

Nickel

Rachel Kornik and Kathryn A. Zug

SO FREQUENTLY POSITIVE in patch-test populations, so commonly suspected from clinical history, this long-standing top allergen seems old news. Because of its common frequency and many highly characteristic patterns of clinical skin disease, some of us have been guilty of often dismissing nickel allergy with a pedestrian “ho hum.” But with the rising incidence of nickel allergy in the United States and elsewhere, high nickel sensitization rates documented in children, and a resurgent issue of biomedical device complications (specifically, nickel allergy) due to metal, to dismiss nickel’s importance and relevance to public health and skin disease would be a mistake. Nickel is an allergen whose time has come—yet again! Let us tell you more about nickel and why we should refocus our attention on it and highlight nickel as Allergen of the Year.

A Short History of Nickel

Nickel is a ubiquitous metal used in a wide range of products in the transportation and aerospace industries and for military, health, household, and architectural applications. It has been found in metallic artifacts dating back some 2,000 years but was first identified in 1751 by Swedish chemist Baron Axel Fredrik.^{1,2} Upon the discovery of a feasible extraction method in the nineteenth century, nickel was soon being used in large amounts because of its attractive qualities, chief among them corrosion resistance and durability. In addition, nickel alloys readily with many other metals, lending them these properties.^{2,3}

As the production of nickel alloys and nickel-containing goods increased, so did reports of allergy. The first case of “galvanization eczema” was described by Blascho in the late 1880s.⁴ At that time, nickel dermatitis was observed in workers of the electroplating and mining industries. Though initially a cause of occupational

dermatitis, nickel allergy shifted to affect the general population as nickel was incorporated into products such as suspenders, zippers and snaps, and jewelry that had prolonged contact with the skin.^{4,5} The prevalence and etiology of nickel sensitization tend to reflect societal trends; nickel allergy was noted to decrease during World War II when imports were diminished and then rose owing to the availability and popularity of nickel suspenders in the 1950s.^{6,7} Blue-jean buttons were the primary culprits in the 1970s.^{4,8} Jewelry and especially ear piercing at an early age (and the recent trend of an increasing number of other body piercings) are consistently linked to the rise in nickel sensitization in the recent decade.^{4,7}

Currently, nickel allergy is the most common cause of contact dermatitis in the industrial world, particularly affecting females.^{5,7,9–13} Several studies have examined the striking discrepancy of sensitization incidence to nickel in females versus males and have associated this with the increased popularity of ear piercing.^{14–16} Moreover, nickel allergy is on the rise in the United States, an increase largely attributed to the increasing rate of allergy in females.¹³ The most recent patch-test data from the North American Contact Dermatitis Group from 2003 to 2004 reveals that 18.8% of patients from this primarily referral population are sensitized to nickel,¹³ a significant increase from the 10.5% reported from 1985 to 1990.¹⁷ Europe had similarly high rates of nickel allergy^{18,19}; however, because of laws regulating nickel products, this fortunately appears to be decreasing in the younger population.

Regulating Nickel

In 1992, in an effort to quell the rising rates of nickel dermatitis, the Danish Ministry of Environment implemented legislation to regulate nickel exposure to products in prolonged contact with the skin.^{20,21} The European Union followed shortly afterward with the Nickel Directive (1994). This directive limited the nickel release threshold from alloys and nickel-plated objects in prolonged contact with the skin to 0.05 µg/cm² per week

From the Dartmouth Hitchcock Medical Center, Lebanon, NH, and the Dartmouth Medical School, Hanover, NH.

Reprints not available.

