

No skin reactions to mineral powders in nickel-sensitive subjects

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doi:10.1111/j.1600-0536.2012.02040.x

Summary

Background. Cosmetic products are known to be able to induce contact dermatitis. Contact dermatitis may also be induced by nickel, and it is estimated that up to 17% of women are allergic to nickel.

Objectives. The aim of the present study was to investigate whether nickel sensitized individuals react to make-up products containing pigments with nickel as an impurity.

Patients/Materials/Methods. Twenty-three individuals with a clinical history of nickel allergy and/or with positive patch test reactions to nickel were exposed to mineral make-up products and individual pigments dispersed in alkylbenzoate (50%) in small Finn Chambers[®] for 48 hr. The skin reactions were evaluated visually and with a non-invasive instrument that quantifies skin erythema.

Results. The results showed that 74% of the included individuals showed a visible reaction to the positive control nickel sulfate, and a significant correlation was found between the visual and instrumental readings. However, none of the nickel sensitive individuals reacted to the test products. A subgroup analysis of the 50% most sensitive individuals also confirmed the absence of skin reactions to the powders.

Conclusions. The bioavailability of the trace amounts of nickel in the particles was below the level needed to elicit an eczematous reaction in any of the nickel-sensitized individuals.

Key words: adverse reaction; eczema; make-up; nickel; pigment; skin penetration.

Cosmetic products are known to be able to induce contact dermatitis (1–3), fragrances and preservatives being the most common culprit sensitizing substances, along with weak irritants. Contact dermatitis may also be induced by nickel, which is common in women because of the wearing of earrings or other items of jewelry releasing nickel. The prevalence of metal allergy is high in the general population, and it is estimated that up to 17% of women

and 3% of men are allergic to nickel (4). Pigmented make-up products may also contain nickel and other metal allergens (5). Eyelid dermatitis has been observed among nickel allergic dermatitis patients following exposure to nickel containing mascara and eye shadow. However, an association between nickel eyelid dermatitis and nickel in make-up products remains controversial. Nickel is not added as such to make-up, but exists as an impurity among other ingredients, such as in iron oxides.

The risk of adverse skin reactions to make-up products containing pigments depends on their absorption and the release of allergens and irritants to the viable skin. Make-up products that are based on particulate matters, that is, so-called 'pure mineral make-up', have entered the market, and such products are promoted as being suitable for people with sensitive skin, as they are marketed as 'free from preservatives, fragrances' etc.

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Conflicts of interest: Letsfaceit Nordic AB, Sweden, sponsored the study but did not influence the study design or reporting. Marie Lodén, Gert Nilsson, Masomeh Parvardeh and Mats Berg were paid consultants for the study. Gert Nilsson is the CEO of Wheelsbridge AB. Kristina Neimert Carne is employed by a distributor of some of the chemicals used in the study.

Accepted for publication 19 October 2011

However, whether these products are safer for the skin is controversial, as the pigments may well release unwanted substances to the skin. For example, individuals who are sensitive to nickel may potentially react to nickel in the pigments. The reaction threshold for nickel is low, but dose–response studies in sensitized individuals show that >90% of sensitized patients fail to react below 1 ppm (6). Furthermore, several mineral powders on the market may contain other allergens, such as preservatives and fragrances.

The aim of the present study was to investigate whether nickel sensitized individuals react to make-up products containing pigments with nickel as an impurity. Other potential irritant reactions to the powders were also monitored. To our knowledge, there are no published studies on this subject.

Material and Methods

Volunteers

Twenty-three individuals (19–65 years old, 23 women and 1 man, mean age 49 years) were recruited among individuals with a clinical history of nickel allergy and/or with positive patch test reactions to nickel. The study was approved by the regional ethics committee in accordance with the Helsinki Declaration of 1975, and later revisions. The volunteers gave written informed consent to participate.

Test products

The test products were black iron oxides (SunCroma C33-5000, Lot 030991, <200 ppm Ni, and SunPuro C33-7001, lot 4B5641, <10 ppm Ni; SunChemical Corporation, Cincinnati, OH, USA), titanium dioxide [Solaveil, CT-100-LQ-(WD) batch 522937, 37% titanium dioxide in C12–15 alkylbenzoate, aluminum stearate, polyhydroxystearic acid, alumina; Croda, North Humberside, UK], bismuth oxychloride (Ronaflair EsQ; Merck Chimica, Darmstadt, Germany), and marketed cosmetic mineral cosmetics [IDUN Minerals, mineral foundation Svea warm medium, containing mica, zinc oxide, CI 77491, CI 77492, CI 77891, and CI 77499 (Letsfaceit Nordic, Stockholm, Sweden), BareMinerals, original SPF 15 Foundation medium containing titanium dioxide, bismuth oxychloride, mica, and iron oxides (Bare Essentials Beauty, San Francisco, California, USA), and Sheer Cover Minerals, [Mineral Foundation SPF 15, containing boron nitride, bisabolol, aspalathus linearis leaf extract, zinc oxide (CI 77497), and titanium dioxide (CI 77491), and possibly bismuth oxychloride, mica, and iron oxides (CI 77491,

CI 77492, CI 77499) Guthy Renker, Santa Monica, California, USA]. The powders were dispersed (50:50 wt/wt) in C12-15 alkylbenzoate (AlB, Bergacare EM-AB; Berg & Schmidt, Hamburg, Germany). AlB is a polar emollient that can be used as a wetting agent for mineral make-up products. Titanium dioxide was used as is. Nickel sulfate, 5% in petrolatum, was used as a positive control.

