

Identification of metallic items that caused nickel dermatitis in Danish patients

JACOB P. THYSEN, TORKIL MENNÉ AND JEANNE D. JOHANSEN

Department of Dermato-Allergology, National Allergy Research Centre, Copenhagen University Hospital Gentofte, University of Copenhagen, Hellerup, Denmark

Introduction: Nickel allergy is prevalent as assessed by epidemiological studies.

Objectives: In an attempt to further identify and characterize sources that may result in nickel allergy and dermatitis, we analysed items identified by nickel-allergic dermatitis patients as causative of nickel dermatitis by using the dimethylglyoxime (DMG) test.

Materials and methods: Dermatitis patients with nickel allergy of current relevance were identified over a 2-year period in a tertiary referral patch test centre. When possible, their work tools and personal items were examined with the DMG test.

Results: Among 95 nickel-allergic dermatitis patients, 70 (73.7%) had metallic items investigated for nickel release. A total of 151 items were investigated, and 66 (43.7%) gave positive DMG test reactions. Objects were nearly all purchased or acquired after the introduction of the EU Nickel Directive. Only one object had been inherited, and only two objects had been purchased outside of Denmark.

Conclusions: DMG testing is valuable as a screening test for nickel release and should be used to identify relevant exposures in nickel-allergic patients. Mainly consumer items, but also work tools used in an occupational setting, released nickel in dermatitis patients. This study confirmed 'risk items' from previous studies, including mobile phones.

Key words: dimethylglyoxime test; EU Nickel Directive; jewellery; nickel allergy; nickel. © John Wiley & Sons A/S, 2010.

Conflict of interests: The authors have declared no conflicts.

Accepted for publication 11 May 2010

Nickel allergy is prevalent as assessed by epidemiological studies (1–3). Recently, a categorization of contact allergy epidemics was proposed (4). According to this proposal, the Danish nickel epidemic may be categorized as 'generalized', because the overall nickel allergy prevalence exceeds 1/100, and as an 'outbreak' in Danish women, as more than 1/20 are nickel allergic (4). We have previously shown that the Danish nickel regulation as well as the EU Nickel Directive have changed the epidemiology of nickel allergy, as a decrease has been observed in young women and young female dermatitis patients (5–9). However, despite a positive effect, nickel allergy remains prevalent. There may be several reasons for the persistent nickel problem: exposure to nickel at work (8, 10–12);

exposure to items not covered by the EU Nickel Directive, such as keys and mobile phones (the latter was recently covered by the Nickel Directive) (13); exposure to nickel-releasing consumer items not fulfilling the criteria of the Nickel Directive (14, 15); genetic predisposition (16–18); and insufficiency of the EU Nickel Directive (19, 20).

Recently, we performed a questionnaire study in nickel-allergic dermatitis patients seen in seven private dermatology clinics, partly to identify metallic items that caused nickel dermatitis on the most recent occurrence (9). Frequent self-reported causes of nickel dermatitis in both sexes included watches, earrings, buttons, jewellery and belt buckles, whereas mascara, coins, work tools and mobile phones were less frequently reported. Participating

dermatologists typically reported the same causes of nickel exposure as their patients, except for coins (9). In an attempt to further identify and characterize sources that may result in nickel allergy and dermatitis, we analysed items identified by nickel-allergic dermatitis patients as causative of nickel dermatitis by using the dimethylglyoxime (DMG) test.

Materials and Methods

Study population

Between October 2007 and October 2009, 1489 (32.2% men and 67.8% women) dermatitis patients aged 7–93 years were patch tested for nickel allergy. Testing was performed with nickel sulfate 5% in petrolatum using Finn Chambers® (8 mm Epitest Ltd; Oy, Finland) on Scanpor® tape (Norgesplaster A/S, Alpharma, Vennesla, Norway). The patch tests were applied to the upper back and were occluded for 2 days. Readings were performed on D2, D3 or D4, and D7, according to the recommendation from the International Contact Dermatitis Research Group (21). Thus, homogeneous redness and infiltration in the entire test area was scored as a 1+ reaction. Homogeneous redness, infiltration and vesicles in the test area were scored as a 2+ reaction, and homogeneous redness, infiltration and coalescing vesicles in the test area as a 3+ reaction. A 1+, 2+ or 3+ reading was interpreted as a positive response. An irritant response, a doubtful (+?) reading or a negative reading was interpreted as a negative response.