DOI 10.2310/6620.2008.07082

and the nickel content of post assemblies (material inserted into pierced parts of the body) to less than 0.05%.²² The legislation was recently revised for post assemblies, amending the content limit of 0.05% to a migration limit of 0.2 $\mu\text{g}/\text{cm}^2$ per week²³ because it is the ability of a substance to release nickel ions, rather than the actual nickel content, that determines the risk of sensitization.^{24,25} The allowed rate of nickel release for post assemblies differs from that for items intended to be next to the surface of skin, such as jewelry, to reflect the increased nickel release in blood plasma compared to the artificial sweat used in sensitization studies. Despite this lower threshold, it is inevitable that a small proportion of sensitized individuals capable of reacting to a very low nickel concentration will continue to react.²⁴ Nevertheless, evidence thus far suggests that the initiative has been successful in reducing nickel sensitization in a younger population.^{18–20} A study by Jensen and colleagues reported in 2002 investigated the prevalence of nickel allergy in Danish schoolgirls to determine if the prevalence was decreased in girls who had their ears pierced subsequent to nickel exposure regulations (1992) as compared to those who had their ears pierced prior to the regulations. The younger girls had significantly less nickel sensitization as detected by patch testing (5.7% vs 19%); this considerable decrease in nickel allergy is most likely explained by these regulations.²⁰

Biomedical Devices

Reports of dermatitis near or at sites of endoprostheses^{26,27} and from dental and orthodontic^{28–30} treatments have peppered the medical literature for years although systemic or localized reactions to medical-grade stainless steel is quite uncommon.^{11,31,32} During the production of stainless steel, a crystal lattice structure forms, locking in the metals and decreasing the likelihood of sensitization.¹¹

Consultation requests from orthopedic surgeons and (less frequently) orthodontists in regard to the safety of permanent or semipermanent metal medical devices in the suspected nickel-sensitized individual continue rather frequently despite the fact that reactions to joint arthroplasty prostheses and orthodontic braces rarely cause a problem in the nickel-sensitized individual. A high variability of care no doubt results for these patients in terms of testing and recommendations, contributing to concern on the part of the patient and their referring physician and to increased health care costs. Medicolegal concerns likely contribute to testing consultations and, in

some instances of joint replacement, the selection of a more expensive and less durable option. As nickel allergy incidence increases, this problem also presumably will increase. An expert consensus panel guideline or evidence-based position paper on specific biomedical devices (joint arthroplasty prostheses, fixed implants, orthopedic braces, and stents) and nickel and other metal allergy is sorely needed.

The potential for complications due to nickel allergy and nickel in biomedical devices has understandably risen anew and come under more critical scrutiny owing to a report questioning the role of metal allergy in endovascular stenting procedures and in-stent restenosis. Can nickel allergy contribute to stent stenosis? Köster and colleagues stimulated this debate with an article in *The Lancet* in 2000 revealing the results of a retrospective study of 131 patients suspected of coronary in-stent restenosis 6 months following 316L stainless steel stent placement. Patch testing was performed 2 months after angioplasty, and not prior to the procedure. Of 131 patients (109 men and 22 women) who were patch-tested, there were 11 positive patch-test reactions in 10 (8%) of the patients. Important, and as noted in other studies of nickel allergy, the clinical history was not predictive of a positive or negative patch-test result. Other risk factors for restenosis were similar among patients with positive and negative patch-test results. All 10 patients with a positive patch-test reaction to metal (7 to nickel and 4 to molybdenum) had in-stent restenosis associated with clinical symptoms, a higher frequency of restenosis than in patients without metal allergy, thus suggesting that allergy to metals, nickel in particular, plays a relevant role in inflammatory fibroproliferatory restenosis.³³ However, Köster and colleagues did not investigate possible metal allergy in patients without suspected re-stenosis, and their study thus lacked a critical control group.³⁴ Since this provocative study, other investigations of this important issue have been reported.^{35–37} Iijima and colleagues, in their prospective study of 174 stented patients (109 restudied for initial placement and 65 restudied for in-stent restenosis), did note that patients with a recurrence of in-stent restenosis had a significantly higher positive patch-test reaction to metals, most commonly nickel and manganese. However, they found no correlation of metal allergy with restenosis after initial stent placement.³⁶ So far, the evidence confirming that nickel allergy contributes to stent restenosis remains in question. Large prospective clinical studies are needed.

