (25-year incidence of 24.4%; and 15-year incidence of 7%) (13, 14). However, this design does not allow the investigation of any time trend. Moreover, the high frequency of new cases of nickel allergy in the Swedish study (13) may be partly attributable to individuals who developed nickel allergy before the Swedish Regulation came into force. Nevertheless, the later study from Denmark also showed a high frequency of new cases among Danish women during 1995–2010, a time period in which the Danish Nickel Regulation (1990) and later the EU Directive (2000) had been implemented (14). In 2009–2010, 15-year-old schoolgirls in Poland had a prevalence similar to that found in Denmark in 1995 (12.3% and 13.7%, respectively), which agrees well with the fact that the EU

Directive was introduced in Poland ~ 14 years after its introduction in Denmark (14, 22). Furthermore, nickel release from metallic items was found to be extensive in Poland 7 years after the implementation of the EU Directive (22), and the effectiveness of regulatory control by the authorities has been questioned (30). In Sweden, a comparable prevalence was found during 2000–2004 (13.3%) in a large study with 4376 schoolgirls, although these schoolgirls were slightly older (14.9–23.4 years) (16).

Investigations of adult dermatitis patients showed a high and unchanged prevalence of nickel allergy during 2002–2012 in EU countries, but with large differences in the prevalence between countries (23–27). Throughout the period, higher prevalences were consistently found in southern EU countries than in northern EU countries (26% versus 12% in 2009–2012) (23). In studies determining age- and sex-standardized prevalences in dermatitis patients, consistent decreases in the prevalence of nickel allergy have been shown. Decreases were found in young girls with dermatitis aged 1–17 years in Germany, Switzerland and Austria during 2005–2012 (17.3% versus 11.6%) (29), in women aged < 30 years in Denmark, Italy, Germany and United Kingdom until 2010 (6), and in children aged 1–16 years in EU countries during 2002–2010 (28). In a study from Germany, Switzerland, and Austria, it is notable that the prevalence of nickel allergy in girls with dermatitis remained stable at a high level after the year 2000 (12.6% in women aged 1–17 years in 2008–2009) (1).

The Nickel Restriction by REACH appears to be less effective in southern EU countries. This may be partly explained by differences in patient selection, but is, to a large extent, thought to be a result of differences in exposure because of the (lack of) enforcement of the EU Nickel Directive (31). Persistence of high nickel release from metallic consumer items such as jewellery, hair clasps, mobile phones, computers, watches and belt buckles has been shown in several EU countries after implementation of the EU Nickel Directive (1, 22, 32–39). These types of study have, to our knowledge, been performed only once in the southern EU (40). In this Spanish study, almost one-quarter of the tested earrings gave a positive dimethylglyoxime test result. Other possible partial explanations for the high observed prevalence in southern EU countries may be cultural factors, such as early ear piercing and the use of inexpensive jewellery (41). Furthermore, a greater corrosion of nickel in metallic items in contact with the skin could be plausible in these countries (42). As we recently pointed out, the accepted exposure limits for nickel release have differed from the limits in the

restriction, and relatively high amounts of release have been considered to comply with the nickel restriction (4). From another public health perspective, the estimated positive economic effects following the introduction of the first Nickel Regulation in Denmark in 1990, as saved costs from sick leave resulting from nickel allergy, reduced healthcare costs, and reduced negative effects on quality of life, were calculated to amount to approximately €1.3 billion over a period of 20 years (2002 value) (43). No unexpected negative effects of the regulation, such as obstruction of technological or industrial development, have been identified.

In the interpretation of our results, the heterogeneity of the included studies must be taken into account. The studies differ in study populations, age and sex distribution, and patch test procedure. One weakness of our review is (partly) overlapping data between some of the included studies, which complicates the interpretation of the results. The largest multicentre study and studies from two networks were selected for the qualitative analysis of the patient studies. This may be regarded as both a weakness, as many studies of patients were only included in the appendices, and a strength, as the large study populations increase the power of these studies. We chose to analyse the development of nickel allergy in EU countries according to region, as a geographical difference has repeatedly been observed. Other interesting perspectives could have been to categorize countries according to preceding national legislation, national surveillance, or similar activities, or the time point for EU membership. Regarding the included studies, relevant weaknesses, overlap between studies or deviation from standard patch test methods were noted as comments in the appendices. For future similar studies, we recommend age and sex stratification in studies presenting the prevalence of nickel allergy. One approach could be to subgroup individuals who have been covered by the EU Nickel Directive according to their year of birth and the year of full implementation of the EU Nickel Directive in the country in question. Such stratification would have been especially useful in our review for the analysis of the adult patients from the

ESSCA network. Additionally, general population studies from EU countries outside of Denmark and Sweden are needed to address the effect of the Nickel Restriction by REACH from a more general perspective. Furthermore, to improve transparency, it would be preferable to avoid overlap between study populations and study periods.

