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An investigation of causes of nickel allergy

A LOUS follow-up project

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An investigation of causes of nickel allergy

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Preface

The List of Undesirable Substances (LOUS) was established by the Danish Environmental Protection Agency (EPA) as a guide for enterprises. It addresses chemical substances of concern based on their hazardous properties and the volumes used in Denmark. The most recent version of LOUS from 2009 includes 40 chemical substances or groups of substances, including nickel (DEPA 2010).

During the period 2012–2015, all substances listed on LOUS were surveyed and any further need for risk management measures was evaluated. In certain cases, implementation projects were launched to achieve the goals laid down in the strategies for each of these substances/substance groups.

The present project "An investigation of causes of nickel allergy" was initiated by the Danish EPA as a LOUS follow-up project. The study's objective was to identify causes and exposures leading to nickel allergy and eczema in patients with proven nickel allergy. Based on the results and a review of the epidemiology of nickel allergy in the EU, the objective extended to assessing whether the current nickel regulation is sufficiently protective.

The project was carried out from July 2015 to March 2016 at the National Allergy Research Centre, Department of Dermato-allergology, Gentofte Hospital, University of Copenhagen, Denmark.

This report was prepared by:
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Anne Marie Topp participated in the collection of data and Jacob Thyssen took part in the overall project.

The report has undergone review and discussion with Trine Thorup Andersen, the Danish Environmental Protection Agency.

The data collected for this report will be published as part of one or more scientific papers.

Summary and conclusion

A nickel regulation was introduced in Denmark in 1990 due to a high frequency of nickel allergy, especially among women. In 1994 a similar nickel regulation was introduced in all EU countries, coming into full force from 2001. Studies indicate that the regulation has been effective in reducing nickel allergy, leading to major economic benefits. Nevertheless, new studies indicate that despite the problem decreasing, a significant proportion of young individuals still become sensitized to nickel.

The aim of this investigation was to evaluate whether the regulation of nickel is sufficiently protective in relation to developing nickel allergy. The evaluation was done by reviewing the recent scientific literature and through a questionnaire study to identify causes and exposures leading to allergy and eczema in patients with existing nickel allergy. This formed the basis of a preliminary assessment of the present nickel regulation and recommendations for changes and further investigations, if needed.

The investigation had three parts corresponding to the above aims.

In the first part a review was made of the scientific literature concerning frequency of nickel allergy in Europe 2005–2015. A literature search was done in Pubmed in September 2015 with the following terms: "general population nickel" "nickel allergy prevalence" and "nickel dermatitis". Original literature and review articles published during 2005–2015 were included if the study concerned investigation of the frequency (prevalence) of nickel allergy either in the general population or in patients in EU countries as well as Switzerland and Norway. Patient studies were included if more than 500 patients were investigated or if the prevalence of nickel allergy over time was assessed. Case reports and studies not published in English were excluded. The population studies are summarized in Appendix 1 and the patient studies in Appendices 2 and 3.

The literature search resulted in the inclusion of 12 population and 30 patient studies. Nickel allergy was the most common contact allergy in the population and among patients. Significantly higher frequencies of nickel allergy were found in Southern Europe compared with Northern Europe and in women compared with men. A significantly lower prevalence of nickel allergy among young women was found in population studies after the implementation of the nickel regulation and among women with pierced ears after compared with before implementation. The prevalence of nickel allergy in the population was more than 10% among young women, and a relatively high frequency (incidence) of new cases among women was also observed after the nickel regulation came into force. In patient studies from the European Surveillance System on Contact Allergies, ESSCA, a high and unchanged prevalence of nickel allergy was seen during 2002–2012, which is in contrast to the significant decline seen in the prevalence of nickel allergy in children aged 1–16 years. There was a clear, consistent pattern of significant decrease in the prevalence of nickel allergy over time in female eczema patients younger than 30 years up to the year 2010 in Denmark, England, Italy and Germany; nevertheless, the prevalence remains high corresponding to 14–27% in this age group. The prevalence of nickel allergy was 11.6% among younger women/girls (aged 1–17 years) in Germany, Switzerland and Austria in 2012.

In conclusion, the literature review showed an effect of the nickel regulation; however, young women are still becoming sensitized to nickel and the prevalence remains high in the population,

corresponding to 8–18%, depending on the European country. Accordingly, a revision of the current nickel regulation seems warranted.

The second part consisted of a questionnaire study performed in nickel-sensitized eczema patients. The aim was to identify causes and exposures leading to nickel allergy and eczema. Patients for inclusion were defined by a positive patch test to nickel sulphate 5% in petrolatum within the past 5 years (1 January 2010–31 December 2014) at the Department of Dermato-Allergology, Gentofte Hospital; 541 nickel-sensitized patients were identified of whom 17 could not be contacted, leaving 524 potential participants. A questionnaire was sent three times to non-respondents with at least 3 weeks between each distribution. The questionnaire included questions about nickel exposure and dermatitis after exposure to consumer goods with a metallic surface.

A questionnaire response was received from 342 of 541 nickel-sensitized patients: 318 women and 24 men, corresponding to a participation rate of 63.2%. Participants were asked about the first time they had experienced a rash from a shiny metal item, what the item was and their age. They were given a list of 15 groups from which to select the culprit item; participants could also add items not covered by the list. First-time rash can be interpreted as the sensitization event; accordingly, items causing such a rash are particularly important. Women were median 16 years and men 18 years when experiencing first-time rash from shiny metal items.

In women, the single most important reason for first-time rash was earrings, followed by buttons on clothing, wrist watches, jewellery other than earrings, zips and belt buckles. These were the causes reported by 19.2%–67.8% of women. Few women reported tools, computers, mobile phones or lighters as causes of their initial rash. Among other culprit items, four persons mentioned hooks on clothing as a cause.

In men, wrist watches and belt buckles were the most important causes of first-time rash (55.6% and 50%, respectively), followed by spectacles, jewellery other than earrings, earrings, buttons on clothing and keys. No men reported computers, mobile phones or scissors as the cause of their initial rash. The few men with nickel allergy make the results less robust.

A subgroup analysis included patients with first-time rash during the past 10 years, i.e. after the EU regulation on nickel had been in force. This group comprised 30 persons: 5 men and 25 women with a median age of 38 years. The order of items in this subgroup was earrings, jewellery other than earrings, belt buckles, and buttons on clothing, wrist watches, keys and spectacles. Another subgroup analysis concerned patients who had experienced their most recent rash during the past 5 years, signifying continued exposures of clinical significance. This group comprised 173 persons: 12 men and 161 women, median age 49 years. The five most prominent causes were earrings, jewellery other than earrings, buttons on clothing, wrist watches and zips.

The REACH Annex XVII restriction setting the limits for nickel release defines 'long-term contact with the skin' as either three contacts of more than 10 minutes over 14 days or one contact of more than 30 minutes' duration. In the questionnaire the patients with nickel allergy were asked how short a contact with a shiny metal item was necessary for an eczematous reaction to occur. Overall, 18.1% reacted after a 10-min contact or less and 26% after a 30-min contact or less.

In conclusion, earrings still seem to play a major role in induction and elicitation of nickel contact allergy. Other exposures such as metal buttons, zips and belt buckles in clothing were also frequent causes of rashes. However, items such as mobile phones, computers, tools — including scissors — were relatively rare causes in view of their widespread use. This may be due to less intensive and intermittent contact with skin and/or less use of nickel in alloys and coatings.

The last part of the investigation entailed assessment and recommendations. Nickel allergy is common and represents a public health issue in the EU. With the introduction of the first national nickel exposure regulations in 1989 and in 2000, the EU nickel legislation has significantly reduced the number of new cases of nickel allergy in the EU population, particularly in the northern part. When the first nickel regulation was introduced in Denmark in 1989 and years later, the estimated positive economic effects, as saved costs from sick leave due to nickel allergy, reduced healthcare costs and the reduced negative effects on quality of life, were calculated to around 10 billion DDK over 20 years. If extrapolated to the entire EU, double digit billion euro amounts have been saved. No unexpected negative effects of the regulation have been identified, such as obstruction of technological or industrial development.

The latest updating of the EU Nickel directive by REACH (2007) gives a scientifically based definition of the concept "direct and prolonged contact with the skin". This phrase originating from the first versions of the regulation has been difficult to translate to the real-life situation for both authorities and industry. Around a quarter of the nickel-allergic patients in the current investigation reported rash after a 30-min contact with nickel-releasing items. This shows that the new definition of "direct and prolonged contact with the skin" defined as minutes of contact over a specific time period is not too stringent. It is expected that this clarification will further strengthen the positive effects of the Directive.

Ear piercing and the use of ear-post assemblies represent a particular problem because of the skin penetration and circumvention of the normal skin barrier. Earrings remain the major cause of nickel sensitization. The scientific investigations that formed the basis of the safe limit of nickel release were performed on intact skin. The relevance of post assemblies has not been investigated, and in the first version of the EU nickel directive a content limit (0.05%) was set for these assemblies. A revision of the regulation was made in 2007 and the content limit was changed to a release limit of 0.2µg/cm²/week nickel for post assemblies and body piercings. However, due to the uncertainty of the analytical method used to measure nickel release, post assemblies and body piercings with a measured nickel release of up to 0.35 µg/cm²/week are considered as complying with the rules according to the standard for the analytical method: EN1811:2011 and A1 2015. Revision should be considered regarding the REACH Annex XVII restriction for nickel so that nickel releasing metals would no longer be permitted in piercing post assemblies. Other materials with no hazard of contact allergy need to be identified and used.

The EU nickel directive seems to be less effective in the subtropical (Mediterranean) EU countries, probably because of greater corrosion of nickel from metallic items in contact with the skin. The effect of climate needs to be further investigated. The enforcement of the REACH restriction for nickel can be improved so it covers all member states in a uniform and transparent way.

1. Introduction

In Denmark regulation of nickel in consumer goods intended for prolonged skin contact has been in force since 1989, first as a national regulation and from 1994 (in force in 2000) as an EU regulation. The regulation itself (Table 1.1), the analytical method to measure nickel release and its interpretation has been changed several times (Table 1.2).

A report from the Danish Environmental Protection Agency, "Survey of nickel (metal)", No. 1723, 2015, showed that despite existing EU regulation limiting the permitted release of nickel from jewellery and other items with expected longer duration of contact with skin, a relative high frequency of nickel allergy exists in the population of Denmark. The frequency is about 10% in younger women, and the same seems to apply in other EU countries. Dermal exposure to nickel in the work environment, e.g. from tools or other items, is little investigated.

Table 1.1: Overview of nickel regulation(s)

Country	Regulation	Maximim Ni content/release	Products category	In force	Analytical Method
Denmark	Bekendtgørelse nr. 472 af 27. juni 1989 amended 16. Dec. 1991	Release ≤0.5µg/cm²/week	Jewellery, watches, spectacles, metal in clothing	10 July 1989	Dimethyl glyoxime test
Sweden	General advice regarding ear piercing. National Board of Health and Welfare, Sweden. SOSFS 1989: 40	Content ≤0.05% nickel or nickel coating thicker than 0.01 micrometer	Ear piercing with nickel-containing piercers or rings	1990	Atomic Absorption
EU	EU communities Directive 94/27/EC	a) Release ≤0.5µg/cm²/week b) Content <0.05%	a) Consumer products in prolonged contact with skin b) Piercing posts	20 July 2000	EN1811 (1999)*
EU	Commission Directive 2004/96/EC In 2006 REACH 1907/2006Entry 27	Changed b) to release: <0.2µg/cm²/week	b) Piercing posts	2007	EN1811 (1999) *

*) The interpretation of the outcome of EN1811 has been amended several times, see Table 1.2.

The analytical method to control the limits of nickel release is laid down in EN 1811. Due to the uncertainty of the analytical method, it was agreed that an adjustment factor of 0.1 could be applied to the measured amount of nickel release. This meant that items with a measured release of nickel 10 times the limit in the regulation would pass (see Table 1.2). In 2011 the uncertainty factor was replaced with an interval, meaning that the release from e.g. post assemblies had to be below 0.11

µg/cm²/week to pass. In the interval 0.11–0.35 no decision could be made, while if above 0.35 µg/cm²/week it would fail to comply with the regulation. From 2016 this has been changed again, so that items in the previous grey zone of inconclusive results now pass the test and are regarded as complying with the regulation. Accordingly, test results of up to 0.35 µg/cm²/week nickel release for post assemblies will now pass, which is three times more nickel release than was accepted during 2011–2015 (Table 1.2). The limits in the nickel regulation have been unchanged since 2007.

Table 1.2: Interpretation of EN1811: the method for measuring nickel release in relation to the nickel directive

	Post assemblies and body piercings			Other components in direct and prolonged contact with the skin		
Limit in regulation	Content 0.05%			≤0.5µg/cm² /wk		
EN 1811 1999-2005	Undefined			≤5µg/cm²/ wk PASS		>5µg/cm²/wk* FAIL
Limit in regulation	≤0.2µg/cm ²/week			≤0.5µg/cm² /wk		
EN 1811 2005-2011	≤2µg/cm²/ wk PASS		>2µg/cm²/wk * FAIL	≤5µg/cm2/ wk PASS		>5µg/cm²/wk* FAIL
EN 1811**	<0.11	0.11 to 0.35	> 0.35	<0.28	0.28 to 0.88	> 0.88
2011-2015	PASS	INCON-CLUSIVE	FAIL	PASS	INCON-CLUSIVE	FAIL
2016-	PASS		FAIL	PASS		FAIL

*) an adjustment factor could be applied to the measured amount of nickel release so that it became 10 times smaller than the measured value. **In 2011 the adjustment factor was replaced with an interval, but this interval contained a grey zone, where no decision could be made. The interpretation of the EN1811 changed again in 2016, meaning that inconclusive test results are now regarded as having passed.

In 2013 the definition of prolonged contact was agreed in EU as being more than 10 minutes on three or more occasions or more than 30 minutes on one or more occasions within a 2-week period (Entry 27[935] of Annex VII to REACH).