Although much attention has been directed towards coronary stents, other stenting procedures have infre-

quently raised the question of complications due to nickel allergy. The evidence for complications is weak and remains on the case report level. For instance, a case report of early biliary stent occlusion thought to be directly related to nickel allergy was noted in the literature³⁸ in addition to a case of generalized dermatitis after endovascular stenting of an abdominal aortic aneurysm.³⁹ The stents used in the above-mentioned examples were composed of a nickel-titanium (NiTi) alloy. NiTi alloy contains nearly equal mixtures of nickel and titanium and is coveted for its “shape memory” properties.⁴⁰ NiTi alloy is used in many biomedical applications where consistency of shape and stress are essential, including dental devices, stents, blood filters, and bone staples.⁴⁰ One risk assessment study using guinea pig sensitization testing of the alloy did not reveal any tissue reaction, and the nickel release was deemed to be within acceptable limits.⁴⁰ Yet this study does point out that the findings cannot be extrapolated to all clinical conditions.

Nickel is commonly used in orthodontics without difficulty, and preorthodontic testing for metal allergy is not routine. However, for patients with contact allergy to orthodontics, nickel is the most common allergen.³² Certain flexible titanium-nickel arch wires used in orthodontics are thought to release increased amounts of nickel as compared to stainless steel, and one article recommends avoiding them in patients known to be nickel sensitive.³²

Dietary Nickel and Oral Hyposensitization

Systemic contact dermatitis from oral ingestion of nickel in the nickel-sensitive individual is a known clinical entity and has been demonstrated by dose-response studies of nickel administration in sensitized subjects.^{41,42} Evidence to support the contribution of dietary nickel to dermatitis exists from studies that have treated nickel dermatitis, particularly vesicular hand eczema, with low-nickel diets^{43,44} and/or the chelating agent disulfiram.⁴⁵ Nickel is found in natural foods such as legumes, nuts, grains, potatoes, chocolate, and fish.^{46,47} Daily nickel intake can vary substantially, depending on the cooking utensils used, whether food is grown in nickel-rich soil, whether the food is fresh or canned, and the nickel level of water ingested.^{11,47} Nickel may also be found in medications, vitamins, and herbal remedies. An example of this is a prescription homeopathic medication for the treatment of acne. Each tablet of Acunol (Plymouth Pharmaceuticals, Inc., Tulsa, OK), an oral acne medication,

contains 0.5 mg of ionized nickel.⁴⁸ The daily dose more than doubles the amount of nickel people normally consume in the average diet (0.22 to 0.35 mg per day⁴² but as high as 0.9 mg per day⁴⁹). Jensen and colleagues, in a meta-analysis of systemic contact dermatitis following oral exposure to nickel, estimated that 1% of patients with allergy to nickel in the studies reviewed would react with a systemic reaction to the nickel content of a normal diet. Their calculations predicted that 10% would react to exposures to 0.55 to 0.89 mg of nickel.⁴²

Whereas decreasing oral nickel ingestion can control flares of dermatitis, perhaps oral nickel intake can actually aid in actually preventing sensitization from cutaneous nickel exposure through immune tolerance induction.^{50–52} Oral tolerance to nickel has been demonstrated in animal models^{53,54} as well as in some retrospective human studies investigating the rate of nickel allergy in young populations with dental braces.^{15,50} In vitro studies of stainless steel braces in artificial saliva demonstrate that metal ions are leached into saliva over time.⁵⁵ Case reports of systemic dermatitis from dental appliances support the conclusion that there is likely absorption of nickel from this nickel leaching.^{30,32,56} This absorption may plague few previously sensitized individuals but may more commonly induce immunologic tolerance to nickel in the previously unsensitized individual. Kerosuo and colleagues studied Finnish adolescents and the effect of age, gender, onset, duration and specific orthodontic treatment, and age of ear piercing on the incidence of nickel sensitization. One striking finding of this study was that 35% of the girls who had ear piercing prior to orthodontic treatment were nickel allergic versus none of the girls who had fixed orthodontic treatment prior to ear piercing.¹⁵ The immune mediators of oral tolerance are beginning to be elucidated, but clearly more research into this area is needed.⁵²