Patients with positive nickel patch test reactions were asked by the treating physician about current exposures to metallic items. On the basis on the medical history, the physician judged whether nickel allergy was of current relevance, past relevance or unknown relevance. Nickel-allergic patients who had dermatitis with current relevance were encouraged to bring personal as well as occupational metallic items (that were in prolonged or repeated contact

with the skin) to the laboratory. Experienced nurses examined the items for nickel release by using the DMG test. They also asked patients about the year of purchase, or first possession, of the item under investigation, as well as the country of origin (Denmark, EU country, non-EU country) and the source of the item (shop, street market, gift, inheritance).

DMG testing

Testing for nickel release was performed with the DMG spot test in our laboratory. It was prepared by a hospital pharmacy in the Capital Region of Copenhagen. The test solutions were 1% DMG in alcohol and 10% ammonium hydroxide in water. All individual parts of the metallic items that came into direct and prolonged skin contact were examined. The test was administered by placing two drops of each solution in succession on a white cotton-wool-tipped applicator that was rubbed for up to 20 seconds against the test object. A positive reaction was indicated by a pink colouration of the applicator, and a negative reaction was registered when no colour change was observed. Doubtful reactions were retested, and if the reaction remained doubtful, it was considered negative.

Statistical analysis

The distribution of age was assessed by the Kolmogorov–Smirnov test. Data analyses were performed using SPSS (SPSS Inc., Chicago, IL, USA) for Windows (release 15.0).

Results

The overall prevalence of positive patch test reactions to nickel was 18.3% among 1849 dermatitis patients (5.8% among men and 24.3% among women). The MOAHLFA index is presented in Table 1. Among 273 patients with nickel allergy, 95 (34.8%) were judged to have nickel allergy of

Table 1. MOAHLFA index in dermatitis patients nickel patch tested at Gentofte Hospital during 2007–2009

Frequency of variables	All patients (<i>n</i> = 1489), % (<i>n</i>)	Nickel-allergic patients (<i>n</i> = 273), % (<i>n</i>)	Nickel-allergic patients who had metallic items investigated (<i>n</i> = 70), % (<i>n</i> / <i>n</i> _{total})
MOAHLFA index*			
Males	32.2 (480)	10.3 (28)	11.4 (8/70)
Occupational dermatitis	23.5 (350)	26.7 (73)	32.9 (23/70)
Atopic dermatitis	18.4 (274)	13.2 (36)	8.6 (6/70)
Hand dermatitis	41.6 (619)	44.7 (122)	44.3 (31/70)
Leg ulcers	2.2 (33)	3.3 (9)	4.3 (3/70)
Facial dermatitis	25.1 (374)	23.4 (64)	25.7 (18/70)
Age >40 years	65.6 (977)	65.6 (179)	60.0 (42/70)

*The MOAHLFA index stands for male, occupational dermatitis, atopic dermatitis, hand dermatitis, leg ulcers, facial dermatitis and age above 40 years. It shows the characteristics of patients tested at a patch test clinic and may be used for comparison (22).

current relevance (46.5% among men and 33.4% among women). The age of the study population was not normally distributed as assessed by the Kolmogorov–Smirnov test ($P = 0.045$). The median age was 46 years (the interquartile range was 25 years).

Among 95 nickel-allergic dermatitis patients, 70 (73.7%) had metallic items investigated for nickel release by the DMG test. A total of 151 items were investigated, and 66 (43.7%) gave positive DMG test reactions. We found that many different items gave positive DMG test reactions, and that these

belonged to both the occupational and the consumer good categories (e.g. keys, watches, knitting needles, scissors and work tools). When we looked at individual types of items (Table 2), we found that all tested hair clasps, keys and key chains gave positive DMG test reactions, and that nearly all tested spectacle frames (75%), knitting needles (80.0%), tools (75.0%) and belt buckles (66.7%) gave positive DMG test reactions. Finally, smaller proportions of watches (41.7%), mobile phones (30.7%), scissors (30.0%) and earrings (5.0%) gave positive DMG test reactions (Table 2).