Exposure and evaluation

The test products were randomized, pipetted into aluminium chambers (20 µl, Finn Chambers® on Scanpor® tape, 8 mm inner diameter; VitaFlo Scandinavia AB, Göteborg, Sweden), and fixed on the upper arm. One of the chambers contained AlB on filter paper, and one was left empty as a control. After 48 hr, the patches were removed, and the area were cleansed and re-marked to facilitate visible and instrumental evaluation of the exposed areas 24 hr after removal. The subjects were also asked to report late skin reactions occurring during the week after evaluation at the clinic.

The exposed areas were evaluated by scoring of the skin with an arbitrary eight-point scale as follows: 0, no reaction; 0.5, slight patchy erythema; 1, slight uniform erythema; 2, moderate uniform erythema; 3, strong erythema; 4, strong erythema spreading outside the patch; 5, strong erythema spreading outside the patch and swelling; and 6, severe reaction with erosion. This scale is considered to be more sensitive for detection of possible differences in the strength of the skin reaction than the commonly used scale for detection of allergy, which was used in the previously reported study on some of the included subjects (7).

After the visual evaluation, the skin reaction was quantified with a non-invasive instrument (Tissue Viability Imaging System, TiVi600; Wheelsbridge AB, Linköping, Sweden). The instrument quantifies skin erythema and blanching of the skin, taking advantage of the wavelength dependence of red blood cell absorption (8, 9). The red blood cells in the blood vessels of the skin strongly absorb light in the green wavelength region (approximately 500–600 nm). When a photograph is taken, the white light from the light-emitting diode illuminator passes through a polarization filter, making the light linearly polarized. When the photograph was analysed, the area of interest was delineated, the processing software separated the red and green colour matrices, and, after application of an algorithm, an output matrix reflecting the local red blood concentration was generated (8). The increase in red blood concentration as compared with an untreated area was calculated by subtracting the mean values from four areas immediately outside the exposed area (nickel

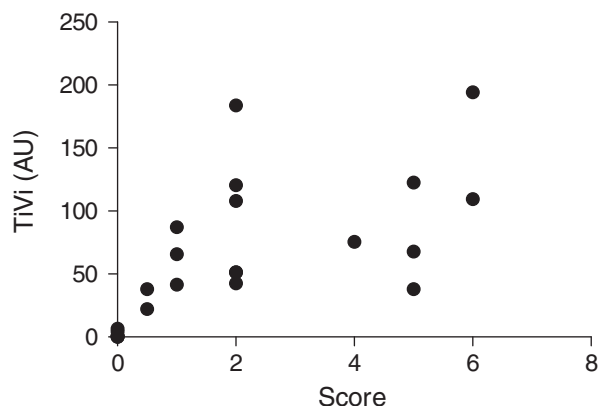


Fig. 1. The correlation between the TiVi value and the visual scoring of the nickel reaction, $r = 0.8098$, $p < 0.0001$.

site) or by subtracting the mean value obtained from the blank reference area (test product site) in each individual.

Calculation and data presentation

Results from the TiVi measurements are presented as boxplots of the increase in TiVi values as compared with the untreated area. The bottom line of the box represents the first quartile (Q1) value, and the top the third quartile (Q3) value. A line is drawn across the box at the median. The whiskers are the lines that extend from the top and bottom of the box to the 90% and 10% percentiles, respectively. Outliers are points outside the lower and upper limits, and are plotted with asterisks.

Non-parametric tests were used to test statistical differences. The Spearman correlation coefficient was applied to the visual and instrumental assessments. The Friedman statistic and Dunn's multiple comparison were used to detect potential differences between the products. A p -value of <0.05 was considered to be significant. GRAPHPAD PRISM 5 (www.graphpad.com) was used for the calculations and drawings.

Results

Of the 23 included subjects, 17 (74%) showed a visible reaction (score 0.5 or above) to the positive control nickel sulfate (Fig. 1). The visual assessments of the nickel reactions correlated significantly with the TiVi values ($r = 0.8098$, $p < 0.0001$) (Fig. 1).