Nickel Allergy in Children

Numerous recent single and multicenter international studies of children have confirmed that nickel is far and away the number-one contact allergen in patch-tested patient populations, ranging in incidence from 20 to 33%.^{57–61} In these studies, the reported relevance of a positive patch-test result varies from little relevance to high relevance, and conclusions regarding relevance are regrettably limited. Of 391 children aged 18 years or less who were patch-tested between 2001 and 2004 by the North American Contact Dermatitis Group, 28% had a positive

patch-test to nickel, and 26% were deemed to have a nickel allergy of either current or past relevance.⁶² Not only is nickel allergy prevalent in the young population, NACDG data show that as in adult females, nickel sensitization in girls is on the rise.¹³

Bruckner and colleagues asked the question, "Does sensitization begin in infancy?" In their study of asymptomatic children and contact allergy, nickel was the most common positive allergen; 12.9% of children aged 6.0 to 67.5 months reacted positively to nickel.⁶³ Remarkable and concerning, children younger than 16 months accounted for 7 of 11 of those positive results to nickel.⁶³ Because nickel may be an irritant, the question of interpreting an irritant versus an allergic result arises commonly although jewelry and fasteners are potential and likely sources of exposure for this age group. Where does this well-documented epidemiology of nickel sensitization lead us? Kütting and colleagues make a case for prevention, recommending that ear piercing be delayed until after 10 years of age⁶⁴ (presumably to allow for the development of immune tolerance).

Prevention

Contact allergy to nickel can range from a nuisance to a frustrating, itch-ridden, and vexatious chronic problem that interferes with sleep, activities of daily living, work, and play. Persistent hand dermatitis, systemic contact dermatitis, and nickel allergy with auto-eczematization are some fairly common and pervasive troublesome examples.

Nickel is ubiquitous and practically unavoidable in everyday life; from coins and tools^{65,66} to pant snaps⁸ and cosmetics,^{11,67} nickel can be found in a variety of both obvious and unlikely products. Prolonged and often unrecognized exposure to sensitizing amounts of nickel nowadays occurs often at a young age in North America and is practically inevitable. Preventing sensitization or implementing strategies to reduce sensitization are likely the most effective methods of reducing the considerable effects of nickel allergy. The development of expert consensus guidelines or an evidence-based position paper on the issue of biomedical devices is another practical relevant proposition whose time has come. Regulation of nickel release from consumer goods that involve contact with skin would be a challenging but potentially successful solution to our current nickel allergy predicament.

Nickel Tidbits

- Expensive white or yellow gold can contain enough nickel to cause sensitization when used in ear piercing. Beware of earrings labeled "hypoallergenic." The Food and Drug Administration says, "There are no Federal standards or definitions that govern the use of the term hypoallergenic. The term hypoallergenic means whatever a particular company wants it to mean."⁶⁸
- Some high-nickel-content foods (in micrograms [μg] of nickel per gram of food) are cocoa (10 μg); licorice (4.4 μg); margarine (4 μg); peanuts (2.9 μg); brown lentils (1.9 μg); walnuts, almonds, or hazelnuts (1.5 μg); and French beans or beans (1.4 μg).⁴⁶
- In 2003 to 2004, 25% of women patch-tested by the North American Contact Dermatitis Group (NACDG) were allergic to nickel, compared to only 8% of men.¹³ Ear piercing was deemed the most likely reason.
- Adolescents constitute a significant portion of the patch-test population allergic to nickel; 36% of girls (aged < 18 years) and 15% of boys patch-tested by the NACDG from 2001 to 2004 had clinically relevant allergy.¹³