The purpose of this project was to identify causes and exposures leading to allergy and eczema in patients with existing nickel allergy. This is a first step in the evaluation of whether the regulation of nickel is sufficiently protective in relation to development of nickel allergy. The assessment can provide knowledge about the type of items, objects and materials that frequently cause nickel allergy and whether occupational exposures, e.g. to tools, play a role.
The results can be used to evaluate whether the existing limits for nickel release are appropriate and whether there is need for a targeted control of certain types of items containing nickel. Previous controls of random samples have shown that 15–20% of investigated earrings released larger amounts of nickel than permitted. The results can also be used to target information about nickel allergy to consumers.

The project consisted of three parts:

- **Part 1:** A review of the scientific literature concerning frequency of nickel allergy indifferent countries in the EU with focus on the previous 5–10 years.

- **Part 2:** A questionnaire study among persons in Denmark who have developed nickel allergy.

- **Part 3:** Based on the results from Parts 1 and 2, a preliminary assessment of the present nickel regulation and recommendations for any further investigations.

2. Nickel allergy in the EU

A review of the scientific literature concerning the frequency of nickel allergy in Europe 2005–2015 was done in this section as background information for evaluating the effect of the nickel regulation.

2.1 Methods

A literature search was conducted online to find information regarding the occurrence / frequency of nickel allergy in EU countries. The search was made in PubMed in September 2015 with the following terms: "general population nickel" "nickel allergy prevalence" and "nickel dermatitis". Both original research and review articles were included, case reports and studies not published in English were excluded. Papers published during 2005–2015 were included if they estimated the frequency (prevalence) of nickel allergy either in the population or in patients in EU countries, Switzerland or Norway. In the case of several papers being published on the same target group for the same period, only one paper was included. All relevant papers concerning population studies were included. Patient studies were included if more than 500 patients were investigated or if the prevalence of nickel allergy over time was assessed. Additionally, relevant references from identified papers were included.

The results are summarized in Appendices 1, 2 and 3. Appendix 1 concerns the population studies, Appendices 2 and 3 concern patient studies with and without age stratification, respectively.

2.2 Results

The results are divided into population surveys and surveys of patients. The following should be borne in mind when interpreting the data:

1) The EU nickel regulation was introduced in 1994 (European Communities Directive 94/27 / EC) but did not come into force before 2000. The Scandinavian countries have been pioneers and introduced regulation of nickel release from / nickel content in metal objects earlier than other countries, e.g. in Denmark in 1989. The release of nickel in the original EU legislation was set to 0.5 μg/cm² /week for objects in close contact with the skin and a limitation of the content of nickel for post assemblies piercing the skin of a maximum of 0.05% nickel. In 2004, the Directive was amended for the post assemblies to release a maximum of 0.2 μg /cm²/week (overview in Table 1.1). The analytical method had an adjustment factor to be applied to the actual measured nickel release of 0.1. This led to a nickel release being permitted 10 times greater than the stipulated limit values. The adjustment factor was replaced with an uncertainty range in January 2011, which came into force in April 2013. This was amended again in 2015, coming into force in 2016 (Table 1.2).

   In 2013 a definition of the minimum duration of contact with a nickel-releasing object was introduced in the regulation pertaining to the objects covered.

2) Different exposures to nickel may be the case for different age groups at a given time. The youngest in today's population have mainly been exposed to jewellery and other items sold after nickel regulation came into force. The earliest indications of a preventive effect of the EU's nickel regulation should therefore be seen in the

younger age groups, while older age groups may have become sensitized prior to implementation of the regulation.

2.2.1 Population-based studies

Studies concerning the frequency of nickel allergy in the population are rare, the majority being published in Scandinavia. A total of 11 articles meeting the inclusion criteria were identified. One study, published in 2002, was included as it was relevant for a correct evaluation of the nickel regulation [1]; accordingly, results from 12 papers are presented. Only 3 studies were non-Scandinavian. The largest of these was a population study comparing the prevalence of contact allergies among 3,119 individuals during 2008–2011 in five EU member states. Nickel allergy was the commonest contact allergy and was found in 14.5% of all those tested, with a significantly higher prevalence in women than in men (22.2% vs. 5.2%) [14]. 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%) [14].

Machovcová et al. [18] and Krecisz et al. [19] examined the prevalence of nickel allergy among schoolchildren in the Czech Republic and Poland, respectively, after the implementation of the EU nickel regulation. In the Czech Republic during 2005–2006, 236 schoolchildren aged 6–16 years were patch tested, of whom 92.8% completed the test. Sensitization to nickel was found in 15.6% of the children (19.2% girls and 13.3% boys). The youngest boys (6–8 years) had a higher prevalence than boys> 13 years (23% vs. 10%). For girls, the trend was reversed: the prevalence was 10% for the 6–8-year-olds and 20% for> 9-year-olds. However, each age group was made up of only a few children. Additionally, it was difficult to judge the quality of the investigation as the inclusion procedure was not accurately described, given the potential for undetected bias [18]. During 2009–2010, 15-year-old schoolchildren from randomized schools in cities and suburbs in central Poland were invited to enter a study on contact allergy. In total 528 schoolchildren (85% of respondents) participated. A positive reaction to nickel was found in 7.8% of all those tested (12.3% girls; 1.4% boys). Compared with a previous study of schoolchildren in the same age group in Poland in the 1990s, it was concluded that the prevalence of nickel allergy was decreasing slightly (the previous study was in Polish and could not be assessed) [19]. The EU nickel regulations became part of national law in Poland in 2004 [20].

Denmark was the first country to introduce a regulation of nickel release. This was in 1989 and Sweden followed as the second country in 1991. Among the 9 remaining studies, there were 2 follow-up studies of schoolchildren in Sweden and Denmark [4;21]. In 2006–2007, Josefson et al. found a prevalence of nickel allergy of 30.1% in 369 women aged 30–40 years in Sweden. This was a follow-up study of 958 girls aged 8, 11 and 15 years patch tested during 1982–1983; at that time a positive allergy test for nickel was seen in 9%. In the follow-up period 1983–2006, 24.4% of women had developed nickel allergy; the nickel regulation had been in force from 1991 [21]. In a similar Danish study by Mortz et al., 7% of persons aged 28–30 years had developed nickel allergy during 1995–2010, a period where nickel release was regulated in Denmark. In 1995, 1146 schoolchildren (54.1% girls) aged 12–16 years were patch tested and 8.6% (13.7% girls; 2.5% boys) were found positive. In 2010, 442 of the same individuals (62% women) were patch tested again (age 28–30 years). In total 11.8% tested positive to nickel (18.3% women compared with 1.2% men) [4]. In the first study from Sweden, the high frequency of new cases of nickel allergy may partly be due to individuals who developed a nickel allergy before the regulation came into force. Nevertheless, the later study from Denmark also shows a high frequency of new cases of nickel allergy even after the regulation of nickel release came into effect. The prevalence of nickel allergy in a large number of schoolchildren (4376 individuals aged 14.9 to 23.4 years, 68% girls) was studied in Sweden during 2000–2004 [22]. Fors et al. found a prevalence of nickel allergy in this population of 9.9% (13.3% in girls compared with 2.5% in boys). This was converted into 11.8% of girls and 1.6% of boys when the many dropouts were considered [22]. The prevalence differs little from that found in schoolchildren in Denmark in 1995 (13.7% girls) or from that found during 1982–1983 in Sweden (9%) [4, 21].

In two population studies the prevalence of nickel allergy was studied over years. Jensen et al. compared two groups of schoolchildren of different ages (resp. 305 boys and 275 girls) in 1999/2000 [1]. A significantly lower prevalence of nickel allergy was found in the younger compared with the older age group (3.9% vs. 17.1%), indicating an effect of the nickel regulation. The same pattern was also reflected in a population study comparing people of different ages over time (total 274 persons in 1990–1991 and 1843 persons in 2006–2008) [2]. A significantly lower prevalence of nickel allergy was seen among the youngest women (18–35 years) in 2006 compared with 1990 (11.4% vs. 19.8%, p = 0.02), whereas there was a significant increase in prevalence over time (6.5% vs. 13%) among the middle-aged women (36–55 years) (p = 0.03) and a non-significant increasing trend (2.3% vs. 5.1%) in older women (56–69 years) (p = 0.4). In the same period, there was a declining trend for men of all ages. It is possible that the prevalence of nickel allergy is underestimated in this study because patch test reading was done only on Day 2.

Ear piercing is reported as the leading cause of nickel allergy [15-17]. In the two aforementioned studies of two different populations, the prevalence of nickel allergy was further studied in those with pierced ears after compared with before the regulation came into force [1;2]. Jensen et al. found a significantly lower prevalence of nickel allergy among those who had had their ears pierced after compared with before 1992 (OR: 0.62, p = 0.0030) [1]. Thyssen et al. found a significantly lower prevalence in 18–69-year-old women who were ear pierced after compared with before 1990 (p = 0.004). In this study, the pattern was especially pronounced among the younger women (18–35 years, p = 0.002). Moreover, the prevalence of nickel allergy was significantly higher among women who had had their ears pierced during 1990–2006 than among those who had never been ear pierced, which could be indicative of an insufficient nickel regulation, poor compliance with the regulation or exposures not covered by the regulation [3]. Mørtz et al. also found a significantly lower prevalence of nickel allergy among women who had been ear pierced after compared with before 1990 (p <0.005) [4].

In 2007 Thyssen et al. published a review article that included patch test results from population studies and unselected subgroups of people of all ages from around the world during 1966–2007. Papers not addressing possible risk factors for developing allergy were excluded. They found a median nickel allergy prevalence equal to 8.6% (17.1% in women vs 3% in men) but with considerable variation (from 0.7 to 28.8 %). Furthermore, a significant correlation between ear piercing and nickel sensitization was found. Over the study period an increase was found in the proportion of nickel allergy among all cases of contact allergy in population studies (p < 0.003). The authors concluded that nickel allergy is the primary contact allergen in the population, both for adults and children [23].

Lastly, in northern Norway two population studies were conducted, both showing a very high prevalence of nickel allergy in the years 1994/1995 [24,25]. In a randomly selected group of adults (18–75 years) from Tromsø, 64% were patch tested, equal to 531 persons and 19.2% responded to nickel (31.1% women vs. 5% men) [24]. In a similar study, but with a slightly larger population from Sør-Varanger, 1236 adults aged 18–69 years were patch tested, corresponding to 79.2% of participants. In this population 17.6% were allergic to nickel (27.5% women vs. 5.1% men). In this study a decreasing trend in nickel allergy with increasing age was found.

Summary: A consistent result from the population studies is that nickel allergy is the commonest cause of contact allergy and the prevalence is significantly higher in women than in men. Jensen et al. and Thyssen et al. have published the only population studies where the prevalence of nickel allergy was assessed both before and after the nickel regulation came into force [1.2]. Jensen et al. demonstrated a significantly lower prevalence of nickel allergy in younger girls compared with older girls (3.9% vs. 17.1%) [26] and Thyssen et al. detected a lower prevalence among women in the youngest age group (18–35 years) of women over time (19.8% vs. 11.4%) [2]. These results indicate an effect of the nickel regulation. By selecting those women who had had their ears pierced before and after the regulation, respectively, the effect of the nickel regulation remained significant [1,3].

In studies following the prevalence of nickel allergy in the same individuals at different times, it was demonstrated that a significant number of new cases of nickel sensitization occurred over time (15-year incidence: 7% respectively; 25-year incidence: 24.4%) [4,21]. This design does not allow investigation of any decline over time. Moreover, in one study, inclusion took place long before the nickel regulation came into force, which complicates interpretation of the results regarding any effect of the nickel regulation [21]. In schoolgirls from 15 years of age in Poland in 2009–2010, a prevalence was seen similar to that seen in Denmark in 1995 (resp. 12.3% and 13.7%), which agrees well with the above, as the nickel regulation was introduced in Poland about 14 years after its introduction in Denmark [4.19]. Sweden saw a similar prevalence during 2000–2004 (13.3%) in large numbers of schoolgirls, albeit somewhat older (14.9–23.4 years) [22]. A study in five EU member states during 2008–2011 showed a persistently high prevalence of nickel allergy (22.2%) among women of all ages, with the lowest measured prevalence in Sweden and the highest in Portugal [14]. The two Norwegian studies included people in a period when no effect of the nickel regulation can be expected [24,25].

Conclusion: Taken together, these studies indicate a preventive effect of the nickel regulation. Nevertheless, nickel allergy remains a significant problem in the population. This is illustrated by a prevalence of 11.4% among young women in 2008 in Denmark and by a recent study showing a prevalence of 8%–18% in other European countries.

2.2.2 Patient surveys

Based on the inclusion criteria, 30 studies were identified that included patch-tested patients; 14 of these studies divided patients by age and are summarized in Appendix 3, and the other 16 are summarized in Appendix 2. The following results come from 9 studies from two major European networks collecting data from patients patch tested for suspected allergic contact dermatitis. These were selected as they have by far the largest data sets and cover many countries.

ESSCA (the European Surveillance System on Contact Allergies) is a network covering several European countries. The network collects data on patch-tested patients. Despite differences between centres in terms of patch testing, for example in patient selection, type of test/allergens, choice of days of reading etc., these studies are valuable for monitoring the development of contact allergy in Europe as they include many patients and can identify time-related changes and differences between countries. There is an increasing number of patch-tested patients over time: almost 10 000 patients were enrolled in the first study published in 2005 and almost 60 000 in the most recent survey in 2015 [5,6].

In the 5 studies from ESSCA, the total proportion of patients with a positive patch test to nickel is virtually unchanged in the period 2002–2012; however, twice as high a prevalence of nickel allergy was seen in countries with the highest prevalence compared with countries with a low prevalence [5-9]. In the first study of patients in 2002–2003 a total of 17.3% with a positive test for nickel was seen, the lowest prevalence was found in Denmark and the highest in Italy (8.1% vs. 31.7%) [6].This pattern repeats itself in all investigations up to 2012 [5.7 to 9]. In 2004, a high prevalence of nickel allergy was observed in clinics where patients were tested on suspicion of work-related dermatitis [9]. In the study from 2005–2006 the European countries were divided by region. A higher proportion of positive tests was observed in Southern Europe (Italy and Spain) compared with Central Europe (the Netherlands, Switzerland, Austria and Germany) (24.4% vs. 19.7%) [8]. In the most recent study from 2009–2012 the prevalence remained the highest in Spain and Italy and the lowest in Germany and Denmark (26.4% / 26.2% vs. 11.9% / 12.6%) [5].