Conclusion

In conclusion, the literature review showed an effect of the Nickel Restriction by REACH. Nevertheless, nickel allergy remains a substantial problem in the population, as shown by prevalences of 9.8% among Swedish women aged 16–19 years in 2011–2013 and 14–18% in adults of both sexes in other EU countries in 2008–2011. Furthermore, a high prevalence (11.6%) is seen among girls patch tested on suspicion of having ACD in 2012 in Germany, Switzerland, and Austria. Steps should be taken for better prevention of nickel allergy, as the prevalence remains unacceptably high in EU countries.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. General population studies.

Appendix S2. Dermatitis patients.

Appendix S3. Dermatitis patients with age stratification.

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Appendix 1. Population-based studies concerning prevalence of nickel allergy

Year of publication												
Author	Country	Population	Age in years	PATCH TEST			Reading	Women/		POSITIVE REACTION NICKEL (%)		
				Year	Type	Day		Number	Men(%)	Total	♀	♂
Diepgen (1)	2016	5 countries	18-74	2008-2011	TRUE test	3	3119	54.9	14.5	22.2	5.2	
		Germany*					1024		13.9			
		Italy*					546		16.4			
		NL *					500		15.8			
		Portugal*					531		18.5			
		Sweden*					518		8.3			
Lagrellius (2)	2016	Sweden	15.8-18.9	2011-2013	TRUE Test	2	2236	52.5	7.5	9.8	4.9	
Mortz (3)	2013	Denmark	12-16	1995	TRUE Test ^a	3 ^b	1146	54.1	8.6	13.7	2.5	15-year incidence of
		Same individuals	28-30	2010	TRUE Test ^a	3/4 ^c	442	62	11.8	18.3	1.2	nickel allergy: 7%
Krecisz (4)	2012	Poland	15	2009-2010	IQ chamber	2 og 4	528	58.5	7.8	12.3	1.4	
Thyssen (5)	2009	Denmark	18-69	1990-1991	TRUE Test	2	537	51	10.9	2.2		
			18-35				190	55.8	19.8	3.6		
			36-55				245	50.6	6.5	1.7		
			56-69				108	40.7	2.3	1.6		
		General population	18-69	2006-2008	TRUE Test	2	3338	55.2	10.3	1 ♂: Falling trend		
Josefson (6)	2009	Sweden*	8,11 and 15	1982-1983	TRUE Test	3	958	100	9	24-25-year incidence of		
		♀ Schoolchildren	30-40	2006-2007	TRUE Test ^d	3	369	100	30.1	nickel allergy: 24.4%		
		Same individuals										
		Schoolchildren	14.9-23.4	2000-2004	TRUE Test	4	4376	68	9.9	13.3 ^e	2.5 ^e	
Fors (7)	2008	Sweden*	18-75	1994-1995	TRUE Test	3	531	54.4	19.2	31.1	5.0	
Dotterud (8)	2007	Norway	18-69	1994	TRUE Test	3	1236	55.8	17.6	27.5	5.1	
Dotterud (9)	2007	Norway	17-22	1999-2000	TRUE Test	2 og 4	275	100	17.1	Significantly lower prevalence in		
Jensen (10)	2002	Denmark	10-14	1999-2000	TRUE Test	2 og 4	305	100	3.9	the younger girls		
		♀ High-school girls ^f										
		♀ Primary-school girls ^f										

Concentration given only when different from 5% (or 0.2 mg/cm2 in TRUE-test)

Bold numbers: significant difference

* Age standardised prevalences

^a Standard concentration supplemented with 66, 33 and 11 ug/cm2.

^b 40 children read D2, D4 eller D7. 6 children read by instructed parents

^c 3 persons read D2, 1 person D5, in 6 persons reading at home following instruction and photo documentation. 39 persons had not been tested 1995. 15-year incidence calculated from 403 tested on both occasions.