References

1. Ostendorp P. Nickel: hidden in plain sight. 2001; [7 screens]. Available at: <http://www.dartmouth.edu/~toxmetal/TXSHni.shtml> (accessed Sept 5, 2007).
2. Wekstoff/Nickel: Materialwissenschaft und Werkstofftechnik 2002; 33:107–8.
3. Savin J. The rise and fall of nickel allergy. *J Cosmet Dermatol* 2003; 2:57.
4. Thyssen JP, Johansen JD, Menné T. Contact allergy epidemics and their controls. *Contact Dermatitis* 2007;56:185–95.
5. Hostynek JJ. Sensitization to nickel: etiology, epidemiology, immune reactions, prevention, and therapy. *Rev Environ Health* 2006;21:253–80.
6. Marcussen PV. The rise in incidence of nickel sensitivity. *Br J Dermatol* 1959;71:97–101.
7. Meding B. Epidemiology of nickel allergy. *J Environ Monit* 2003;5: 188–9.
8. Brandrup F, Larsen FS. Nickel dermatitis provoked by buttons in blue jeans. *Contact Dermatitis* 1979;5:148–50.
9. Machovcova A, Dastychova E, Kostalova D, et al. Common contact sensitizers in the Czech Republic. Patch test results in 12,058 patients with suspected contact dermatitis. *Contact Dermatitis* 2005;53:162–6.
10. Uter W, Hegewald J, Aberer W, 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; 53:136–45.
11. Rietschel RL, Fowler JF, editors. Contact dermatitis and other reactions to metals. In: *Fisher's contact dermatitis*. 4th ed. Baltimore: Williams & Wilkins; 1995. p. 808–85.