As mentioned earlier, any effect of the nickel regulation on the incidence of nickel allergy will be more nuanced if the various age groups are taken into account. By comparing the prevalence among the youngest persons in different years, both before and after the nickel regulation came into force, any effect will be more obvious.

Fortina et al. found a decrease in the prevalence of nickel allergy during 2002–2010 in a study of children aged 1–16 years of both sexes from ESSCA centres [10]. A total of 6583 children were patch tested and nickel was the commonest contact allergy: 16.7% had a positive test. The highest prevalence (26.7%) was found among the youngest children, 1–5 years. No reason for the high prevalence could be found, but it was speculated whether it could be due to stricter selection criteria or false-positive results in the very young. The lowest prevalence was found in children from Southern Europe (Spain, Italy and Slovenia) and the highest in children from the north-eastern region (Finland and Poland) (5.2% of 1–5-year-old children from Southern Europe versus 25.8% among 1–16-year-olds from north-eastern Europe).

A significant decrease of positive patch tests to nickel among the youngest girls aged 1–17 years, 17.3% vs. 11.6%, was found in a large study comprising almost 75,000 patients from IVDK (Der Informationsverbund Dermatologischer Kliniken) from the German-speaking parts of Germany, Switzerland and Austria, in the period 2005–2012 [13]. There are differences in nickel exposure over time in the different groups. In 2005–2006 the majority of women aged 1–17 years had been pierced before 2004, whereas in 2011–2012 most had been pierced after 2004.

The same study showed that women in the age groups 18–30 years and 31–44 years had a significant decrease in nickel allergy during 2005–2012, whereas in women aged 45–60 years a significant increase was seen [13]. This increase is explained by a cohort effect: the phenomenon that young persons sensitized to nickel before the nickel regulation came into force in 1994 still have nickel allergy when they age.

In a large study of 180 000 patients in Denmark (1985–2010), Germany (1995–2010), Italy (1997–2010) and England (2004–2010), the same pattern was seen over time as in the previously mentioned large IVDK study [27]. Thus a significant decrease of nickel allergy was seen over time in women younger than 30 years of age in all countries. In contrast, in women older than 30 years, a significant increase over time was seen in all countries.

In a further study of patients from Germany, Switzerland and Austria, Schnuch et al. found that the prevalence of nickel allergy had stabilized at a high level after 2000. Notably, there was a significant decrease in the prevalence of nickel allergy during 1994–2009 in women aged 1–17 and 18–30 years and in men aged 1–17 years. However, the prevalence did not decrease further in the youngest group (1–17 years) during 2000–2009 [12]. The prevalence was 12.6% in women aged 1–17 years in 2008/2009. In women > 30 years, an increase of nickel allergy during the period was seen, which is probably explained by a cohort effect.

Summary: Investigations of adult patients showed a high and unchanged prevalence of nickel allergy during 2002–2012 in Europe, but with large differences in the prevalence between countries [5,6,8,9,28]. Throughout the period, a pattern was seen of the highest prevalence rates being in Southern Europe compared with Northern Europe (26% vs. 12% in 2009–2012) [5]. In children aged 1–16 years a high prevalence was seen, but this was significantly declining from 2002 to 2010. In a study from Germany, Switzerland and Austria, a significant decrease in the prevalence of nickel allergy was seen during 2005–2012 in young girls aged 1–17 years (17.3% vs. 11.6%), suggesting an effect of the nickel regulation [13]. In the same study a significant decrease in women aged 18–30 years and 31–44 years was found, but a significant increase in women aged 45–60 years was seen, suggestive of a cohort effect. The same pattern of significantly decreasing prevalence rates over time until 2010 is also seen in Denmark, Italy and England in women younger than 30 years and an increase in women older than 30 years [27]. In a study from Germany, Switzerland and Austria, it is notable that the prevalence of nickel allergy in young women had stabilized at a high level after 2000 (12.6% in women aged 1–17 years 2008/2009) [12].

Conclusion: The prevalence of nickel allergy has decreased significantly over time in young women patch tested on suspicion of allergic dermatitis; nevertheless, it appears to remain high, corresponding to 11.6% of 1–17-year-old female eczema patients in Germany, Switzerland and

Austria [13]. As the most recent major amendment in nickel regulation was not implemented until 2013, there is a need for continuous surveillance and evaluation of the effect of the regulation.

2.2.3 Hand eczema

Historically, an association between nickel allergy and hand eczema has been observed [2;4]. It has been speculated whether a systemic exposure to nickel from either food or large nickel-plated items in direct contact with the skin could maintain vesicular hand eczema in patients with nickel allergy. Today, any such cases are rare.

Hand eczema in patients with nickel allergy should be treated according to the standard guidelines for the disease and should include investigation of both private and occupational exposures according to the limits and definitions in the current REACH version of the nickel directive.

2.3 Overall summary and conclusion

The literature search resulted in the inclusion of 12 population and 30 patient studies. Nickel allergy was the commonest contact allergy in both the general population and among patients. Significantly higher frequencies of nickel allergy were found in Southern Europe compared with Northern Europe, and in women compared with men. A significantly lower prevalence of nickel allergy among young women was found in population studies after implementation of the nickel regulation and among women with pierced ears after compared with before implementation [1-3]. The prevalence of nickel allergy in the population was over 10% among young women, and a relatively high frequency (incidence) of new cases among women was also observed after the nickel regulation came into force [4]. In patient studies from the European network ESSCA, a high and unchanged prevalence of nickel allergy was seen during 2002–2012. In contrast, a significant decline in the prevalence of nickel allergy was seen in children aged 1–16 years [5-10]. There was a clear, consistent pattern of significant decreases in the prevalence of nickel allergy over time in female eczema patients younger than 30 years of age up to the year 2010 in Denmark, England, Italy and Germany [11]. However, the prevalence remains high in this age group, corresponding to 14–27% [12]. The prevalence of nickel allergy was 11.6% among younger women (aged 1–17 years) in Germany, Switzerland and Austria in 2012 [13].

Conclusion

The literature review showed an effect of the nickel regulation [1-3,11,13]. However, young women continue to be sensitized to nickel [4] and the prevalence remains high in the population, corresponding to 8–18 % [14], depending on the European country. Accordingly, a revision of the current nickel regulation seems warranted.

References

1. 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; 146:636–642.

2 Thyssen JP, Linneberg A, Menné T, Nielsen NH, Johansen JD. The association between hand eczema and nickel allergy has weakened among young women in the general population following the Danish nickel regulation: Results from two cross-sectional studies. Contact Dermatitis 2009; 61:342–348.

3 Thyssen JP, Johansen JD, Menné T, Nielsen NH, Linneberg A. Nickel Allergy in Danish Women before and after Nickel Regulation. New English J Med 2009; 360:2259–2260.

4 Mortz CG, Bindslev-Jensen C, Andersen KE. Nickel allergy from adolescence to adulthood in the TOACS cohort. Contact Dermatitis 2013; 68:348–356.

5 Uter W, Gefeller O, Giménez-Arnau A, Frosch P, Duus Johansen J, Schuttelaar M-L, et al. Characteristics of patients patch tested in the European Surveillance System on Contact Allergies (ESSCA) network, 2009-2012. Contact Dermatitis 2015; 73:82–90.

6 Uter W, Hegewald J, Aberer W, Ayala F, Bircher a. J, Brasch J, et al. The European standard series in 9 European countries, 2002/2003 - First results of the European Surveillance System on Contact Allergies. Contact Dermatitis 2005; 53:136–145.

7 Uter W, Aberer W, Armario-Hita JC, Fernandez-Vozmediano JM, Ayala F, Balato A, et al. Current patch test results with the European baseline series and extensions to it from the "European Surveillance System on Contact Allergy" network, 2007-2008. Contact Dermatitis. 2012; 67:9–19.

8 Uter W, Rämsch C, Aberer W, Ayala F, Balato A, Beliauskiene A, et al. The European baseline series in 10 European Countries, 2005/2006 - Results of the European Surveillance System on Contact Allergies (ESSCA). Contact Dermatitis 2009; 61:31–38.

9 Uter W. The European surveillance system of contact allergies (ESSCA): Results of patch testing the standard series, 2004. J Eur Acad Dermatology Venereol 2008; 22:174–181.

10 Belloni Fortina A, Cooper SM, Spiewak R, Fontana E, Schnuch A, Uter W. Patch test results in children and adolescents across Europe. Analysis of the ESSCA Network 2002-2010. Pediatr Allergy Immunol 2015; 26:n/a–n/a.

11 Garg S, Thyssen JP, Uter W, Schnuch A, Johansen JD, Menné T, et al. Nickel allergy following EU regulation in Denmark, Germany, Italy and the United Kingdom. Br J Dermatol Oct;169(4):854-8

12 Schnuch A, Wolter J, Geier J, Uter W. Nickel allergy is still frequent in young German females - Probably because of insufficient protection from nickel-releasing objects. Contact Dermatitis. 2011; 64:142–150.

13 Schnuch A, Schwitulla J. Decrease in nickel allergy in women after the second EU nickel directive. Contact Dermatitis 2013; 69:253–256.

14 Diepgen TL, Ofenloch RF, Bruze M, Bertuccio P, Cazzaniga S, Coenraads P-J, et al. Prevalence of contact allergy in the general population in different European regions. Br J Dermatol 2015;173(6):1411-9.

15 Mortz CG, Lauritsen JM, Bindslev-Jensen C, Andersen KE. Nickel sensitization in adolescents and association with ear piercing, use of dental braces and hand eczema: The odense adolescence cohort study on atopic diseases and dermatitis (TOACS). Acta Derm Venereol 2002; 82:359–364.

16 Larsson-Stymne B, Widström L. Ear piercing--a cause of nickel allergy in schoolgirls? Contact Dermatitis 1985; 13:289–293.

17 Nielsen NH, Menné T. Nickel sensitization and ear piercing in an unselected Danish population. Glostrup Allergy Study. Contact Dermatitis 1993; 29:16–21.

18 Machovcová A. The frequency of contact allergy in children and adolescents in the Czech Republic. Acta Dermatovenerol Croat 2012; 20:75–79.

19 Krecisz B, Chomiczewska D, Palczynski C, Kiec-Swierczynska M. Contact allergy to metals in adolescents. Nickel release from metal accessories 7 years after the implementation of the EU Nickel Directive in Poland. Contact Dermatitis 2012; 67:270–276.

20 The Commission of the European Communities. COMMISSION REGULATION (EC) No 552/2009 of 22 June 2009 amending Regulation (EC) No 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction. Off J Eur Union 2009; L164:7–31.

21 Josefson a., Färm G, Magnuson a., Meding B. Nickel allergy as risk factor for hand eczema: A population-based study. Br J Dermatol 2009; 160:828–834.

22 Fors R, Persson M, Bergström E, Stenlund H, Stymne B, Stenberg B. Nickel allergy - Prevalence in a population of Swedish youths from patch test and questionnaire data. Contact Dermatitis 2008; 58:80–87.

23 Thyssen JP, Linneberg A, Menné T, Johansen JD. The epidemiology of contact allergy in the general population--prevalence and main findings. Contact Dermatitis 2007; 57:287–299.

24 Dotterud LK. The prevalence of allergic contact sensitization in a general population in Tromso, Norway. Int J Circumpolar Health 2007; 66:328–334.

25 Dotterud LK, Smith-Sivertsen T. Allergic contact sensitization in the general adult population: a population-based study from Northern Norway. Contact Dermatitis 2007; 56:10–15.

26 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; 146:636–642.

27 Garg S, Thyssen JP, Uter W, Schnuch a., Johansen JD, Menné T, et al. Nickel allergy following European Union regulation in Denmark, Germany, Italy and the U.K. Br J Dermatol 2013; 169:854–858.

28 Uter W, Aberer W, Armario-Hita JC, Fernandez-Vozmediano JM, Ayala F, Balato A, et al. Current patch test results with the European baseline series and extensions to it from the "European Surveillance System on Contact Allergy" network, 2007-2008. Contact Dermatitis 2012; 67:9–19.

3. Questionnaire study

A questionnaire study in patients sensitized to nickel was done in Denmark in 2015. The aim was to identify causes and exposures leading to nickel allergy and eczema.

3.1 Method

3.1.1 Patients

Patients for inclusion were defined by a positive patch test to nickel sulphate 5% in petrolatum within the past 5 years (1 January 2010–31 December 2014) at the Department of Dermato-Allergology, Gentofte Hospital; 541 nickel-sensitized patients were identified. Of these individuals, 6 had died, 9 could not be contacted and 2 had emigrated, leaving 524 potential participants.

If multiple patch tests had been conducted in the inclusion period, the result of the most recent test was used. The study was reported to the Regional Ethics Committee of Copenhagen (H-15010935) and approved by the Data Protection Agency.

3.1.2 Patch test

The European baseline patch test series was used for testing and included nickel sulphate 5% in petrolatum (Trolab®). Patches were applied on the upper back and left in place for 2 days. Readings were done on Day 2, 3 or 4 and Day 7 using the criteria of the European Society of Contact Dermatitis [1]. A positive reaction (1+) was defined as at least homogenous redness and palpable infiltration in the test area. Reactions not fulfilling these criteria were classified as negative.

3.1.3 Questionnaire

A questionnaire was sent to the 524 potential participants medio 2015. Non-respondents were sent the questionnaire up to three times with at least three weeks between each distribution. The questionnaire included questions about nickel exposure and dermatitis after exposure to consumer goods with a metallic surface.

An overview of the main questions can be found in Appendix 4.

3.1.4 Data processing

All patients included were registered with the date of their patch test, date of birth, sex, the maximal reaction of nickel, and the basic characteristics regarding their eczema disease.