^d 38.5% of those tested 1982-1983 were re-tested 2006-2007. 15/29 persons with doubtful results additionally tested with 5%, 2.5%, 1.0%, 0.3% and 0.1% nickel sulfate.

Positive reactions were defined as ++ reaction for 5% NISO4 AND ++ or weaker reaction in one or more of dilutions

^e predicted prevalence taking drop-outs into consideration; ♀: 11.8 %. ♂: 1.6 %

^f drop-outs: primary school: 28.6%, high school: 48.5%

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Appendix 2. Studies concerning prevalence of nickel allergy in patients

Year of publication						Women/ Positive reaction nickel (%)					
Author	Country	Population	Age	Patch Test	Reading	Number (n)	Men (%)	Total	♀	♂	Development over time
Boonstra (1)	2015 Netherlands	Hand eczema	9-80	2002-2013	TRUE Test	1571	54.8	18.8			
Muris (2)	2015 All ^a	Obs. ACD	>18	2011-2012		906	70	25.2			
	Netherlands				Van der Bend	66		31.8			
	Spain				Finn Chamber	117		20.3			
	Italy				Van der Bend	90		34.4			
	Switzerland				IQ Ultra	175		22.9			
	Portugal				Finn Chamber	189		29.5			
Smith (3)	2015 UK b	Obs. ACD	0-16	2005-2014	IQ chambers	500	59.4	4.8	Significant decrease compared to 1995-2004 (Clayton)		
	2015 Czech Republic	Obs. ACD	5-83	2008-2012	Curatest	1941	69.7	15.4	19.4	6.0	No change over time
				2008		337	65.9	13.9	18	6.1	
				2009		376	67.6	16.2	20.5	7.4	
				2010		474	68.6	12.7	16.0	5.4	
				2011		382	73.3	15.4	19.6	3.9	
Uter (5)	2015 ESSCA ^c	Obs. ACD	-	2009-2012	Finn Chamber/ TRUE Test	59728		11.9-26.4			
	Austria					1113	73.9	21.6			
	Denmark					2582	69.6	12.6			
	Finland					1057	62.1	22.4			
	Germany					7628	59.6	11.9			
	Italy					9267	66.6	26.2			
	Lithuania					865	80.5	14.3			
	Netherlands					4385	66	19.4			
	Polen					2828	71.1	25			
	Spain					4257	68.3	26.4			
	Switzerland					4990	61.1	20.9			
	UK					15532	68.1	17.4			
García-Rabasco (6)	Slovenia					5224	69.3	16.9			
	2014 Spain	Obs. ACD	μ=48.3	2000-2010	-	3404	62.3	24.2			
	2014 Germany, Austria and Switzerland ^d	Obs. ACD	-	2010-2012	Finn chamber/ 2010 Haye's chamber/ 2011 IQ chamber/ 2012 Curatest F	38878	64.1				
						13117		14.9			
						13320		15.6			
						12529		15.3			
Aguilar-Bernier (8)	2012 Spain	-	12-90	2005-2010	Curatest	839	73.7	25.9	37.7	5.5 ♀ og ♂: the prevalence increases with age	
					2, 4 ^e or TRUE Test						