Most DMG-positive items were acquired or purchased after the introduction of the Danish nickel regulation (1990) and the EU Nickel Directive (1994) (Table 3). Thus, among 47 DMG-positive items for which the year of purchase was registered, 93.6% were purchased after 1994. Most items were purchased recently. Mobile phones were registered for the period 2003–2009. Other items were randomly spread over the years (Table 3). Most products (90%) were purchased in stores in Denmark. Only one item was registered as a gift and one item as inherited.

Discussion

This study showed that nearly half of 151 metallic items retrieved from nickel-allergic dermatitis patients from a tertiary referral centre released nickel when examined by the DMG test. The sample was fairly representative, as 73% of dermatitis patients with nickel allergy of current relevance

Table 2. Type of metallic item that resulted in positive dimethylglyoxime (DMG) test reactions

Item	Proportion of positive DMG test reactions, % (n/66)	Proportion of positive DMG test reactions of all tested in that category, % (n/n _{total})
Mobile phones	12.1 (8)	30.7 (8/26)
Spectacle frames	9.1 (6)	75.0 (6/8)
Hair clasps	9.1 (6)	100 (6/6)
Watches	7.6 (5)	41.7 (5/12)
Keys	7.6 (5)	100 (5/5)
Necklaces	6.1 (4)	26.7 (4/15)
Knitting needles	6.1 (4)	80.0 (4/5)
Work tools	4.5 (3)	75.0 (3/4)
Scissors	4.5 (3)	30.0 (3/10)
Belt buckles	3.0 (2)	66.7 (2/3)
Key chains	3.0 (2)	100 (2/2)
Ear rings	1.5 (1)	5.0 (1/20)
Pens	1.5 (1)	100 (1/1)
Other or unknown	24.3 (16)	47.1 (16/34)
Total	100 (66)	—

Table 3. Self-reported information on 66 dimethylglyoxime-positive items from nickel-allergic patients seen at Gentofte Hospital 2007–2009

Year of purchase/ possession	% (n)	Type of item (number)	Country of purchase (number)	Source (number)
1972	1.5 (1)	Necklace (1)	DK (1)	Gift (1)
1977	1.5 (1)	Necklace (1)	DK (1)	Inheritance (1)
1990	1.5 (1)	Watch (1)	DK (1)	Shop (1)
1998	3.0 (2)	Watch (1)	DK (2)	Shop (2)
2000	3.0 (2)	Spectacle frames (1), knitting needle (1)	DK (2)	Shop (2)
2003	3.0 (2)	Mobile phone (2)	DK (2)	Shop (2)
2004	4.5 (3)	Scissors (1)	DK (2), EU (1)	Shop (3)
2005	6.1 (4)	Mobile phone (1), knitting needle (1), spectacle frames (1), scissors (1)	DK (4)	Shop (2)
2006	4.5 (3)	Spectacle frames (1), belt buckle (1)	DK (2), EU (1)	Shop (1), market (1)
2007	9.1 (6)	Watch (1), belt buckle (1), spectacle frames (1), hair clasp (3)	DK (5), EU (1)	Shop (5)
2008	24.2 (16)	Watch (2), earring (1), knitting needle (1), hair clasp (3), mobile phone (3), necklace (2), work tools (2)	DK (13), non-EU (2)	Shop (13), market (1)
2009	9.1 (6)	Pen (1), mobile phone (1), key (1)	DK (5), EU (1)	Shop (3)
Unknown year	28.8 (19)	Work tools (1), knitting needle (1), scissors (1), key (4), key chain (2), mobile phone (1), spectacle frames (2)	DK (14)	Shop (5)
Total	100 (66)	See Table 2	DK (54), EU (4), non-EU (2)	Shop (40), market (2), gift (1), inheritance (1)

DK, Denmark.

had objects examined. The overall frequency of DMG-positive items was much higher than the frequencies found in DMG test studies where random objects were examined (11, 14, 15, 23–25). This indicates that aimed DMG testing may increase the frequency of positive test reactions, and underscores the fact that the DMG test may serve as a useful screening tool in dermatology clinics. We are aware of only one other study that systematically investigated nickel release from metallic consumer objects retrieved from dermatitis patients (26). In 1998, Ingber et al. showed that 36.8% of 1037 metallic consumer items (e.g. watches, rings, earrings and spectacle frames) collected from 500 random Israeli patients gave positive DMG test reactions (26). The authors noted that 90% of patients with known nickel allergy were aware of their sensitivity but continued to wear at least one piece of nickel-releasing jewellery (26).