All data from the questionnaires were entered into Epidata software by two investigators and analysed by SPSS. Before the analysis, 10% of randomly chosen questionnaires (35 questionnaires) were checked for typing errors. Of these, incorrect inputs were found in 0.23% of the questions.

3.2 Results

The questionnaire was answered by 342 of 541 nickel-sensitized patients: 318 women and 24 men, corresponding to a participation rate of 63.2%. Non-respondents were younger than respondents, i.e. more often younger than 40 years of age ($p<0.01$), whereas no significant difference in sex was found.

Table 3.2.1 shows the participants' characteristics. There were no differences between female and male participants apart from ear-piercing, where 95.8% of women with nickel contact allergy had pierced ears compared with 30.4% of men ($p<0.001$).

Table 3.2.1: Characteristics of participants

	Women N= 318	Men N=24	Total N=342	p-value*
Age at test (median; 25/75)	47 years 35–55	56 years 45–66	47 years 36–56	
Atopic dermatitis	63(19.8%)	5(20.8%)	68(19.9%)	n.s.
Hand eczema at time of test	114(35.8%)	8(33.3%)	122(35.7%)	n.s.
Facial eczema at time of test	96(30.2%)	6(25%)	102(29.8%)	n.s.
Leg eczema at time of test	3(0.9%)	1(4.2%)	4(1.2%)	n.s.
Pierced ears	299/312 (95.8%)	7/23 (30.4%)	306/335 (91.3%)	<0.001
Other piercings	60/312(19.2%)	2/23(8.6%)	62/335 (18.5%)	n.s.

*: Chi-square test, except if n<6, then Fishers test was used.

Participants were asked about the first time they had experienced a rash from a shiny metal item, their age and what the item was. They were given a list of 15 groups of items to select from and could also add items not listed. Table 3.2.2. shows the results. The initial rash can be interpreted as the sensitization event; accordingly, the items causing the first rash are particularly important. Women were median 16 years and men 18 years when they experienced their first rash from a shiny metal item.

In women the single most important cause of first-time rash was earrings, followed by buttons on clothing, wrist watches, other jewellery, zips and belt buckles. These causes were reported by 19.2%–67.8% of women. Few women reported tools, computers, mobile phones or lighters as causes of first-time rash. Among the additional items, four persons mentioned hooks on clothing as a cause.

More than one item could be cited as causing rash. The group of women whose initial rash stemmed from jewellery—earrings, other jewellery and/or wrist watches—comprised 88.7%, while the group with first-time rash from metal items on clothing—buttons, zips and belt buckles—comprised 62%.

In men, wrist watches and belt buckles were the items most often cited as causing the initial rash (55.6% and 50%, respectively), followed by spectacles, jewellery other than earrings, earrings, buttons on clothing and keys, as shown in Table 3.2.2. No men reported computers, mobile phones or scissors as the cause of first-time rash. Those with their initial rash from jewellery—earrings, other jewellery and/or wrist watches—comprised 66.7%, while the group with the initial rash from metal items on clothing—buttons, zips and belt buckles—comprised 55.6%. The few men with nickel allergy make the results less robust.

Table 3.2.2: Rash from shiny metal items: first time

	Women N=276	Men N=18	Total N=294	p-value*
Age at first rash Median;25/75	16 years 12–25	18 years 25–50	16 years 13–25	
Items causing first-time rash				
Earrings	187 (67.8%)	3 (16.7%)	190 (64.6%)	<0.001
Buttons on clothing	153 (55.4%)	3 (16.7%)	156 (53.1)	0.001
Wrist watches	142(51.4%)	10 (55.6%)	152 (51.7%)	n.s.
Jewellery	138 (50%)	4 (22.2%)	142 (48.3%)	0.02
Zips	65 (23.6%)	1 (5.6%)	66 (22.4 %)	n.s.
Belt buckles	53 (19.2%)	9 (50%)	62 (21.1%)	0.002
Spectacles	20 (7.2%)	4 (22.2%)	24 (8.2%)	0.048
Hair clips	21 (7.6%)	0	21 (7.1%)	n.s.
Keys	16 (5.8%)	3 (16.7%)	19 (6.5%)	n.s.
Coins	16 (5.8%)	1 (5.6%)	17 (5.8%)	n.s.
Scissors	6 (2.2%)	0	6 (2.0%)	n.s.
Tools	3 (1.1%)	1 (5.6%)	4 (1.4%)	n.s.
Computers	3 (1.1%)	0	3 (1.0%)	n.s.
Mobiles phones	1 (0.4%)	0	1 (0.3%)	n.s.
Lighters	1 (0.4%)	0	1 (0.3%)	n.s.

Other items mentioned were: cutlery (1); hooks on clothing (brassieres) (4); door handles (1); pins (1); combs (1); water taps (1); pens (1); needles (1). *: Chi-square test, except if n<6, then Fishers test was used.

As can be seen from Table 3.2.2, the participants questioned about first-time rash often cited more than one item as the cause. In total, 73 (33%) participants cited only one item: 31 (42%) cited earrings, followed by wrist watches (n=13) and buttons (n=11). A statistically significant overlap was found between earrings and wrist watches as causes of the first rash ($p<0.001$) earrings and buttons ($p<0.001$), earrings and other jewellery ($p<0.001$) and earrings and zips ($p<0.01$).

Table 3.2.3: Rash from shiny metal items: most recent rash

	Women N=276	Men N=18	Total N=294	p-value*
Age at most recent rash Median;25/75	40 years 30–51	47 years 33–63	40 years 30–51	
Items causing most recent rash				
Earrings	133/276(48.2%)	1/18(5.6%)	134/294 (45.6%)	<0.001
Other jewellery	96/276(34.8%)	2/18(11.1%)	98/294 (33.3%)	0.04
Buttons on clothing	85/276(30.8%)	3/18(16.7%)	88/294(29.9%)	n.s.
Wrist watches	62/275(22.5%)	5/18(27.8%)	67/293(22.9%)	n.s.
Zips	33/276(12.0%)	1/18(5.6%)	34/294 (11.6%)	n.s
Belt buckles	26/276(9.4%)	9/18(50%)	35/294 (11.9%)	<0.001
Keys	27/275(9.8%)	2/18(11.1%)	29/293 (9.9%)	n.s.
Coins	23/276(8.3%)	0	23/294 (7.8%)	n.s
Spectacles	21/276(7.6%)	4/18(22.2%)	25/294 (8.5%)	0.05
Hair clips	17/276(6.2%)	0	17/294 (5.8%)	n.s
Scissors	4/276(1.4%)	0	4/294 (1.4%)	n.s.
Tools	3/276(1.1%)	1/18(5.6%)	4/294 (1.4%)	n.s.
Computers	4/276(1.4%)	0	4/294 (1.4%)	n.s.
Mobiles phones	3/276(1.1%)	0	3/294 (1%)	n.s
Lighters	2/276(0.7%)	0	2/294 (0.7%)	n.s.

Other items mentioned were: cutlery (1); hooks on clothing (brassieres) and coat hangers (7); door handles (1); shoes (2); pins/knives (1); MP3 ear plugs (1); workplace identity card holders (1); handles of office stamps (1); water taps (2).

Table 3.2.3 shows the items those with nickel allergy cited as causing their most recent rash. Women were median 40 years and men 47 years when they experienced their most recent rash from a shiny metal item. In women, the five most frequent causes were earrings, other jewellery, buttons on clothing, wrist watches and zips. These items are the same as those cited as causing the initial rash.

In men, the most prominent cause of the most recent rash was belt buckles (n=9), followed by wrist watches (n=5), spectacles (n=3), buttons on clothing (n=3) and jewellery (n=2). Only one man cited an earring as causing his most recent rash. No men reported their most recent rash as coming from computers, mobile phones or scissors. The change in order may partly be due to the low number of males with nickel allergy.

Table 3.2.4 on the next page shows the results from subgroup analyses. The first subgroup of interest is the young patients with nickel allergy. They are 25 years or younger and have thus lived their entire lives under the protection of a nickel regulation; the first regulation came into force in Denmark in 1990.

Only 20 persons fulfilled the criteria of being 25 years or younger: 1 man and 19 women. The foremost causes of first-time rash were earrings, other jewellery, buttons on clothing, belt buckles, wrist watches, zips and hair clips. One person cited a computer as causing the first rash. No one reported any of the other items, see Table 3.2.4.

Another subgroup analysis concerned patients with a first rash in the previous 10 years i.e. during the time the EU regulation on nickel has been in force in Denmark. This group comprised 30 persons: 5 men and 25 women with a median age of 38 years. The order of items was earrings, other jewellery, belt buckles, buttons on clothing, wrist watches, keys and spectacles.

The last subgroup analysis concerned patients who had had their most recent rash in the past 5 years, indicating continued exposures of clinical significance. This group comprised 173 persons: 12 men and 161 women, median age 49 years. The five most prominent causes were earrings, other jewellery, buttons on clothing, watches and zips.

Table 3.2.4: Rash from shiny metal items in subgroups of patients

	Patients ≤25 years First rash	Patients First rash during the past 10 years	Patients Most recent rash during the past 5 years
Number	20	30	173
Sex m:w	1:19	5:25	12:161
Age: Median 25/75 percentiles	21 years 19–24	38 years 25–58	49 years 35–58
Items causing rash:			
Earrings	11 (55%)	10 (33.3%)	73 (42.2%)
Other jewellery	11 (55%)	9 (30 %)	58 (33.5%)
Buttons on clothing	4 (20%)	8 (26.7%)	49 (28.3%)
Wrist watches	2 (10%)	4 (13.3%)	28(16.2%)
Zips	2(10%)	3 (10%)	26 (15%)
Keys	0	4(13.3%)	22 (12.7%)
Belt buckles	4 (20%)	9(30%)	23 (13.3%)
Coins	0	3 (10%)	16 (9.2%)
Spectacles	0	4(13.3%)	17 (9.8%)
Hair clips	2(10%)	1 (3.3%)	11 (6.4%)
Scissors	0	0	4 (2.3%)
Tools	0	1 (3.3%)	4 (2.3%)
Computers	1(5%)	2 (6.7%)	4 (2.3%)
Lighters	0	1 (3.3%)	2 (1.2%)
Mobiles phones	0	0	2 (1.2%)

The same patient may occur in more than one column of this table.

The results from the different tables are summarized in Table 3.2.5. The order is displayed of the different items causing the initial and the most recent rash and the different subgroups are shown. A score was given from 1 to 15 for each item depending on the order as cause of reaction. The item causing the most reactions was given a score of 1 and the one causing the least, 15.

It can be seen in Table 3.2.5 that earrings are the foremost cause of reactions to nickel-releasing items, followed by other jewellery, buttons on clothing, wrist watches and belt buckles. Some items were rarely reported as causes and others were not reported at all in some subgroups.

Table 3.2.5: Summary table: Rash from shiny metal items in priority order

	Initial rash	Most recent rash	Patients ≤25 years	Initial rash during the past 10 years	Most recent rash during the past 5 years	Summary
Items causing rash:						
Earrings	1	1	1	1	1	**5**
Other jewellery	4	2	1	2	2	**12**
Buttons on clothing	2	3	3	4	3	**15**
Wrist watches	3	4	4	5	4	**18**
Belt buckles	6	6	3	3	6	**24**
Zips	5	5	4	8	5	**27**
Spectacles	7	8	7	5	8	**35**
Keys	9	7	7	5	7	**35**
Coins	10	9	7	8	9	**43**
Hair clips	8	10	6	11	9	**44**
Computers	13	11	7	10	11	**52**
Tools	12	11	7	11	11	**52**
Scissors	11	11	7	14	11	**54**
Lighters	14	15	7	11	14	**61**
Mobiles phones	14	14	7	14	14	**63**

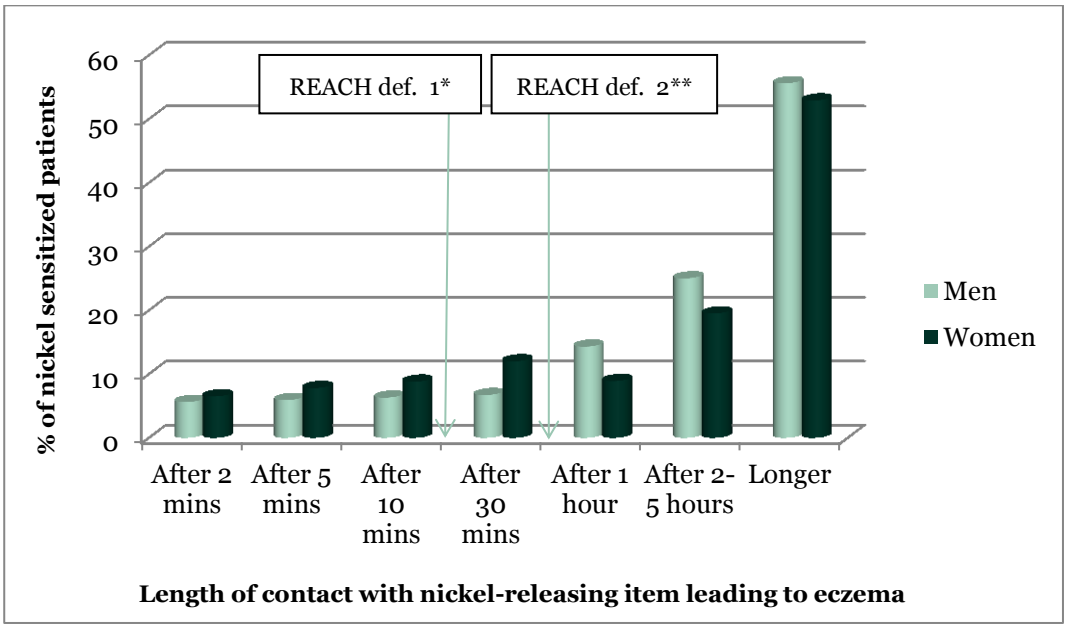
This table (3.2.5) ranks the items according to the frequency of causing rash in nickel-sensitized individuals. The items of most relative importance have the lowest numbers. The numbers are

based on the priority of each item in Tables 3.2.2, 3.2.3 and 3.2.4. with a ranking from 1 to 15 within each category of patients. The red numbers indicate that the result was negative, i.e. no persons had developed a rash from that item.