Appendix 2-continued

Author	Year of publi.	Country	Population	Age	Patch test		Reading Days	Women/ Positive reaction nickel (%)			
					Year	Type		Number (n)	Men (%)	Total	♀ ♂ Development over time
Uter (9)	2012	ESSCA ¹	Obs. ACD	-	2007-2008	Finn Chamber or TRUE Test	3-5 *	25181		11.9-27.4	
		Austria						678	66	25.2	
		Denmark						1318	67	11.9	
		Finland						760	62	21.3	
		Germany						2694	61	16.8	
		Italy						2938	66	27.4	
		Lithuania						680	74	18	
		Netherlands						2168	64	14.9	
		Polen						789	68	24.3	
		Spain ^g						1845	65	26.5	
		Schweizerland						2402	60	22	
		UK						8909	67	18.6	
	2010	Greece	Obs. ACD	<16	1980-1993		2 and 4	232	62.5	16.4	24.1
Millingou (10)					1994-2007			255	63.5	21.6	31.5
O'Connell (11)	2010	UK ^h	Hairdressers	15-71	1980-2007	Finn chamber	2/3 and 4/5	725	91.1	32.1	
Uter (12)	2009	ESSCA ¹	Obs. ACD	-	2005-2006	-	3-5 *				
		West						8468		20.8	
		South						2666		24.5	
		Central						5708		19.7	
		Northeast						1585		22.4	
Bordel-Gómez (13)	2008	Spain	-	25-58	2000-2005	Curatest	2 and 4	1092	61.6	29.3	42.5
The ESSCA Writing Group (14)	2008	ESSCA ¹	Obs. ACD	-	2004	Finn chamber or TRUE Test	3-5 *	9871		20.6	8.1
Mäkelä (15)	2007	Finland	History of atopy	20-31	1982-1983	Finn chamber ^k	3/4	801	62.5	16	
Tomljanović-Veselski (16)	2007	Croatia	-	-	2004-2006	-	2 and 3	955	-	12.9	
Clayton (17)	2006	UK	Obs. ACD	0-17	1995-2004	Finn chamber	2 and 4	500	62	8.8	
Machovcova (18)	2005	Czech Republic	Obs. ACD	6-75	1997-2001	Curatest or Leukotest	2 and 3	12058	63.4	13.8	19 4.7
Seidenari ¹ (19)	2005	Italy	Obs. ACD	7 mont- hs-12 yr	1995-2001	Finn chamber	3	1094	53.5	10.9	13.5
Uter (20)	2005/	ESSCA ^m	Obs. ACD	-	2002-2003	Finn Chamber	3-5 *	9520		17.3 ⁿ	7.9
	2006										

Concentration mentioned only if different from 5% (or 0.2 mg/cm2 in TRUE-test)

- : not given

ACD= Allergic contact dermatitis

µ=mean age

* Patch test exposure 2 days, except for 1 day exposure in German departments

^a Overlap with Uter (2015) and Teixeira (Appendix 3).

^b Overlap with Uter (2015, 2012 and 2009)

^c 53 department of dermatology in 12 countries; Austria (1), Denmark (1), Finland (2), Germany (8), Italy (6), Lithuania (1), The Netherlands (NL) (2), Polen (3), Schweizerland (4), Spain (7), Slovenia (6) and UK (13)

^d Overlap between Uter (2012,2015) and Mahler (2014)

^e Only positive results D4 included.

^f 39 dermatological departments in 11 countries; Austria (1), Denmark (1), Finland (2), Germany (6), Italy (3), Lithuania (1), NL (2), Polen (3), Switzerland (3), Spain (5) and UK (12)

Appendix 2-continued

- ^g Partly the same population as García-Garvín 2011 (Appendix 3)
- ^h Overlap in patients year 2002-2007 with Garg 2013 (Appendix 3)
- ⁱ 31 dermatological departments in 10 countries; Austria (1), Finland (2), Germany (5), Italy(4), Lithuania (1), NL (2), Polen (1), Switzerland (2), Spain (1) and UK (12). Prevalence divided into 14 geographical regions in Europe. West= UK. South= Spain and Italy. Central= NL. Switzerland, Austria, Germany. Northeast=Finland, Lithuania and Polen.
- ^j 31 dermatological departments in 11 countries; Austria (1), Denmark (1), Finland (2), Germany (6), Italy (5), Lithuania (1), NL (2), Polen (1), Switzerland (1), Spain (1) and UK (10). Highest prevalence in Italy (Bolzano: 32.2%), lowest prevalence in Denmark (9.7%)
- ^k concentration of allergen not given
- ^l Overlap in patients with Garg (2013) <30 year in the period 1997-2001 (Appendix 3). Patch test occlusion 72 h.
- ^m 17 dermatological departments in 9 countries; Austria (1), Denmark (1), Finland (2), Germany (5), Italy (4), NL (1), Polen (1), Schweizerland (1) and UK (1). Highest prevalence in Italy (31.7%), lowest prevalence in Denmark (8.1%)
- ⁿ standardised for age and sex

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Appendix 3. Studies concerning the frequency of nickel allergy in patch-tested patients stratified by age