Overall, only a few occupational items such as work tools were analysed for nickel release in the current study. However, skin contact with scissors, mobile phones and keys was, in some cases, occupational. We were unable to identify the proportion of items that came from patients' work environments. Lidén used the DMG test to investigate work tools and equipment in different occupations, and found nickel release from various objects (10). Subsequently, Lidén et al. investigated the proportion of DMG-test positive work tools in Sweden, and found that 27% of 565 handheld work tools were positive (11). Furthermore, the Swedish research group and researchers from the UK have shown that nickel is deposited on the skin in certain risk occupations (12, 27). Recently, a Danish DMG test study found nickel release from 1 of 200 scissors and 7 of 13 crochet hooks used in hairdressers' salons (8). Thus, excessive nickel release from work items should continuously be suspected in patients with nickel allergy and dermatitis, and the DMG test should be performed when possible.

The highest rates of DMG-positive items observed within each category were found for hair clasps (6/6), keys (5/5), key chains (2/2), knitting needles (4/5) and spectacle frames (6/8) (Table 2). The high frequency of DMG-positive hair clasps was in line with results from a recent study performed in Copenhagen where, respectively, 19% and 79% of hair clasps intended for adults and children were DMG-positive (15). Furthermore, a DMG test study from Stockholm performed in 2002–2003 showed that 57% of hair clasps were DMG-positive (14). A recent Danish case report described a woman with scalp dermatitis following the use of hair clasps, both new, inexpensive ones and expensive ones from a well-known Danish manufacturer (28). The hair clasp nickel problem should

be closely followed, as this may be a previously neglected cause of nickel sensitization, especially in children. The high frequency of DMG-positive spectacle frames was surprising, although high levels of nickel release from these have been found by others. In 1998, Walsh and Mitchell investigated nickel release from 373 new and 50 used spectacle frames by using the DMG test (29). They found that 96% of the used frames tested positive and that 24.5% of the new frames tested positive. In further studies from 2002, they found that 6.5% of 395 new spectacle frames gave positive DMG test reactions (30). DMG-positive spectacle frames from the present study were purchased in 2000, 2005, 2006 and 2007, respectively (for two, the year of purchase was unknown) (Table 2). It is possible that a coating had worn off, but no details were recorded.

A fairly large number of mobile phones ($n = 26$) were analysed over the 2-year period, and about 30% were positive. This finding is in line with previous studies and reports that have documented frequent nickel release from mobile phones. A Canadian study investigated 22 random mobile phones from eight different manufacturers with the DMG test, and found that 10 of these gave positive test reactions (31). In 2008, we visited two international mobile phone manufacturers in Denmark and performed the DMG test on-site on 41 mobile phones (24). We found that eight (19.5%) phones gave positive DMG test reactions, and learned that one cannot generalize results from DMG testing and assume that other identical phones will give the same result, as many different suppliers of components are used by the companies (24). One DMG-positive phone had been produced in more than 100 million copies worldwide (24). An evening programme about mobile phone dermatitis was broadcast on national Danish television (the Danish Broadcasting Corporation). The station performed its own investigation preceding this programme, and found that 13 (26%) of 50 mobile phones released more than $0.5 \mu\text{g}$ nickel/ cm^2/week (13). In January 2009, the Danish Minister of Environment officially suggested that mobile phones should be covered by the EU Nickel Directive. The European Commission agreed to this shortly afterwards (13). However, new cases of mobile phone dermatitis frequently occur, and we believe that the mobile phone nickel problem should also be carefully followed to determine whether the new recommendations are being followed.