Length of contact needed to elicit a reaction

Patients with nickel allergy were asked how short a contact with a shiny metal item was necessary for an eczematous reaction to occur; 18.1% (16.7% of men and 21.4% of women) reacted after a 10-min contact or less and 26% (22.2% of men and 30.8% of women) after a 30-min contact or less.

Figure 3.1: Length of contact with nickel-releasing items leading to eczema in patients sensitized to nickel.



*Prolonged contact with skin, REACH definition 1: Prolonged contact defined as contact for more than 10 mins on three or more occasions within a 2-week period.
**Prolonged contact with skin, REACH definition 2: Prolonged contact defined as contact for more than 30 minutes on one or more occasions within a 2-week period
(Definitions are given in REACH Annex XVII Entry 27, Q&A no. [935]).

Occupational aspects

There was no significant relationship between nickel allergy and occupational contact dermatitis among the patients tested (n=4666) with the European baseline series in the study period 2010–2014. However, significant occupational exposure to nickel may occur in some patients. Patients were not directly asked about nickel exposures at work, but some of the items reported as causing the first and the most recent rash could have been present in the workplace, for example tools, keys, coins, scissors, computers and mobile phones. These items were among the less frequent causes of rash. In the text where items not featured on the list could be noted, patients specifically mentioned holders for workplace identity cards (1) and handle of stamps in the office (1) as causes of their most recent rash. Accordingly, nickel allergy can impact the work situation and 12.6% of the patients reported that they had taken sick leave due to nickel allergy, 9.1% had had changes made at the workplace due to nickel allergy and 7.0% reported that they had taken early retirement due to their nickel allergy.

3.3 Discussion

This investigation concerned shiny metal items that have caused rash/eczema in patients with contact allergy to nickel. Patients diagnosed at the Department of Dermato-Allergology, Gentofte Hospital, University of Copenhagen during the past 5 years (2010–2014) were included and answered a questionnaire about their symptoms. The response rate was 63.2%, which was satisfactory.

Most patients diagnosed with nickel allergy were women (M:W: 1:13). This is known from many other investigations [2] also in the population base [3] and is due to differences in exposure between the sexes.

The key exposure event leading to nickel contact allergy seems to happen early in life. In this investigation, the initial rash caused by nickel-releasing items was experienced at the age of 16 years (median) for women and 18 years (median) for men (Table 3.2.2).

Earrings were the items most often causing the initial rash in women (67.8%), followed by buttons on clothing (55.4%) and wrist watches (51.4%). The initial rash is taken as an indication of the sensitization event as the items causing this rash are usually worn every day for prolonged periods. It is well known that earrings for pierced ears constitute a special risk of inducing nickel sensitization [4,5] as the skin is broken and the surface of the metal items is exposed to tissue fluids. In a subgroup analysis of patients younger than 25 years, earrings ranked the highest in causing the initial rash (Table 3.2.4.). This young group should have been protected by different nickel regulations. The findings were similar in the group who experienced their first rash within the past 10 years. This is during the period in which the nickel directive has been in force. Earrings were also cited as the most common reason for eczema in the past 5 years. Accordingly, earrings continue to play a major role in induction and elicitation of nickel contact allergy. Other exposures were also frequent causes of rashes, for example, metal items on clothing—buttons, zips and belt buckles. Items such as mobile phones, computers, tools and scissors were relatively rarer causes of reported rash. This may be due to the less intensive and intermittent contact with the skin and/or less use of nickel in alloys and coatings.

In this investigation patients could select the culprit object from a list of 15 different types of shiny metal item, which may mean that exposures were overlooked, but it was possible to add items not listed. The most frequently added item was hooks on underwear. This is an exposure known to lead to problems with nickel allergy due to the close and prolonged contact with the skin.

It is well established that certain occupational exposures, such as cashiers' coin handling, may give a significant deposit of nickel on the skin [6,7]. No increased risk of occupational contact dermatitis among the patients with nickel allergy was found in the current investigation. Nevertheless, this may conceal a significant problem in individual patients or subgroups of patients.

The way the questionnaire was constructed was not optimal for an in-depth description of occupational aspects and further investigations are recommended to qualify the nature and extent of occupational exposures to nickel.

In REACH, 'contact of long duration' is defined as more than 10 minutes of exposure to a nickel-releasing item three times in 14 days or one single exposure of more than 30 minutes. If this is fulfilled, the item falls under the nickel regulation. The definitions are based on various assumptions and estimations. The question has been whether such duration of exposures will cause symptoms in a significant proportion of those with nickel allergy. In this investigation, 18.1% reported developing a rash from a shiny metal item if exposed for 10 mins or less to the object and 26% reported rash with exposures of 30 mins or less (Figure 3.1). This has not been investigated before in individuals with nickel allergy. However, from experiments with black hair dye (p-phenylenediamine), it is known that even 2 mins' exposure can produce a positive patch test, when read after 48 hours [8]. The results from this questionnaire point in the same direction for nickel.

References

1 Johansen JD, Aalto-Korte K, Agner T, Andersen KE, Bircher A, Bruze M, Cannavó A, Giménez-Arnau A, Gonçalo M, Goossens A, John SM, Lidén C, Lindberg M, Mahler V, Matura M, Rustemeyer T, Serup J, Spiewak R, Thyssen JP, Vigan M, White IR, Wilkinson M, Uter W. European Society of Contact Dermatitis guideline for diagnostic patch testing - recommendations on best practice. Contact Dermatitis. 2015 Oct;73(4):195-221

2 Thyssen JP. Nickel and cobalt allergy before and after nickel regulation-evaluation of a public health intervention. Contact Dermatitis. 2011 Sep;65 Suppl 1:1-68.

3 Thyssen JP, Johansen JD, Menné T, Nielsen NH, Linneberg A. Nickel allergy in Danish women before and after nickel regulation N Engl J Med. 2009 May 21;360(21):

4 Boss A, Menné T . Nickel sensitization from ear piercing. Contact Dermatitis.1982;8:211-213.

5 Warshaw EM, Kingsley-Loso JL, DeKoven JG, Belsito DV, Zug KA, Zirwas MJ, Maibach HI, Taylor JS, Sasseville D, Fowler JF Jr, Mathias CG, DeLeo VA, Pratt MD, Marks JG Jr, Fransway AF. Body piercing and metal allergic contact sensitivity: North American contact dermatitis group data from 2007 to 2010. Dermatitis. 2014 Sep-Oct;25(5):255-64.

6 Lidén C, Skare L, Nise G, Vahter M. Deposition of nickel, chromium, and cobalt on the skin in some occupations - assessment by acid wipe sampling. Contact Dermatitis. 2008 Jun;58(6):347-54

7 Staton I, Ma R, Evans N, Hutchinson RW, McLeod CW, Gawkrodger DJ. Dermal nickel exposure associated with coin handling and in various occupational settings: assessment using a newly developed finger immersion method. Br J Dermatol. 2006 Apr;154(4):658-64.

8. Hextall JM, Alagaratnam NJ, Glendinning AK, Holloway DB, Blaikie L, Basketter DA, McFadden JP. Dose-time relationships for elicitation of contact allergy to para-phenylenediamine. Contact Dermatitis. 2002 Aug;47(2):96-9.

4. Assessment and recommendation

4.1 Introduction

Legislation has been implemented in the EU to prevent contact allergy in consumers and workers. The best examples are regulations of allergens in cosmetics and metallic allergens such as chromium and nickel. The regulation of hexavalent chromate in wet cement has almost eradicated the once severe occupational cement dermatitis among building workers in Europe [1]. The intervention has not led to any unexpected technological or economic problems. It has had the expected positive effect on an important health problem. This positive outcome supports the idea that it is possible to prevent allergic contact dermatitis by targeting specific contact allergens present in specific products. The need for such initiatives is clear as a recent study disclosed that 27% of the general population in Europe reacted to one or more contact allergens during a standard test procedure [2].

An assessment of the EU nickel regulation should be seen in this general perspective. The intention behind this regulation is to diminish the public health burden of nickel allergy by minimizing the nickel release from metallic items designed to be in direct and prolonged contact with the skin. Compared with the chromate-cement regulation and the chromate-leather regulation, it is an advantage that, for all real-life exposures, the nickel ion occurs only in the divalent state; however, exposure may come from a variety of metal items (Table 3.2.3.).

The literature review in Section 2 of this report shows a significant effect of the nickel regulation. The effect is the most prominent in the northern countries of Europe. A significantly lower prevalence of nickel allergy was demonstrated among young women after implementation of the nickel regulation and among women ear-pierced after compared with before implementation. Moreover, a significant decline in the prevalence of nickel allergy among eczema patients aged 1–16 years was seen when data were collected by a European network. However, the prevalence of nickel allergy in the population was over 10% among young women, and a relatively high incidence of new cases among women was also observed after the nickel regulation came into force. This means that despite the nickel regulation having a major impact on the prevalence and incidence of nickel allergy in the population, a significant problem still exists, especially among young women.
The present document highlights the success and also the weaknesses of the EU nickel regulation in its present form. The following sections focus on the main problems and address possible solutions.

4.2 Ear piercing and earrings

Earrings are the items identified the most frequently by individuals with nickel allergy as the cause of their initial rash (Table 3.2.2.). This is an observation of particular interest as it also points to the most likely onset of nickel sensitization. Historically (1930s–1970s), nickel-plated suspenders and later nickel-plated buttons in blue jeans were the dominant causes of primary nickel sensitization [3]. Today, ear piercing and the use of ear posts for earrings is very frequent and has taken over as the commonest cause of primary nickel sensitization [4]. The piercing process and the insertion of posts in an artificial skin channel is an exposure that differs from the application of a metal alloy on the skin because the exposure circumvents the normal epidermis, including the normal skin barrier. It has previously been shown that the EU nickel directive is particularly effective in the group of women who have never had their ears pierced [5]. During the process of ear piercing, the metal alloys used are in direct contact with blood and interstitial fluid. This is known to have an increased

corrosive effect as compared with contact with only the skin surface [6]. The pivotal limit of nickel release, 0.5µg/cm²/week, used in the EU regulation has been standardized only for metallic items placed on the skin [7]. In the first version of the EU directive, a content limit (0.05%) was set for post assemblies, which was probably inspired by the preceding Swedish regulation [8]. It has been demonstrated that even alloys with a contents below 0.01% nickel may cause allergic reactions in nickel-sensitized individuals [9].
The safety of piercing in relation to the use of different metal alloys is little investigated. Even the use of high quality stainless steel ear piercing post assemblies does not exclude allergic reactions in those who are allergic to nickel [10]. Ingbar et al [10] did a study where they used AISI 316 L stainless steel ear piercing post assemblies. The posts were used for ear piercing in 25 individuals with proven nickel allergy. Within 48 hours of the piercing, two of those with nickel sensitivity developed redness and itching related to the piercing area. The authors concluded in the title and in the manuscript's discussion section that there were no signs of eczema and the procedure was safe. Redness and itching are the initial symptoms of allergic contact dermatitis. No control group was included in the study. The objective conclusion based on the data is that ASNI 316 L stainless steel is probably not safe for ear piercing in nickel allergic individuals, even if the studs comply with the recommended nickel release test. A revision of the nickel regulation led to a change in the original limit from a content of 0.05% to the current content of up to 0.2µg/cm²/week nickel release for post assemblies and body piercings (Table 1.1). However, the analytical method used for measuring nickel release (EN1811:2011) specifies that the maximum values considered as complying with the limits for release can exceed the regulatory limit values and still be considered compliant due to the uncertainty of the analytical methods. These limits have been adjusted several times. Currently, a measured maximum release of nickel of 0.35 µg/cm²/week from earring post assemblies is considered compliant with the regulation (Table 1.2.). For other items in direct and prolonged contact with the skin, the maximum release of nickel considered compliant is 0.88 µg/cm²/week (Table 1.2).
Clearly, ear piercing remains a major problem as 64.6% of the 294 nickel-allergic eczema patients investigated in the current project (see Section 3) developed a rash to earrings as a primary event. Even the youngest part of the female eczema population, which has been protected by nickel regulations, still reports earrings as the most important primary cause of rash.

In substituting nickel in ear piercing and earring studs, it should be remembered that it is not possible to use other contact sensitizing metals or metal alloys containing sensitizing metals independent of the coating. Coatings can be very thin and cracks can appear, which will allow nickel to be released from the nickel lining underneath the coating. The knowledge concerning wear and tear of different coatings is sparse. Titanium is a possible alternative to nickel and it is also possible to use non-metallic materials, for example, composite or carbon-based materials.

4.3 Occupational aspects

No new aspects concerning occupational exposure to nickel-releasing items were revealed in the current investigation; however, this may be due to the design of the study. Occupational exposure to nickel can significantly impact the working situation and ability of the individual and should be investigated in a more targeted way.

4.4 Temperate and subtropical parts of the EU

The present literature review demonstrates a clear difference in the frequency of nickel allergy, based both on population and patient studies, between the north and south (Mediterranean countries). The most important environmental factors for corrosion from metals and metal alloys are skin temperature and sweating. All the published studies concerning skin and nickel release from metallic items come from the temperate part of the EU. The corrosion from metal items might be significantly higher in the southern part of the EU, leading to the EU nickel regulation being less effective in these areas.

These observations call for studies investigating the nickel release to the skin from different nickel alloys under different climatic circumstances.

4.5 Direct and prolonged contact

It has been seen clinically that some patients with nickel allergy have an immediate reaction with itching and redness after only a brief contact with nickel-releasing metallic objects. In Section 3 of this report, data were collected by questionnaire from 342 nickel-sensitized eczema patients. We found that following up to 30 minutes of exposure, 26% of nickel-allergic patients reported reactions to shiny metals with symptoms compatible with an allergic reaction (Fig. 3.1). This is a surprisingly high number and may represent an even larger group as some of those exposed to a short contact may react after 30 minutes. This is the first study using systematic data on the subject and a comparison with similar data is therefore not possible. The recent REACH estimations to better define and understand the notion “direct and prolonged contact” as either repeated contacts of more than 10 minutes or one contact of more than 30 minutes are relevant and in good agreement with the data presented in this present report.