Author	Year of		Age	Year	Patch tests	Type	Reading days	Women/ Positive reaction nickel (%)				
	publ.	Country						Number	Men (%)	Total	♀	♂
Fortina (1)	2015 ESSCA ^a	1-16	2002-2010	Finn Chamber	3-5 *	6583		16.7	2002-2010: decrease over time in all regions. Highest prevalence in the youngest age group			
		1-5		or TRUE Test	1588		26.7					
		6-12			2692		13.2					
		13-16			2303		13.9					
		1-5			40		15,0					
		6-12			226		10.6					
		13-16			542		17.3					
		1-16			155		25.8					
		1-5			542		17.3					
		6-12			959		5.3					
		13-16				1021		10.1				
		1-5			1341		30.2					
		6-12			1450		18.1					
		13-16			644		15.2					
		m=39	1991-1993	Finn chamber	3	3662	64.7	21.4				
		<40		or TRUE test		1891	63.9	33.8		7.3		
		≥40				1771	65.6	25.2		5.4		
		m=40	1999-2001	Finn chamber	3 and 6/7	3825	63.2	19.8		31.1 ^c	6.7 ^c	
		<40		or TRUE test		1864	62.7	29.4		6.4		
		≥40				1961	63.6	26.3		6.2		
Fall (2)	2015 Sweden ^b	m=43	2008-2009	Finn chamber	3 and 6/7	3112	64.0	17.6	26.7 ^c	7 ^c	♀ all ages: 1992-2009: Significant decrease, especially <40 years.	
		<40		or IQ chamber		1396	63.7	23.3	6.1			
		≥40				1716	64.3	24.7	6.2			
		All	1992-2011	Finn chamber	2/3 and 4/ 7	5250	69.3	26.5	34.4	6.3		No significant change during 1992-2011
		≤ 15		or IQ chamber				2.7	2.6	6.4		
		16-30						38.4	40.7	6.5		
		31-64						54.5	53	6.6		
		≥ 65						4.3	3.6	6.7		
		All	1992-1996			1238	68.2	26.4	35.3	6.8		
		≤ 15						3.7	3.7	6.9		
Teixeira (3)	2014 Portugal	16-30						46.8	49	6.10		
		31-64						47.1	45	6.11		
		≥ 65						2.4	2.3	6.12		
		All	1997-2001			1473	66.7	24.8	33.5	7.6		
		≤ 15						2.7	3.0	0		
		16-30						41.8	44.1	21.6		
		31-64						52.7	51.1	67.6		
		≥ 65						2.7	1.8	10.8		

Appendix 3-continued.

Author	Year of publ. country	Age	Year Patch tests	Type	Reading days	Number	Women/ Men (%)	Positive reaction nickel (%)	Development over time
Teixerira (3)	All	2002-2006				1039	68.6	28.9 36.3 12.6	
	≤ 15							2.3 2.3 2.4	
	16-30							36.3 38.6 22.0	
	31-64							55.7 54.8 61.0	
	≥ 65							5.7 4.2 14.6	
	All	2007-2011				1500	73.1	26.6 33.1 8.9	
	≤ 15							2.3 1.7 8.3	
	16-30							30.1 32.2 8.3	♀ 16-30 years: Significant decrease during 2007-2011
	31-64							61.4 60.3 72.2	compared with during 1992-1996
	≥ 65							6.3 5.8 11.1	
Garg (4)	All	1985-2010	-		4 and 7	19 828	64.6	12.3 17.4 3.1	
	<30					21.2%		14.2 18.9	3 ♀ <30 years: significant decrease
	30-60					52.7%		14.5 20.7 3.4	♀ and ♂ 30-60 years: significant increase
	>60					26.1%		6.5 8.9 2.6	
	All	1995-2010	-		3 *	104 933	62.2	13.6 18.9 5.1	
Germany	<30					18.9%		18.8 26.0 5.9	♀ and ♂ <30 years: significant decrease.
	30-60					52.4%		15.8 23.1 5.4	♀ 30-60 years: significant increase.
	>60					28.7%		6.2 7.6 3.9	
	All	1997-2010	-		4	20 231	67.1	25.0 31.9 10.8	
	<30					28.5% ^e		27.2 35.2 10.6	♀ <30 years: significant decrease. ♂ <30 years: increasing trend
Italy	30-60					52.4%		27.9 35.9 11.4	♀ and ♂ 30-60 years: significant increase
	>60					19%		13.7 15.8 9.4	
	All	2002-2010	-		4	35 398	67.1	17.7 23.4 6.2	
	<30					26.7%		16.1 20.4 6.0	♀ and ♂ <30 years: significant decrease
	30-60					51.7%		21.2 28.4 7.3	♀ and ♂ 30-60 years: significant increase
UK	>60					21.5%		11.3 15.6 3.9	
	All	2005-2012	3(4)			74854	62.2	♂ all ages: no trend	
Schnuch (5)	All	2005-2012	3(4)			278	100	17.3	
	1-17	2005-2006				1386	100	26.41	
	18-30					1844	100	36.17	
	31-44					2793	100	20.5	
	45-60					3237	100	9.48	
	61-99					239	100	15.06	
	1-17	2007-2008				1547	100	23.97	
	18-30					1902	100	34.81	
	31-44					3129	100	21.6	
	45-60					3603	100	8.74	
2013 Germany, Switzerland and Austria ^d	All	2005-2012	3(4)			74854	62.2	♂ all ages: no trend	
	1-17	2005-2006				1386	100	26.41	
	18-30					1844	100	36.17	
	31-44					2793	100	20.5	
	45-60					3237	100	9.48	
	61-99					239	100	15.06	
	1-17	2007-2008				1547	100	23.97	
	18-30					1902	100	34.81	
	31-44					3129	100	21.6	
	45-60					3603	100	8.74	