We have previously wondered whether consumer items acquired from countries without regulations on nickel exposure, and imported by patients for personal use, could be a quantitative problem in Denmark. However, this study showed that only 2 of 54 DMG-positive items had been purchased

outside the EU zone (Table 3). Also, we have wondered whether subjects may develop nickel allergy and dermatitis caused by inherited items or items acquired before the 1990 Danish nickel regulation and the 1994 EU Nickel Directive were introduced. However, this seemed to be only a minor problem, as 93% of objects were purchased/acquired after 1994, and only one item had been inherited (Table 3). Taken together, the nickel problem in Denmark seems to be caused by excessive nickel exposure in the past as well as presently.

The value of the DMG test for predicting the risk of nickel dermatitis has previously been evaluated (19). A Danish study showed that metallic alloys that resulted in dermatitis in most nickel-allergic dermatitis patients following patch testing released more than 0.5 µg nickel/cm²/week in chemical analysis and resulted in positive DMG test reactions (19, 32). The DMG test has recently been validated (33). The sensitivity of the DMG test was 59.3% and the specificity was 97.5% (33). The sensitivity describes the proportion of true-positive reactions that were correctly identified by the DMG test, i.e. the probability that the DMG test is positive given that the metal object under investigation releases >0.5 µg nickel/cm²/week. Thus, the proportion of earrings that release >0.5 µg nickel/cm²/week may be even higher than we estimated in this study.

Taken together, these findings show that DMG testing is valuable as a screening test for nickel release and should be used to identify relevant exposures in nickel-allergic patients. Mainly consumer items, but also work tools used in an occupational setting, released nickel in dermatitis patients. Although this study confirmed 'risk items' shown in previous studies, the low sample size prevents quantitative analysis of the type and magnitude of residual nickel exposure following nickel regulation. A follow-up study could be interesting to detect changing exposure trends over the years.

References

1. Thyssen J P, Linneberg A, Menné T, Johansen J D. The epidemiology of contact allergy in the general population – prevalence and main findings. *Contact Dermatitis* 2007; 57: 287–299.
2. Thyssen J P, Linneberg A, Menné T, Nielsen N H, Johansen J D. Contact allergy to allergens of the TRUE-test (panels 1 and 2) has decreased modestly in the general population. *Br J Dermatol* 2009; 161: 1124–1129.
3. ESSCA Writing Group. The European baseline series in 10 European countries, 2005/2006 – results of the European Surveillance System of Contact Allergies (ESSCA). *Contact Dermatitis* 2009; 61: 31–38.
4. Thyssen J P, Menné T, Schnuch A et al. Acceptable risk of contact allergy in the general population assessed by CE-DUR – a method to detect and categorize contact allergy epidemics based on patient data. *Regul Toxicol Pharmacol* 2009; 54: 183–187.
5. Schnuch A, Geier J, Lessmann H, Uter W. Decrease in nickel sensitization in young patients – successful intervention through nickel exposure regulation? Results of the IVDK, 1992–2001. *Hautarzt* 2003; 54: 626–632.
6. Thyssen J P, Johansen J D, Menné T, Nielsen N H, Linneberg A. Nickel allergy in Danish women before and after nickel regulation. *N Engl J Med* 2009; 360: 2259–2260.
7. Thyssen J P, Johansen J D, Carlsen B C, Menné T. Prevalence of nickel and cobalt allergy among female patients with dermatitis before and after Danish government regulation: a 23-year retrospective study. *J Am Acad Dermatol* 2009; 61: 799–805.
8. Thyssen J P, Milting K, Bregnhøj A, Sosted H, Duus J J, Menné T. Nickel allergy in patch-tested female hairdressers and assessment of nickel release from hairdressers' scissors and crochet hooks. *Contact Dermatitis* 2009; 61: 281–286.
9. Thyssen J P, Hald M, Avnstrøm C 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.
10. Lidén C. Occupational contact dermatitis due to nickel allergy. *Sci Total Environ* 1994; 148: 283–285.
11. Lidén C, Rönndell E, Skare L, Nalbanti A. Nickel release from tools on the Swedish market. *Contact Dermatitis* 1998; 39: 127–131.
12. 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; 58: 347–354.
13. Thyssen J P, Johansen J D. Mobile phones are now covered by the European Union Nickel Directive. *Contact Dermatitis* 2009; 61: 57.
14. Lidén C, Norberg K. Nickel on the Swedish market. Follow-up after implementation of the Nickel Directive. *Contact Dermatitis* 2005; 52: 29–35.
15. Thyssen J P, Menné T, Johansen J D. Nickel release from inexpensive jewelry and hair clasps purchased in an EU country – are consumers sufficiently protected from nickel exposure? *Sci Total Environ* 2009; 407: 5315–5318.
16. Bryld L E, Hindsberger C, Kyvik K O, Agner T, Menné T. Genetic factors in nickel allergy evaluated in a population-based female twin sample. *J Invest Dermatol* 2004; 123: 1025–1029.
17. Menné T, Holm N V. Nickel allergy in a female twin population. *Int J Dermatol* 1983; 22: 22–28.
18. Novak N, Baurecht H, Schäfer T et al. Loss-of-function mutations in the filaggrin gene and allergic contact sensitization to nickel. *J Invest Dermatol* 2008; 128: 1430–1435.
19. Menné T, Brandup F, Thestrup-Pedersen K et al. Patch test reactivity to nickel alloys. *Contact Dermatitis* 1987; 16: 255–259.
20. Thyssen J P, Johansen J D, Menné T et al. A spot test for detection of cobalt release – early experience and findings. *Contact Dermatitis* 2010; 63: 63–69.
21. Wilkinson D S, Fregert S, Magnusson B et al. Terminology of contact dermatitis. *Acta Derm Venereol* 1970; 50: 287–292.
22. Uter W, Gefeller O, Geier J, Schnuch A. Changes of the patch test population (MOAHLFA index) in long-term participants of the Information Network of Departments of Dermatology, 1999–2006. *Contact Dermatitis* 2008; 59: 56–57.
23. Lidén C, Johnsson S. Nickel on the Swedish market before the Nickel Directive. *Contact Dermatitis* 2001; 44: 7–12.
24. Thyssen J P, Johansen J D, Zachariae C, Menné T. The outcome of dimethylglyoxime testing in a sample of cell phones in Denmark. *Contact Dermatitis* 2008; 59: 38–42.
25. Thyssen J P, Maibach H I. Nickel release from earrings purchased in the United States: the San Francisco earring study. *J Am Acad Dermatol* 2008; 58: 1000–1005.