To further investigate this new finding, it is important to design studies with real-life skin exposure to nickel alloys and measurements of nickel release in $\mu g/cm^2$ over time in individuals with and without nickel allergy and to quantify the clinical reactions [9]. Such studies are in progress at the National Allergy Research Centre as part of a PhD study. It is also important to cover the north and south geographical aspect in clinical and epidemiological investigations.

From an academic viewpoint, the phenomenon of fast and slow reactors is interesting and may stimulate research both within the area of the skin barrier function and the response from the immune system.

4.6 Analysis of nickel release from articles

The dimethylglyoxime test (DMG) [12] has long been used as a screening test for nickel release from metal items (Table 3.2.2.) suspected of causing allergic skin reactions. The test is inexpensive, fast and reasonably correct as an initial screening for nickel release. The test was validated in a sample of 96 components from earrings. The sensitivity of the DMG test was 59.3% and the specificity was 97.5% based on DMG test results and nickel release concentrations, defined as $\geq 0.5\ \mu g/cm^2$ and determined by the EN 1811 reference method without application of any adjustment factors [12]. In market surveys using the DMG test, a high number of positive tests have repeatedly been found among the items listed in Table 3.2.2. [13, 14]. The immediate impression from such studies is that the EU regulation on nickel release is, in general, poorly controlled. In this respect it should be remembered that the DMG test can be both false negative and false positive [12]. To verify whether the Directive has not been adhered to, a follow-up with the laboratory sweat test (EN 1811) is needed.

Commercial laboratories perform a large number of tests for the European Jewellery Industry. According to data discussed at the NIPERA meeting in Brussels in June 2015 by Dippal Manchanda

(Birmingham Assay Office), it is not uncommon to identify items covered by the EU nickel regulation that do not comply with the nickel release limits [15]. It is expected that such products will not reach the market place; nevertheless, their fate is unknown. It would be interesting to gain insight into such data concerning alloys and coatings of items that fail to comply with the nickel regulation.
The data in the present report (Section 3) indicate that apart from earrings, metal items on clothing were also frequent causes of rash, also in the youngest group of patients. These are possibly items (e.g. buttons, zips, belt buckles) that should undergo further market-place control.
The continued high number of nickel-sensitive individuals in the general population indicates that control needs to be better organized. It is suggested that a group representing authorities, consumers, industry and academia is given the task of creating a standardized control programme including all member states to ensure uniformity, efficacy and transparency.

4.7 Conclusions

Nickel allergy is common and represents a public health issue in the EU. With the introduction of the first national nickel exposure regulations in the 1990s and in 2000, the EU nickel legislation has significantly reduced the number of new cases of nickel allergy in the EU population, particularly in the northern part. When the first nickel regulation was introduced in Denmark in 1989 and years later, the estimated positive economic effects, as saved costs from sick leave due to nickel allergy, reduced healthcare costs and reduced negative effects on quality of life, were calculated to around 10 billion DDK over 20 years [14]. If extrapolated to the whole EU, approximately 100 billion Euro has been saved. No unexpected negative effects of the regulation, such as obstruction of technological or industrial development, have been identified.
The most recent update of the EU Nickel directive by REACH gives a scientifically based definition of the concept “direct and prolonged contact with the skin”. This phrase, originating from the first versions of the regulation, has been difficult to translate to the real-life situation for both authorities and industry. The data on nickel-allergic patients in the present investigation show that the new definition of “direct and prolonged contact with the skin” defined as minutes of contact over a specific time period is clinically relevant and not too stringent. It is expected that this clarification will strengthen the positive effects of the nickel restriction. Piercing and the use of ear-post assemblies represent a particularly problem because of the skin penetration and circumvention of the normal skin barrier. Earrings remain the major cause of nickel sensitization. Revision of the nickel restriction according to REACH should be considered so that nickel-releasing metals would no longer be allowed in piercing post assemblies. Other materials with no hazard of contact allergy need to be used. Table 4.2 gives recommendations for further improvement of the legislation.
The EU regulation on nickel is less effective in the subtropical (Mediterranean) EU countries, probably because of the greater corrosion of nickel from metallic items in contact with the skin. The effect of climate needs further investigation. The enforcement of the EU regulation on nickel can be improved so that it covers all member states in a uniform and transparent way.
Table 4.3 outlines the most important gaps in the knowledge and research needs.

Table 4.2: Recommendations concerning needed changes related to regulation

Legislation	Rationale
Nickel-releasing material should not be allowed for piercing post assemblies.	Piercing is the major cause of nickel allergy (both sensitization and elicitation)

More focus of market-place inspections on items that frequently cause rash, for example, earrings and metal items on clothing.	Several investigations show that to up to 20% of products give positive results using the nickel spot test (DMG-test).
A working group with representatives from all stakeholders should develop a standardized control programme to be offered to all member states.	Uniform, efficient and transparent enforcement is needed of the Nickel Directive in all EU member states.

Table 4.3: Recommendations concerning research

Research needs	Rationale
The effect of climate needs to be further investigated in epidemiological and experimental studies.	The EU nickel directive seems to be less effective in the subtropical (Mediterranean) EU countries, probably because of greater corrosion of nickel from metallic items in contact with the skin.
The release of nickel required to produce allergic reactions in pierced skin.	All dose-response studies determining thresholds of reactions have been performed on intact skin. Absorption in the piercing channel is likely to lead to differences.
Investigations into the mechanisms of fast and slow reactors among nickel-sensitized individuals.	A high proportion of nickel-allergic individuals react to nickel releasing items after a short contact. This may have implications for prevention and treatment.
Work exposures to nickel-releasing items should be studied in relevant groups of workers and/or patients e.g. by exposure assessment of the workplace and/or hands. Effect of intervention with elimination of nickel-releasing items in the workplace should be done.	Occupational nickel exposures are important in individual patients and sub- groups of patients. May impact the work ability significantly.
Qualitative interview concerning product types causing reactions.	It is important to better understand the exposures and sequence of events.
Wear and tear of different coatings.	Little knowledge exists about the durability of different coatings to protect against nickel release.

References

1 Bregnbak D, Johansen JD, Jellesen MS et al . Chromium allergy and dermatitis: prevalence and main findings. Contact dermatitis 2015;73:261-280.

2 Diepgen TL, Ofenloch RF, Bruze M, Bertuccio P, Cazzaniga S, Coenraads P-J, et. Prevalence of contact allergy in the general population in different European regions. Br J Dermatol 2015;173(6):1411-9

3 Thyssen JP. Nickel and cobalt allergy before and after nickel regulation-evaluation of a public health intervention. Contact dermatitis2011; 65:Suppl 1.

4 Boss A, Menné T . Nickel sensitization from ear piercing. Contact Dermatitis.1982;8:211-213.

5 Thyssen JP, Johansen JD, Menne T et al. Nickel allergy in Danish women before and after nickel regulation. N. Engl. J. Med.2009;360:2259-2260.

6 Suzuki H. Nickel and gold in skin lesions of pierced earlobes with contact dermatitis. A study using scanning electron microscopy and X-ray microanalysis.Arch.Dermatol.Res.1998;290:523-527.

7 Menne T, Brandrup F, Thestrup-Pedersen K, et al . Patch test reactivity to nickel alloys. Contact Dermatitis1987;16:255-259.

8 Lidén C. Nickel in jewellery and associated products. Contact Dermatitis 1992:26:73-75

9 Lidén C, Menné T, Burrows D. Nickel-containing alloys and platings and their ability to cause dermatitis. British Journal of Dermatology 1996:134:193-198.

10 Ingber A, Herskho K, Horor L. AISI 316 L stainless-steel ear piercing post assembly does not cause dermatitis in nickel sensitive subjects. Exog.Dermatol 2003;2:195-200.

11 Erfani B, Liden C, Midander K. Short and frequent skin contact with nickel. Contact Dermatitis 2015;73:22-230.

12 Thyssen JP, Skare L, Lundgren L et al. Sensitivity and specificity of the nickel spot (dimethylglyoxime) test. Contact Dermatitis 2010;62:279-288.

13 Thyssen JP, Menné T, Johansen JD. Identification of metallic items that caused nickel dermatitis in Danish patient 2010;63:151-156.

14 Hamann D,Thyssen JP,Hamann et al . Jewellery: alloycomposition and release of nickel,cobalt and lead assessed with the EU synthetic sweat method. Contact Dermatitis 2015;73:231-238.

15 Nickel Institute. Workshop on nickel restriction. Articles in direct and prolonged contact with skin. Meeting report. Brussels, June 2015.

16 Serup-Hansen N, Gudum A, Sørensen MM. Valuation of chemcial releated health impacts. Environmental project 2004. No 929. Published at www.MST.dk (last accessed 11.01.2016)

Appendices

Appendix 1 Population-based investigations concerning prevalence of nickel allergy in 2005–2015.

Author	Year of publication	Land	Population	PATCH TEST Year	Type	Reading Day	Age in years	Number	Women/ Men(%)	POSITIVE REACTION NICKEL (%) Total	Women	Men	Development over time
Diepgen (1)	2015	5 countries	General population	2008-2011	True test	3	18-74	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			
Mortz (2)	2013	Denmark	Schoolchildren	1995	TRUE Test[a]	3[b]	12-16	1146	54.1	8.6	13.7	2.5	15-year incidence of
			Same individuals	2010	TRUE Test[a]	3/4[c]	28-30	442	62	11.8	18.3	1.2	nickel allergy: 7%
Machovcová (3)	2012	czech-reput	Schoolchildren	2005-2006	Curatest F	2 og 3	6-16	218	47.7	15.6	19.2	12.3	
							6-8	23	43.5		10	23.1	
							9-12	97	56.7		20	11.9	
							13-16	98	39.8		20.5	10.2	
Krecisz (4)	2012	Polen	Schoolchildren	2009-2010	IQ chambers	2 og 4	15	528	58.5	7.8	12.3	1.4	
Thyssen (5)	2009	Denmark	General population	1990-1991	TRUE Test	2	18-69	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	40.1		2.3	1.6	
				2006-2008	TRUE Test	2	18-69	3338	55.2		10.3	1	♂: Falling trend
							18-35	622	59.3		**11.4**	1.2	♀: Significant reduction
							36-55	1625	55.8		**13**	1.4	♀: Significant increase
							56-69	1091	52		5.1	0.4	♀: Increasing trend
Josefson (6)	2009	Sweden*	♀ Schoolchildren	1982-1983	TRUE Test	3	8,11 and 15	958	100		9		24-25-year incidence of
			Same individuals	2006-2007	TRUE Test[d]	3	30-40	369	100		30.1		nickel allergy: 24.4%
Thyssen (7)	2009	Denmark	♀ pierced<1990 [e]	1990	TRUE Test	2	18-69	179	100		**15.6**		
							18-35	95	100		**22.1**		
			♀ pierced 1990-2006 [e]	2006	TRUE Test		18-69	245	100		**6.9**		
							18-35	145	100		**8.3**		
Dotterud (8)	2007	Norway	General population	1994/1995	TRUE Test	3	18-75	531	54.4	19.2	31.1	5	
Dotterud (9)	2007	Norway	General population	1994	TRUE Test	3	18-69	1236	55.8	17.6	27.5	5.1	
Fors (10)	2007	Sweden*	Schoolchildren	2000-2004	TRUE Test	4	14,9-23,4	4376	68	9.9	13.3[f]	2.5[f]	
Thyssen (11)	2007	Denmark	General population Subgroups	1966-2007	TRUE Test, standard		All ages			8.6	17.1	3	
Jensen (12)	2002	Denmark	♀ High-school girls [g]	1999-2000	TRUE Test	2 og 4	17-22	275	100		17.1		Significantly lower prevalence
			♀ Primary-school girls [g]	1999-2000	TRUE Test	2 og 4	10-14	305	100		3.9		

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

Bold numbers: significant difference

* Age standardised prevalences

[a] Concentration: 0.2 mg/cm2 and 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

[d] 15/29 persons with doubtful results additionally tested with 2.5%, 1.0%, 0.3% and 0.1% nickel sulfate from Chemotechnique

[e] population: ear pierced from (4)

[f] estimated prevalence taking drop-outs into consideration; ♀: 11.8 %. ♂: 1.6 %

[g] drop-outs: primary school: 28.6%, high school: 48.5%

Appendix 2 Investigations concerning prevalence of nickel allergy in patients.