12. Freireich-Astman M, David M, Trattner A. Standard patch test results in patients with contact dermatitis in Israel: age and sex differences. *Contact Dermatitis* 2007;56:103–7.
13. Rietschel RL, Fowler JF, Warshaw EM, et al. Detection of nickel sensitivity has increased in North America patch test patients. 2007. [DOI].
14. Kalimo K, Mattila L, Kautiainen H. Nickel allergy and orthodontic treatment. *J Eur Acad Dermatol Venereol* 2004;18:543–5.
15. Kerosuo H, Kullaa A, Kerosuo E, et al. Nickel allergy in adolescents in relation to orthodontic treatment and piercing of ears. *Am J Orthod Dentofacial Orthop* 1996;109:148–54.
16. Larsson-Stymne B, Widstrom L. Ear piercing—a cause of nickel allergy in schoolgirls? *Contact Dermatitis* 1985;13:289–93.
17. Marks JG, Jr, Belsito DV, DeLeo VA, et al. North American Contact Dermatitis Group patch-test results, 1996–1998. *Arch Dermatol* 2000;136:272–3.
18. Johansen J, Menné T, Christophersen J, et al. Changes in the pattern of sensitization to common contact allergens in Denmark between 1985–86 and 1997–98, with a special view to the effect of preventive strategies. *Br J Dermatol* 2000;142:490–5.
19. Lindberg M, Edman B, Fischer T, Stenberg B. Time trends in Swedish patch test data from 1992 to 2000. A multi-centre study based on age- and sex-adjusted results of the Swedish standard series. *Contact Dermatitis* 2007;56:205–10.
20. Jensen CS, Lisby S, Baadsgaard O, et al. Decrease in nickel sensitization in a Danish schoolgirl population with ears pierced after implementation of a nickel-exposure regulation. *Br J Dermatol* 2002;146:636–42.
21. Danish Ministry of Environment. Statutory Order of the Danish Ministry of Environment regarding prohibition of sale and labeling of certain nickel containing products. Statutory Order no. 854, 16 Dec 1991.
22. European Parliament and Council Directive 94/27/EEC. The European Directive restricting the use of nickel. 1994; [4 screens]. Available at: <http://www.teg.co.uk/teg/nickel/94-27-EC.htm> (accessed September 5, 2007).
23. Commission Directive 2004/96/EC of September 2004 amending Council Directive 76/769/EEC as regards restriction on the marketing and use of nickel for piercing post assemblies for the purpose of adapting its Annex I to technical progress. 2004; [screens]. Available at: http://eur-lex.europa.eu/LexUriServ/site/en/oj/2004/L_301/L_30120040928en00510052.pdf (accessed September 5, 2007).
24. Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE): Opinion of CSTEE on the LGC's report on "risk of sensitisation of humans to nickel by piercing post assemblies": Final report, 31 March 2003. Contract No.: EDT/FIF.2001592. Adopted by the CSTEE during the 40th plenary meeting of 12–13 November 2003; [7 screens]. Available at: http://ec.europa.eu/health/ph_risk/committees/sct/documents/out211_en.pdf (accessed August 30, 2007).
25. Liden C, Norberg K. Nickel on the Swedish market. Follow-up after implementation of the Nickel Directive. *Contact Dermatitis* 2005;52:29–35.
26. Cramers M, Lucht U. Metal sensitivity in patients treated for tibial fractures with plates of stainless steel. *Acta Orthop Scand* 1977;48:245–9.
27. Kanerva L, Forstrom L. Allergic nickel and chromate hand dermatitis induced by orthopaedic metal implant. *Contact Dermatitis* 2001;44:103–4.
28. Kerosuo H, Kanerva L. Systemic contact dermatitis caused by nickel in a stainless steel orthodontic appliance. *Contact Dermatitis* 1997;36:112–3.
29. Staerkjaer L, Menné T. Nickel allergy and orthodontic treatment. *Eur J Orthod* 1990;12:284–9.
30. Schultz JC, Connelly E, Glesne L, Warshaw EM. Cutaneous and oral eruption from oral exposure to nickel in dental braces. *Dermatitis* 2004;15:154–7.
31. Dermatitis from metals used in medical devices and implants. In: Rietschel R, Fowler JF, editors. *Fisher's contact dermatitis*. 4th ed. Baltimore: Williams & Wilkins; 1995. p. 414–47.
32. Rahilly G, Price N. Nickel allergy and orthodontics. *J Orthod* 2003;30:171–4.
33. Köster R, Vieluf D, Kiehn M, et al. Nickel and molybdenum contact allergies in patients with coronary in-stent restenosis. *Lancet* 2000;356:1895–7.
34. Keane FM, Morris SD, Smith HR, Rycroft RJ. Allergy in coronary in-stent restenosis [author reply appears in *Lancet* 2001;357:1206–7]. *Lancet* 2001;357:1205–6.
35. Norgaz T, Hobikoglu G, Serdar ZA, et al. Is there a link between nickel allergy and coronary stent restenosis? *Tohoku J Exp Med* 2005;206:243–6.
36. Iijima R, Ikari Y, Amiya E, et al. The impact of metallic allergy on stent implantation: metal allergy and recurrence of in-stent restenosis. *Int J Cardiol* 2005;104:319–25.
37. Hillen U, Haude M, Erbel R, Goos M. Evaluation of metal allergies in patients with coronary stents. *Contact Dermatitis* 2002;47:353–6.
38. Khan SF, Sherbondy MA, Ormsby A, Velanovich V. Occlusion of metallic biliary stent related to nickel allergy. *Gastrointest Endosc* 2007;66:413–4.
39. Gimenez-Arnau A, Riambau V, Serra-Baldrich E, Camarasa JG. Metal-induced generalized pruriginous dermatitis and endovascular surgery. *Contact Dermatitis* 2000;43:35–40.
40. Wever DJ, Veldhuizen AG, Sanders MM, et al. Cytotoxic, allergic and genotoxic activity of a nickel-titanium alloy. *Biomaterials* 1997;18:1115–20.
41. Jensen CS, Menné T, Lisby S, et al. Experimental systemic contact dermatitis from nickel: a dose-response study. *Contact Dermatitis* 2003;49:124–32.
42. Jensen CS, Menné T, Johansen JD. Systemic contact dermatitis after oral exposure to nickel: a review with a modified meta-analysis. *Contact Dermatitis* 2006;54:79–86.
43. Veien NK, Hattel T, Laurberg G. Low nickel diet: an open, prospective trial. *J Am Acad Dermatol* 1993;29:1002–7.
44. Veien NK, Hattel T, Justesen O, Norholm A. Dietary treatment of nickel dermatitis. *Acta Derm Venereol* 1985;65:138–42.
45. Kaaber K, Menné T, Veien N, Hougaard P. Treatment of nickel dermatitis with Antabuse; a double blind study. *Contact Dermatitis* 1983;9:297–9.
46. Schiavino D, Nucera E, Alonzi C, et al. A clinical trial of oral hyposensitization in systemic allergy to nickel. *Int J Immunopathol Pharmacol* 2006;19:593–600.
47. Donma MM, Donma O. Arsenic and nickel: unavoidable constituents of our everyday diet. *Med Hypotheses* 2006;66:681.