26. Ingber A, Klein S, David M. The nickel released from jewelry in Israel and its clinical relevance. *Contact Dermatitis* 1998; 39: 195–197.
27. Staton I, Ma R, Evans N, Hutchinson R W, McLeod C W, Gawkrödger D J. Dermal nickel exposure associated with coin handling and in various occupational settings: assessment using a newly developed finger immersion method. *Br J Dermatol* 2006; 154: 658–664.
28. Thyssen J P, Jensen P, Johansen J D, Menné T. Contact dermatitis caused by nickel release from hair clasps purchased in a country covered by the EU Nickel Directive. *Contact Dermatitis* 2009; 60: 180–181.
29. Walsh G, Mitchell J W C. The leaching of nickel from new and used metal spectacle frames. *Ophthalmic Physiol Opt* 1998; 18: 372–377.
30. Walsh G, Mitchell J W C. Free surface nickel in CE-marked and non-CE-marked spectacle frames. *Ophthalmic Physiol Opt* 2002; 22: 166–171.
31. Bercovitch L, Luo J. Cellphone contact dermatitis with nickel allergy. *Can Med Assoc J* 2008; 178: 23–24.
32. Menné T, Andersen K E, Kaaber K et al. Evaluation of the dimethylglyoxime stick test for the detection of nickel. *Derm Beruf Umwelt* 1987; 35: 128–130.
33. Thyssen J P, Skare L, Lundgren L et al. Sensitivity and specificity of the nickel spot (dimethylglyoxime) test. *Contact Dermatitis* 2010; 62: 279–288.

Address:

Jacob Pontoppidan Thyssen, MD, PhD
Department of Dermato-Allergology
National Allergy Research Centre
Copenhagen University Hospital Gentofte
University of Copenhagen
Ledreborg Allé 40 1
2820 Gentofte
Denmark
Tel: +45 3977 7307
Fax: +45 3977 7118
e-mail: jacpth01@geh.regionh.dk