Author	Year of publi.	Country	Population	Patch Test Year	Type	Reading Days	Age	Number (n)	Women/ Men (%)	Positive reaction nickel (%) Total	♀	♂	Changes over time (in the observation period)
Uter (1)	2015	ESSCA[a]	Obs. ACD	2009-2012	Standard/ TRUE Test	3-5	-	59728		11.9-26.4			
		Austria						1113		21.6			
		Denmark						2582		12.6			
		Finland						1057		22.4			
		Germany						7628		11.9			
		Italy						9267		26.2			
		Lithuania						865		14.3			
		NL						4385		19.4			
		Polen						2828		25			
		Spain						4257		26.4			
		Switzerland						4990		20.9			
		England						15532		17.4			
		Slovenia						5224		16.9			
Mahler (2)	2014	Germany,	Obs. ACD	2010-2012	Finn chamber/	2 og 3/4	-						
		Austria and		2010	Haye´s chamber/			13117		14.9			
		Schwizerland [b]		2011	IQ chamber/			13320		15.9			
				2012	Curatest F			12529		15.3			
Aguilar-Bernier (3)	2012	Spain	-	2005-2010	Curatest /TRUE Test	2 og 4 [e]	12-90	839	63.3	25.9	37.7	5.5	♀ og ♂: the prevalence increases with age
Uter (4)	2012	ESSCA [c]	Obs. ACD	2007-2008	-	3-5	-	25181		11.9-27.4			
		Austria						678		25.2			
		Denmark						1318		19.9			
		Finland						760		21.3			
		Germany						2694		16.8			
		Italy						2938		27.4			
		Lithuania						680		18			
		NL						2168		14.9			
		Polen						789		24.3			
		Spain [d]						1845		26.5			
		Schwizerland [b]						2402		22			
		England						8909		18.6			
Milingou (5)	2010	Greece	Obs. ACD	1980-2007	-	49 h og D4	<16						♀ og ♂ 1994-2007: Non-significant increase
				1980-1993				232	62.5	16.4	24.1	3.4	in prevalence compared with 1980-1993
				1994-2007				255	63.5	21.6	31.5	4.3	
O´Connell (6)	2010	England [f]	Hairdressers	1980-2007	Finn chamber	2/3 og 4/5	15-71	725	91.1	32.1			

Author	Year published	Land	Population	Patch test Year	Type	Reading Days	Age	Number (n)	Women/ Positive reaction nickel (%) Men (%)	Total	♀	♂	Changes over time in the observation period
Uter (7)	2009	ESSCA [g]	Obs. ACD	2005-2006	-	3-5	-						
		West						8468		20.8			
		South						2666		24.5			
		Central						5708		19.7			
		Northeast						1585		22.4			
Bordel-Gómez (8)	2008	Spain	-	2000-2005	Curatest	2 og 4	-	1092	61.6	29.3	42.5	8.1	
Uter (9)	2008	ESSCA [h]	Obs. ACD	2004	Finn chamber/	3-5	-	9871		20.6			
		Italy [i]			True Test			342		13.7			
		Lithuania [j]						41		12			
		Finland [k]						140		27.1			
		Polen [l]						360		25.9			
		Italy [m]						370		30.6			
Bocca (10)	2007	Italy	Earlope eczema	1994	Finn chamber [n]	[o]	-	931		54.3			
				2005	Finn chamber [n]	[o]	-	867		53.3			No change in prevalence between 1994 and 2005.
Mäkelä (11)	2007	Finland	Atopikere	1982-1983	Finn chamber [n]	3/4	20-31	801	62.5	16			
Tomljanović-Veselski (12)	2007	Croatia	-	2004-2006	-	2 og 3	-	955	-	12.9	♀: 114	♂: 9	
Kuljanac (13)	2006	Croatia	Obs. ACD	1994-2003	Curatest [p]	2 og 3	7-81	1102	67.2	33.4			
Clayton [t] (14)	2005	England	-	1995-2004	Finn chamber	2 og 4	0-17	500	62	8.8			
Seidenari [u] (15)	2005	Italien	Obs. ACD	1995-2001	Finn chamber	3	7 mån-12 år	1094	53.5	10.9	13.5	7.9	
Uter (16)	2005	ESSCA [r]	Obs. ACD	2002-2003	Standard	3-5	-	9520		17.3 [s]			

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

- : not mentioned

ACD= Allergic contact dermatitis

[a] 53 department of dermatology in 12 countries; Austria (1), Denmark (1), Finland (2), Germany (8), Italy (6), Lituania (1), NL (2), Polen (3), Schwizerland (4), Spain (7), Slovenia (6) and England (13)

[b] 56 DKG og IVDK clinics-partly overlap with (1).

[c] 39 dermatological departments in 11 countries; Austria (1), Denmark (1), Finland (2), Germany (6), Italy (3), Lituania (1), NL (2), Polen (3), Schwitzerland (3), Spain (5) and England (12)

[d] Partly the same population as García-Garvín (CD 2011)-see age-stratified table.

[e] Only positive results Day 4 included.

[f] possible overlap in patients year 2002-2007 with Garg (2013)

[g] 31 dermatological departments in 10 countries; Austria (1), Finland (2), Germany (5), Italy(4), Lituania (1), NL (2), Polen (1), Schwitzerland (2), Spain (1) and England (12).
Prevalence divided into i 4 geografical regions in Europe. West= England. South= Spain and Italy. Central= NL, Schwitzerland, Austria, Germany. Northeast=Finland, Lituania and Polen.

[h] 31 dermatological departments in 11 countries; Austria (1), Denmark (1), Finland (2), Germany (6), Italy (5), Lituania (1), NL (2), Polen (1), Schwitzerland (1), Spain (1) and England (10).

Appendix 2: Continued

[i] Padova- Specialised clinic for children with eczema

[j] Kaunas- Specialised clinic for facial eczema

[k] Helsinki- Specialised clinic for occupational eczema

[l] Lodz- Specialised clinic for occupational eczema

[m] Trieste-Specialised clinic for occupational eczema

[n] concentration of allergen not given

[o] reading according to ICDRG criteria, I

[p] allergen preparation produced at institute for immunology in Zagreb

[r] Austria, Denmark, Finland, Germany, Italy, NL, Polen, Schwizerland and England. Highest prevalence in Italy (31.7%), lowest prevalence in Denmark (8.1%)

[s] standardised for age and sex

[t] likely overlap in patients in the years 2002-2004 with patients from Fortina (2015). See age-stratified table.

[u] possible overlap in patients with Garg (2013) <30 year in the period 1997-2001. See age-stratified table. Patch test occlusion 72 h.

Appendix 3 Papers on the frequency of nickel allergy in patch-tested patients stratified by age in 2005–2015.

Author	year of publ.	country	year Patch tests	Type	Reading days	age	number	Women/ Men (%)	Positive reaction nickel (%) total	♀	♂	development over time
Fortina (1)	2015	11 countries divided into 4 geographical regions	2002-2010	Standard + TRUE Test	3-5	1-16	6583		16,7			2002-2010: decrease over time in all regions.
						1-5	1588		26,7			Highest prevalence in the youngest age group
						6-12	2692		13,2			
						13-16	2303		13,9			
		Central=Austria, Schwitzerland Germany, Denmark and Netherlands				1-5	40		15,0			
						6-12	226		10,6			
						13-16	542		17,3			
		Northeast=Finland and Polen				1-16	155		25,8			
		West=England				1-5	542		17,3			
						6-12	959		5,3			
						13-16	1021		10,1			
		South=Spain, Italy and Slovenia				1-5	1341		5,2			
						6-12	1450		5,8			
						13-16	644		2,6			
Fall (2)	2015	Sweden	1992	Finn chamber	3	m=39	3662	64,7	21,4			
						<40 år	1891	63,9		33,8	7,3	
						≥40 år	1771	65,6		25,2	5,4	
			2000	Finn chamber	3 and 6/7	m=40	3825	63,1	19,8	31,1	6,7	Year 2000 og 2009: Significant higher prevalence in ♀
						<40 år	1864	62,7		29,4	6,4	compared with ♂
						≥40 år	1961	63,6		26,3	6,2	
			2009	Finn chamber/ IQ chamber	3 and 6/7	m=43	3112	64	**17,6**	26,7	7	♀ all ages: 1992-2009: Significant decrease, especially <40 years.
						<40 år	1396	63,7		**23,3**	6,1	
						≥40 år	1716	64,3		**24,7**	6	
Simonsen (3)	2013	Danmark	2003-2011	Standard/ TRUE Test	3/4 and often 2 and 7	1-17	2495	65,9	9,7	12,4	4,7	Significantly higher prevalence in ♀ than in ♂
						1-4			14,5			
						5-8			8,5			
						9-12			8,3			
						13-17			10,2			
Teixeira (4)	2014	Portugal	1992-2011	Finn chamber/ IQ chamber	2/3 and 4/ 7	All	5250	69,2	26,5	34,4	8,9	No significant change during 1992-2011
						≤ 15			2,7	2,6	3,5	
						16-30			38,4	40,7	19	
						31-64			54,5	53,0	67	
						≥ 65			4,3	3,6	11	
			1992-1996			All	1238	68,2	26,4	35,3	7,4	
						≤ 15			3,7	3,7	3,4	
						16-30			46,8	**49,0**	24	
						31-64			47,1	45,0	69	
						≥ 65			2,4	2,3	3,4	

Appendix 3: Continued

Author	year of publ.	country	year Patch tests	Type	Reading days	age	number	Women/ Men (%)	Positive reaction nickel (%) total	♀	♂	development over time
Teixerira (4)			1997-2001			All	1473	66,7	24,8	33,5	7,6	
						≤ 15			2,7	3,0	0	
						16-30			41,8	44,1	22	
						31-64			52,7	51,1	68	
						≥ 65			2,7	1,8	11	
			2002-2006			All	1039	68,6	28,9	36,3	13	
						≤ 15			2,3	2,3	2,4	
						16-30			36,3	38,6	22	
						31-64			55,7	54,8	61	
						≥ 65			5,7	4,2	55	
			2007-2011			Alle	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	compared with during 1992-1996
						≥ 65			6,3	5,8	11	
Garg (5)	2013	Denmark	1985-2010	-	4 and 7	All	19 828	64,6	12,3	17,4	3,1	
						<30	21,20%		14,2	18,9	3	♀ < 30 years: significant decrease
						30-60	52,70%		14,5	20,7	3,4	♀ and ♂ 30-60 years: significant increase
						>60	26,10%		6,5	8,9	2,6	
		Germany	1995-2010	-	3	All	104 933	62,4	13,6	18,9	5,1	
						<30	18,90%		18,8	26,0	5,9	♀ and ♂ <30 years: significant decrease.
						30-60	52,40%		15,8	23,1	5,4	♀ 30-60 years: significant increase.
						>60	28,70%		6,2	7,6	3,9	
		Italy	1997-2010	-	4	All	20 231	67,1	25,0	31,9	11	
						<30	28,50%		27,2	35,2	11	♀ <30 years: significant decrease. ♂ <30 years: increasing trend
						30-60	52,40%		27,9	35,9	11	♀ og ♂ 30-60 years: significant increase.
						>60	19%		13,7	15,8	9,4	
		England	2002-2010	-	4	All	35 398	67,1	17,7	23,4	6,2	
						<30	26,70%		16,1	20,4	6	♀ <30 years: significant decrease[a]. ♂ <30 years: significant decrease.
						30-60	51,70%		21,2	28,4	7,3	♀ 30-60 years: significant increase[a]. ♂ 30-60 years: sigificant increase.
						>60	21,50%		11,3	15,6	3,9	
Schnuch (6)	2013	Germany, Schwitzerland	2005-2012		3(4)	All	74854	62,2				♂ all ages: no trend
		and Austria[b]	2005-2006			1-17				**17,3**		
						18-30				**26,4**		
						31-44				**36,2**		
						45-60				**20,5**		
						61-99				9,5		

Appendix 3: Continued

Author	year of publ.	country	year Patch tests	Type	Reading days	age	number	Women/ Men (%)	Positive reaction nickel (%) total	♀	♂	development over time
Schnuch (6)			2007-2008			1-17				15,1		
						18-30				24,0		
						31-44				34,8		
						45-60				21,6		
						61-99				8,7		
			2009-2010			1-17				14,1		
						18-30				20,0		
						31-44				30,0		
						45-60				21,2		
						61-99				7,7		
			2011-2012			1-17				**11,6**		♀ 1-17 years: significant decrease
						18-30				**19,8**		♀ 18-30 years and 31-44 years: significant decrease
						31-44				**31,1**		
						45-60				**23,9**		♀ 45-60 years: significant increase
						61-99				9,0		♀ 61-99: no trend.
Turčić (7) [c]	2013	Croatia	2007-2011	[d]	2 and 3	3-80	2185	69,5				
						3-20			13,7			
						21-60			11,7			
						61-80			9,9			
Fortina (8)	2011	Italy	2002-2008	Finn chamber	2 and 4	0-3	321	55,1	26,8			
						0-2	90		33,3			
						2-3	231		24,2			
Carøe (9) [f]	2011	Denmark	1992-2009	TRUE Test	3/4 and 5-7	2-95	9138	63,7		21,7	5,2	♂ 2-95 years: 2 u-formed patterns with nadir 1996-1997 and 2005.
						2-30				24,4		♀ 2-30 years: 1992-1997 to 2004-2009: significant decrease
						31-60				24,6		♀ 31-60 years: no significant change
						>60				9,7		♀>60 years: 1992-1997 to 2004-2009: significant increase
			1992-1997			All				22,0		
						2-30				29,8		
						31-60				22,9		
						>60				6,9		
			2004-2009			All				20,8		
						2-30				19,6		
						31-60				25,2		
						>60				11,1		Significantly lower prevalence in ♀ > 60 years
García-Garvín (10) [g]	2011	Spain	2008	Finn chamber/ TRUE Test	-	1-99	1161	63,7	25,9			
						1-20				36,1	9,1	
						21-40				36,3	8,2	
						41-60				40,1	11	
						61-99				22,9	7,9	

Author	year of publ.	country	year Patch tests	Type	Reading days	age	number	Women/ Men (%)	Positive reaction nickel (%) total	♀	♂	development over time
Schnuch (11)	2011	Germany, Schwitzerland and Austria	1994-2009	-	3(4)	1-17	3652	64,5		18,3[e]	5,04[f]	♀ 1-17 years: 1994-2009 : significant decrease, but 2000-2009: no change
						18-30	21766	64		28,9	6,1	♀/♂ 18-30 years: 1994-2009 significant decrease.
						31-44	28156	58,5		30,7	6,4	♀ 31-44 years: 1994-2000: significant increase, ♀ 2000-2009: no change
						45-60	37497	60,9		17,3	4,9	♀ 45-60 years: 1994-2000 and 2000-2009: significant increase
						61-99	36027	64,4		8,1	4,2	♀ 61-99 years: 1994-2000: significant increase, ♀ 2000-2009: no change
Janach (12) [g]	2010	Schwitzerland	2000-2004	Finn chamber [ш]	2 and 3/4	All	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	
Thyssen (13)	2009	Denmark	2006-2007	True test	2/3 and 5/7	17-91	634	69,4	18,5	17,0	1,4	
						17-22				14,6		♀ 17-22 years: Significantly lower prevalence compared with
						23-34				31,8		♀ 23-34 years and 35-46 years
						35-46				31,9		
						47-58				27,0		
						59-91				11,4		
Rudzki (14) [m]	2005	Polen	1995	- [ш]	-	-	1712		14,0			
						0-20			15,9			
						>20			84,1			
			1997	-	-	-	1690		13,0			
						0-20			16,0			
						>20			84,0			
			1999	-	-	-	1418		15,7			
						0-20			16,6			
						>20			83,4			
			2003	-	-	-	1504		13,1			
						0-20			12,2			
						>20			87,8			
			2004	-	-	-	1664		16,9			
						0-20			10,0			
						>20			90,0			

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

- : not given

[ш] concentration not given

*data given only for reading D3 in the test periods, except for prevalences in women and men in all age groups in years 2000 and 2009, where 2 readings are pooled.

m: median

[a]For England concerning the period 2004-2010

[b]IVDK(Information Network of Departments of Dermatology). Partly overlap with data from Garg et al(4) from Germany in the period 2005-2010, and Mahler et al(see patient investigations (2) in the period 2010-2012, and Schnuch et al(8) in the period 2005-2009)). NB: Different exposures in the group 1-17 years, as the 2005-2006 were pierced before 2004, but in 2011-2012 the majority were pierced after 2004

[c]Patient population: Patients diagnosed with ACD(72,6%), ICD (9,3%) eller AD(18,2%). ♀ and ♂: significantly higher prevalence in the youngest compaired to the youngest compaired to the older.