Appendix 3-continued

Author	Year of publ.	Country	Age	Year Patch tests	Type	Reading days	Women/ Positive reaction nickel (%)		
							Number	Men (%)	total
Schnuch (5)			1-17	2009-2010			306	100	14.05
			18-30				1908	100	19.97
			31-44				2251	100	30.03
			45-60				4140	100	21.16
			61-99				4292	100	7.69
			1-17	2011-2012			328	100	11.58
			18-30				2046	100	19.75
			31-44				2373	100	31.14
			45-60				4467	100	23.88
			61-99				4481	100	8.98
Simonsen (6)		2013 Denmark ^f	1-17	2003-2011	Finn Chamber or TRUE Test	3/4 and often 2 and 7	2587	65.9	9.7
			1-4						12.4
			5-8						4.7
			9-12						14.5
			13-17						8.5
Turčić (7)		2013 Croatia ^g	3-80	2007-2011	- ^h	2 and 3	2185	69.6	13.7
			3-20						11.7
			21-60						9.9
			61-80						
			All				19029	67.2	25.4
Rui (8) ⁱ		2012 Italy	≤ 26	1996-1998	Finn Chamber	2 and 3			32.5
			27-35						10.8
			36-45						38.3
			46-58						8.4
			≥ 59						48.2
			≤ 26	2008-2010					7.6
			27-35						35.7
			36-45						7.0
			46-58						27.5
			≥ 59						5.8
			≤ 26		Finn Chambers	2 and 3			14.2
			27-35						5.4
			36-45						29
			46-58						12.7
			≥ 59						1996-2010; ♀ ≤ 26 years: significant decrease
Bellauskine (9)		2011 Lithuania ^j	18-87	2006-2008	Finn Chambers	2 and 3	816	73.7	43.1
			<40				320		11.1
			≥40				496		15.1
			18-87				9138	63.7	37.7
			≥40						8.5
Carøe (10)		2011 Denmark ^k	2-95	1992-2009	TRUE Test	3/4 and 5-7			21.7
			2-30						5.2
			31-60						24.4
			>60						24.6
									9.7

Significantly higher prevalence in ♀ <40 years compared to ♀ ≥40 years
♂ 2-95 years; 2 u-formed patterns with nadir 1996-1997 and 2005
♀ 2-30 years: significant decrease
♀ 31-60 years: no significant change
♀ >60 years: significant increase