48. Plymouth Pharmaceuticals [1 screen]. Available at: <http://www.plymouthpharmaceuticals.com/html/home.htm> (accessed Sept 3, 2007).
49. Flyvholm MA, Nielsen GD, Andersen A. Nickel content of food and estimation of dietary intake. *Z Lebensm Unters Forsch* 1984;179:427–31.
50. van Hoogstraten IM, Andersen KE, Von Blomberg BM, et al. Reduced frequency of nickel allergy upon oral nickel contact at an early age. *Clin Exp Immunol* 1991;85:441–5.
51. van Hoogstraten IM, von Blomberg BM, Boden D, et al. Effects of oral exposure to nickel or chromium on cutaneous sensitization. *Curr Probl Dermatol* 1991;20:237–41.
52. White JM, Goon AT, Jowsey IR, et al. Oral tolerance to contact allergens: a common occurrence? A review. *Contact Dermatitis* 2007;56:247–54.
53. van Hoogstraten IM, Boos C, Boden D, et al. Oral induction of tolerance to nickel sensitization in mice. *J Invest Dermatol* 1993;101:26–31.
54. van Hoogstraten IM, de Groot J, Boden D, et al. Development of a concomitant nickel and chromium sensitization model in the guinea pig. *Int Arch Allergy Immunol* 1992;97:258–66.
55. Jensen CS, Lisby S, Baadsgaard O, et al. Release of nickel ions from stainless steel alloys used in dental braces and their patch test reactivity in nickel-sensitive individuals. *Contact Dermatitis* 2003;48:300–4.
56. de Silva BD, Doherty VR. Nickel allergy from orthodontic appliances. *Contact Dermatitis* 2000;42:102–3.
57. Beattie PE, Green C, Lowe G, Lewis-Jones MS. Which children should we patch test? *Clin Exp Dermatol* 2007;32:6–11.
58. Wöhrl S, Hemmer W, Focke M, et al. Patch testing in children, adults, and the elderly: influence of age and sex on sensitization patterns. *Pediatr Dermatol* 2003;20:119–23.
59. Roul S, Ducombs G, Taieb A. Usefulness of the European standard series for patch testing in children. A 3-year single-centre study of 337 patients. *Contact Dermatitis* 1999;40:232–5.
60. Duarte I, Lazzarini R, Kobata CM. Contact dermatitis in adolescents. *Am J Contact Dermat* 2003;14:200–2.
61. Clayton TH, Wilkinson SM, Rawcliffe C, et al. 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;154:114–7.
62. Zug KA, McGinley-Smith DE, Belsito DV, et al. Pediatric contact dermatitis, The North American Contact Dermatitis Group (NACDG) experience 2001–2004 [abstract]. *Dermatitis* 2007;18:106.
63. Bruckner AL, Weston WL, Morelli JG. Does sensitization to contact allergens begin in infancy? *Pediatrics* 2000;105:e3.
64. Kütting B, Brehler R, Traupe H. Allergic contact dermatitis in children: strategies of prevention and risk management. *Eur J Dermatol* 2004;14:80–5.
65. Gollhausen R, Ring J. Allergy to coined money: nickel contact dermatitis in cashiers. *J Am Acad Dermatol* 1991;25:365–9.
66. Liden C, Rondell E, Skare L, Nalbanti A. Nickel release from tools on the Swedish market. *Contact Dermatitis* 1998;39:127–31.
67. van Ketel WG, Bruynzeel DP. Allergic contact dermatitis from nickel in eyeshadow. *Contact Dermatitis* 1989;21:355.
68. U.S. Food and Drug Administration Center for Food Safety and Applied Nutrition Office of Cosmetics and Colors. Hypoallergenic cosmetics. 1994; [1 screen]. Available at: <http://www.cfsan.fda.gov/~dms/cos-224.html> (accessed September 4, 2007).