[d] Allergen preparation produced at the institute of immunology in Zagreb

[e]: Prevalence year 2000-2009 is presented. Same population as Uter (2012)- see patient investigations.

[f] partly overlap with children from Simonsen et al(7) from Odense in the period 2003-2009.

[g] probably partly overlap with data from Schnuch (8) patch tested 1994-2009.

Appendix 4 Core questions in the questionnaire (translated from Danish)

Questions	Answers
Have you ever had an eczema reaction after skin contact with earrings or ear studs, watches, buttons or metal fastenings?	("yes", "no").
"If yes, how old were you at the first occurrence?"	(Give age in years)
"If yes, which metal items led to eczema at the first occurrence?"	("earring/ear stud", "other jewellery", "watch", "key", "button", "spectacles", "scissors", "belt buckle", "coin", "tool", "mobile phone", "hair clip", "zip", "lighter", "computer", "other". Lastly, patients who responded "other" were asked to specify causative items)
"If yes, which metal items led to dermatitis at the most recent occurrence?"	("earring/ear stud", "other jewellery", "wrist watch", "key", "button", "spectacles", "scissors", "belt buckle", "coin", "tool", "mobile phone", "hair clip", "zip", "lighter", "computer", "other". Lastly, patients who responded "other" were asked to specify causative items)
How old were you at the last occurrence?	(Give age in years)
"Do you develop eczema following short skin contact with metal items?"	("yes; after 2 minutes", "yes; after 5 minutes", "yes; after 10 minutes", "yes, after 30 minutes", "yes, after 1 hour", "yes, after 2–5 hours", "no, longer contact is needed").

References

Appendix 1

1) Diepgen TL, Ofenloch RF, Bruze M, Bertuccio P, Cazzaniga S, Coenraads P-J, et al. Prevalence of contact allergy in the general population in different European regions. Br J Dermatol Published Online First: 2015. doi:10.1111/bjd.14167

2) Mortz, C. G., Bindslev-Jensen, C., & Andersen, K. E. (2013). Nickel allergy from adolescence to adulthood in the TOACS cohort. Contact Dermatitis, 68(6), 348–356.

3) Machovcová, A. (2012). The frequency of contact allergy in children and adolescents in the Czech Republic. Acta Dermatovenerol Croat, 20(2), 75–79.

4) Krecisz, B., Chomiczewska, D., Palczynski, C., & Kiec-Swierczynska, M. (2012). Contact allergy to metals in adolescents. Nickel release from metal accessories 7 years after the implementation of the EU Nickel Directive in Poland. Contact Dermatitis, 67(5), 270–276.

5) Thyssen, J. P., Linneberg, A., Menné, T., Nielsen, N. H., & Johansen, J. D. (2009). The association between hand eczema and nickel allergy has weakened among young women in the general population following the Danish nickel regulation: Results from two cross-sectional studies. Contact Dermatitis, 61(6), 342–348.

6) Josefson, a., Färm, G., Magnuson, a., & Meding, B. (2009). Nickel allergy as risk factor for hand eczema: A population-based study. British Journal of Dermatology, 160, 828–834.

7) Thyssen, J. P., Johansen, J. D., Menné, T., Nielsen, N. H., & Linneberg, A. (2009). Nickel Allergy in Danish Women before and after Nickel Regulation. The New English Journal of Medicine, 360(21), 2259–2260.

8) Dotterud, L. K. (2007). The prevalence of allergic contact sensitization in a general population in Tromso, Norway. International Journal of Circumpolar Health, 66(4), 328–334.

9) Dotterud, L. K., & Smith-Sivertsen, T. (2007). Allergic contact sensitization in the general adult population: a population-based study from Northern Norway. Contact Dermatitis, 56(1), 10–15.

10) Fors, R., Persson, M., Bergström, E., Stenlund, H., Stymne, B., & Stenberg, B. (2008). Nickel allergy - Prevalence in a population of Swedish youths from patch test and questionnaire data. Contact Dermatitis, 58(2), 80–87.

11) Thyssen, J. P., Linneberg, A., Menné, T., & Johansen, J. D. (2007). The epidemiology of contact allergy in the general population--prevalence and main findings. Contact Dermatitis, 57(5), 287–299.

12) Jensen, C. S., Lisby, S., Baadsgaard, O., Vølund, a., & Menné, T. (2002). Decrease in nickel sensitization in a Danish schoolgirl population with ears pierced after implementation of a nickel-exposure regulation. British Journal of Dermatology, 146(4), 636–642.

Appendix 2

1 Uter W, Gefeller O, Giménez-Arnau A, Frosch P, Duus Johansen J, Schuttelaar M-L, et al. Characteristics of patients patch tested in the European Surveillance System on Contact Allergies (ESSCA) network, 2009-2012. Contact Dermatitis 2015; 73:82–90.

2 Mahler V, Geier J, Schnuch A. Current trends in patch testing - new data from the German Contact Dermatitis Research Group (DKG) and the Information Network of Departments of Dermatology (IVDK). JDDG J der Dtsch Dermatologischen Gesellschaft 2014; 12:583–592.

3 Aguilar-Bernier M, Bernal-Ruiz a. I, Rivas-Ruiz F, Fernández-Morano MT, de Troya-Martín M. Contact Sensitization to Allergens in the Spanish Standard Series at Hospital Costa del Sol in Marbella, Spain: A Retrospective Study (2005–2010). Actas Dermo-Sifiliográficas (English Ed 2012; 103:223–228.
4 Uter W, Aberer W, Armario-Hita JC, Fernandez-Vozmediano JM, Ayala F, Balato A, et al. Current patch test results with the European baseline series and extensions to it from the "European Surveillance System on Contact Allergy" network, 2007-2008. Contact Dermatitis 2012; 67:9–19.
5 Milingou M, Tagka A, Armenaka M, Kimpouri K, Kouimintzis D, Katsarou A. Patch tests in children: A review of 13 years of experience in comparison with previous data. Pediatr Dermatol 2010; 27:255–259.
6 O'Connell RL, White IR, Mc Fadden JP, White JML. Hairdressers with dermatitis should always be patch tested regardless of atopy status. Contact Dermatitis 2010; 62:177–181.
7 Uter W, Rämsch C, Aberer W, Ayala F, Balato A, Beliauskiene A, et al. The European baseline series in 10 European Countries, 2005/2006 - Results of the European Surveillance System on Contact Allergies (ESSCA). Contact Dermatitis 2009; 61:31–38.
8 Bordel-Gómez MT, Miranda-Romero a., Castrodeza-Sanz J. Isolated and concurrent prevalence of sensitization to transition metals in a Spanish population. J Eur Acad Dermatology Venereol 2008; 22:1452–1457.
9 Uter W. The European surveillance system of contact allergies (ESSCA): Results of patch testing the standard series, 2004. J Eur Acad Dermatology Venereol 2008; 22:174–181.
10 Bocca B, Forte G, Senofonte O, Violante N, Paoletti L, De Berardis B, et al. A pilot study on the content and the release of Ni and other allergenic metals from cheap earrings available on the Italian market. Sci Total Environ 2007; 388:24–34.
11 Mäkelä L, Lammintausta K, Kalimo K. Contact sensitivity and atopic dermatitis: Association with prognosis, a follow-up study in 801 atopic patients. Contact Dermatitis 2007; 56:76–80.
12 Tomljanović-Veselski M, Žilih-Ostojić C, Jovanović I. Nickel hypersensitivity in Slavonia-Brod County 2004-2006. Acta Dermatovenerologica Croat 2007; 15:84–87.
13 Kuljanac I, Knezević E, Cvitanović H. Epicutaneous patch test results in patients with allergic contact dermatitis in Karlovac county--a retrospective survey. Acta dermatovenerologica Croat ADC / Hrvat dermatolosko Drus 2006; 14:156–159.
14 Clayton TH, Wilkinson SM, Rawcliffe C, Pollock B, Clark SM. Allergic contact dermatitis in children: should pattern of dermatitis determine referral? A retrospective study of 500 children tested between 1995 and 2004 in one U.K. centre. Br J Dermatol 2006; 154:114–117.
15 Seidenari S, Giusti F, Pepe P, Mantovani L. Contact sensitization in 1094 children undergoing patch testing over a 7-year period. Pediatr Dermatol 2005; 22:1–5.
16 Uter W, Hegewald J, Aberer W, Ayala F, Bircher a. J, Brasch J, et al. The European standard series in 9 European countries, 2002/2003 - First results of the European Surveillance System on Contact Allergies. Contact Dermatitis 2005; 53:136–145.

Appendix 3

1 Belloni Fortina A, Cooper SM, Spiewak R, Fontana E, Schnuch A, Uter W. Patch test results in children and adolescents across Europe. Analysis of the ESSCA Network 2002-2010. Pediatr Allergy Immunol 2015; 26:n/a–n/a.
2 Fall S, Bruze M, Isaksson M, Lidén C, Matura M, Stenberg B, et al. Contact allergy trends in Sweden - a retrospective comparison of patch test data from 1992, 2000, and 2009. Contact Dermatitis 2015; 72:297–304.
3 Simonsen AB, Deleuran M, Mortz CG, Johansen JD, Sommerlund M. Allergic contact dermatitis in Danish children referred for patch testing - A nationwide multicentre study. Contact Dermatitis 2014; 70:104–111.

4 Teixeira V, Coutinho I, Goncalo M. Allergic Contact Dermatitis to Metals over a 20 Year Period in the Centre of Portugal : Evaluation of the Effects of the European Directives. Acta Med Port 2014; 27:295–303.
5 Garg S, Thyssen JP, Uter W, Schnuch a., Johansen JD, Menné T, et al. Nickel allergy following European Union regulation in Denmark, Germany, Italy and the U.K. Br J Dermatol 2013; 169:854–858.
6 Schnuch A, Schwitulla J. Decrease in nickel allergy in women after the second EU nickel directive. Contact Dermatitis 2013; 69:253–256.
7 Turčić P, Kulišić SM, Lipozenčić J. Patch Test Reactions to Metal Salts in Patients with Different Types of Dermatitis. Acta Dermatovenerol Croat 2013; 21:180–184.
8 Belloni Fortina A, Romano I, Peserico A, Eichenfield LF. Contact sensitization in very young children. J Am Acad Dermatol 2011; 65:772–779.
9 Carøe C, Andersen KE, Mortz CG. Fluctuations in the prevalence of nickel and cobalt allergy in eczema patients patch tested after implementation of the nickel regulation in Denmark. Contact Dermatitis 2011; 64:126–131.
10 García-Gavín J, Armario-Hita JC, Fernández-Redondo V, Fernández-Vozmediano JM, Sánchez-Pérez J, Silvestre JF, et al. Nickel allergy in Spain needs active intervention. Contact Dermatitis 2011; 64:289–302.
11 Schnuch A, Wolter J, Geier J, Uter W. Nickel allergy is still frequent in young German females - Probably because of insufficient protection from nickel-releasing objects. Contact Dermatitis. 2011; 64:142–150.
12 Janach M, Kühne A, Seifert B, French LE, Ballmer-Weber B, Hofbauer GFL. Changing delayed-type sensitizations to the baseline series allergens over a decade at the Zurich University Hospital. Contact Dermatitis 2010; 63:42–48.
13 Pontoppidan Thyssen J, Hald M, Avnstorp C, Veien NK, Lauerberg G, Nielsen NH, et al. Characteristics of nickel-allergic dermatitis patients seen in private dermatology clinics in Denmark: A questionnaire study. Acta Derm Venereol 2009; 89:384–388.
14 P Rudzki E. Rebandel. Changes in the pattern of sensitization to nickel in different age groups in Poland. Contact Dermatitis 2005; :177.

An investigation of causes of nickel allergy

The objective of this project was to identify causes and exposures leading to nickel allergy and eczema in patients with proven nickel allergy. The project included a questionnaire study among more than 500 Danish nickel allergy patients and a review of the epidemiology of nickel allergy in the EU. Based on the findings of the questionnaire and the literature study a preliminary assessment of the present nickel regulation was made and recommendations for further investigations were given.

Nickel is one of the most frequent causes of contact allergy. Since 2000 the release of nickel from consumer goods intended for direct and prolonged contact with the skin has been regulated at EU level. However, the frequency of development of nickel allergy is still high, especially among young women.

Formålet med dette projekt var at identificere årsager og eksponering, der forårsager nikkel allergi og eksem hos patienter med dokumenteret nikkelallergi. Projektet omfattede en spørgeskema undersøgelse blandt mere end 500 danske nikkelallergi patienter og en gennemgang af forekomsten af nikkel allergi i EU. På baggrund af resultaterne af spørgeskemaundersøgelsen samt litteraturstudiet er der foretaget en foreløbig vurdering af den nuværende regulering af nikkel og givet anbefalinger om yderligere undersøgelser.

Nikkel er en af de hyppigste årsager til kontaktallergi. Siden år 2000 har frigivelsen af nikkel fra forbrugerprodukter beregnet til direkte og længerevarende hudkontakt været reguleret på EU niveau. Dog ses fortsat en relativt høj hyppighed af udvikling af nikkelallergi, særligt hos yngre kvinder.

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