Appendix 3-continued

Author	Year of		Year	Patch tests	Type	Reading days	Women/		Positive reaction nickel (%)	
	publ.	Country					Number	Men (%)	total	♀ ♂ Development over time
Carøe (10)	All		1992-1997						22	
	2-30								29.8	
	31-60								22.9	
	>60								6.9	
	All		2004-2009						20.8	
	2-30								19.6	
	31-60								25.2	
	>60								11.1	♀ > 60 years: significantly lower prevalence compared to ♂ aged 2-30
Fortina (11)	2011	Italy	2002-2008	Finn chamber	2 and 4		321	55.1	26.8	
	0-3						90		33.3	
	0-2									
	>2-3						231		24.2	
García-Garvín (12)	1-99	2011 Spain ^m	2008	Finn chamber	-		1161	63.7	25.9	
	1-20			or TRUE Test					36.1	9.1
	21-40								36.3	8.2
	41-60								40.1	10.5
	61-99								22.9	7.9
Kulkanac (13)	4-18	2011 Croatia	1994-2009	Curatest ^h	2 and 3		412	66.5	25.4	No statistically significant difference in prevalence between children and adults
	19-81						4440	65.7	32.6	
	19-40						1708		33.5	
	41-60						1570		34.8	
	61-81						1162		23.2	
Schnuch (14)	1-99	2011 Germany, Switzerland and Austria ^j	1994-2009	-	3(4)		127098	62		
	1-17		1994				242	66.5	29.2	7.5
	18-30						2049	68.1	36.6	6.6
	31-44						2045	62.5	30.7	5.5
	45-60						2601	61.8	12.3	4.5
	61-99						1711	63.7	7.6	3.9
	1-17		2000				245	61.2	12.0	2.1
	18-30						1284	60.0	26.7	5.3
	31-44						1831	58.2	32.6	7.6
	45-60						2268	59.3	14.5	5.1
	61-99						2151	64.2	7.0	3.0
	1-17		2009				223	59.6	14.3	6.7
	18-30						1261	66.0	20.2	4.9
	31-44						1725	57.4	29.7	5.3
	45-60						2863	63.5	19.9	5.2
	61-99						3069	64.1	7.7	3.1

♀ 1-17 years: 1994-2009 : significant decrease but 2000-2009 no change
 ♀/♂ 18-30 years: significant decrease.
 ♀ 31-44 years: 1994-2000: significant increase but 2000-2009 no change
 ♀ 45-60 years: significant increase
 ♀ 61-99 years: 1994-2000: significant increase but 2000-2009 no change

Appendix 3-continued

Author	Year of		Age	Patch tests	Type	Reading days	Women/			Positive reaction nickel (%)		
	publ.	Country					Number	Men (%)	total	♀	♂	Development over time
Janach (15)	2010	Switzerland	17-91	2000-2004	Finn Chamber ⁿ	2 and 3/4	4094	58.3	19.3	28.0	7.2	
			<30				931	62.4		36.3	6.9	
			30-44				1153	52.2		37.9	8.3	
			45-59				1073	59		24.8	7.3	
			≥ 60				937	61		12.8	5.8	
Marinović-Kulišić (16)	2006	Croatia	3-80	1999-2003	-	2 and 3	3293	70.9		21.3	8.8	
			3-20				315		17.6			
			21-60				965		18.4			
			61-80				73		10.8			

Concentration given only if different from 5% (or 0.2 mg/cm2 I TRUE-test)

- : not given

m: median

* Patch test exposure 2 days, except for 1 day exposure in German departments

a 11 countries divided into 4 geographical regions; Central=Austria, Switzerland, Germany, Denmark and The Netherlands (NL). Northeast=Finland and Polen. West=UK. South=Spain, Italy and Slovenia. Overlap with Uter (2015, 2012, 2009, 2005) and The ESSCA Writing Group (2008) (Appendix 2)

b 14 departments of dermatology or occupational and environmental dermatology in different cities.

c Pooled data from readings D3 and D6-D7, all other reading from D3.

d IVDK (Information Network of Departments of Dermatology): Overlap with data from Garg et al (2013) in the period 2005-2010, and Mahler (2014) (Appendix 2) in the period 2010-2012 and Schnuch (2011) in the period 2005-2009. NB: Different exposures in the group aged 1-17 years; in 2005-2006 they were pierced before 2004, in 2011-2012 the majority were pierced after 2004.

e proportion of patients <30 years of age slightly higher in Italian population

f 12 dermatology clinics throughout Denmark

g Patient population: Patients diagnosed with ACD (72.6%), ICD (9.3%) and AD (18.2%).

h Allergen preparation at the institute of immunology in Zagreb

i Overlap with Garg (2013)

j Overlap with Uter (2012) Appendix 2

k % positive standardized

l Overlap with Simonsen(2013) in the period 2003-2009.

m Overlap with Uter (2012) Appendix 2

n Concentration not given