None of the individuals reacted visually to the test products, and there were no significant differences in the TiVi readings between the products ($p = 0.358$). None of the products induced any significant change in the TiVi readings as compared with the untreated area

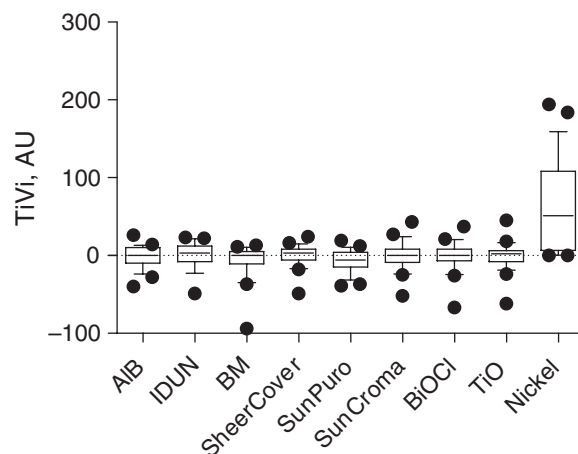


Fig. 2. The TiVi value (AU) on the different skin sites exposed to the test products and the positive control after subtraction of the TiVi control area (empty Finn Chamber®) ($n = 23$). No significant change was seen in any of the areas exposed to the test products, $p > 0.05$. AIB, C12–15 alkylbenzoate; BM, BareMinerals; SunPuro, Sun Puro extra pure iron oxides; SunCroma, Sun Croma iron oxide; BiOCl, bismuth oxychloride; TiO, titanium dioxide; Nickel, nickel sulfate. The line in the box is the medium value, and the whiskers are the lines that extend from the top and bottom of the box to the 90% and 10% percentiles, respectively. Outliers are points outside the lower and upper limits, and are plotted with asterisks.

(Fig. 2). A subgroup analysis of the 50% most nickel-sensitive individuals (score 2 or higher) confirmed the absence of skin reactions to the test products, as no significant differences between the products were found and no increases in TiVi values were detected (results not shown). None of the individuals reported any late skin reactions.

Discussion

The investigated formulations are mixtures of iron oxides, silica, kaolin, bismuth oxychloride, titanium dioxide, zinc oxide, or individual ingredients dispersed in polar oil. The products were chosen to be representative of this type of mineral cosmetic, and they contain naturally occurring compounds with trace amounts of impurities, such as nickel. The level of nickel and other heavy metals in the test products were not analysed, which is a limitation. The ingredients are used as pigments in a variety of other coloured make-up products, such as mascaras, blushers, rouge, liquid, and mineral foundations. Starting materials for the pigments may be derived from the earth, and will therefore contain trace amounts of heavy metals. The colorants investigated in the present study are listed in Annex IV, Part I (colouring agents allowed for use

in cosmetic products) of the Cosmetics Directive of the European Union, and are allowed to be used without restrictions when purity requirements are fulfilled. The pigment grades are used to impart colour to make-up products, whereas nano-structured particles may be used in sunscreens to increase the transparency of the formula. Titanium dioxide is also allowed to be used as a sunscreen active ingredient to protect against sunburn as aggregates of primary particles ranging from 30 to 150 nm in size. In the present study, 'nano' titanium dioxide was tested as single ingredient to enhance the possibility of detecting potential cutaneous reactions, whereas in the products the pigment grade was used.

The stratum corneum is the rate-limiting barrier to penetration of substances through the skin, where the major route of penetration is considered to be the highly convoluted and tortuous intercellular lipid pathway. An increased risk of nickel sensitivity was found to be associated with mutations in the gene coding for filaggrin, a protein that is important for skin barrier function (10). The skin appendages are also potential routes for absorption, despite their relatively small total fractional area (~0.1%) (11, 12). The appendages allow for deposition of particles, and may allow the passage of hydrophilic salts (13). The patchy skin reactions observed after testing for nickel allergy are reported to be compatible with higher concentrations of nickel in the appendages, especially in the concentration range between definite positive and negative reactions (14–16). Multiple studies have shown that particles can be present in the follicles, but neither nano-structured titanium dioxide nor zinc oxide penetrates beyond the stratum corneum of the skin (17).

The occlusive exposure of the skin to the formulations in the present study is considered to exaggerate the effects of ordinary use and to increase the possibility of detecting potential adverse reactions. However, a repeated open application test (ROAT) might have lowered the threshold for nickel reactions in the sensitive individuals, and is a useful test design for future studies of the pigments (18). In addition to the use of the sensitive scale for grading

of the reactions, the non-invasive TiVi instrument was used to detect and quantify the skin erythema, defined as an excessive red blood cell concentration in the test site after subtraction of that from an adjacent reference site. With this arrangement, the influence of skin pigmentation could also be compensated for, as melanin in the epidermal layer manifests itself as a pure off-set of the TiVi signal (19). This subtraction process makes the readings from skin with different degrees of pigmentation comparable. The results showed that 74% of the included individuals showed a visible reaction to the positive control nickel sulfate, and a significant correlation was found between the visual and instrumental readings (Fig. 1). However, none of the nickel-sensitive individuals reacted to the test products. In addition, a subgroup analysis of the 50% most sensitive individuals confirmed the absence of skin reactions to the powders. No late reactions occurred. A possible explanation for the high tolerability to the pigments in the present study may be a lower level of nickel impurities in modern make-up than in those used in the previous millennium (5). Interestingly, a recent cross-sectional general population study also found no association between having nickel allergy and reporting cosmetic dermatitis caused by mascara or eye shadow use (20). Nevertheless, no guarantee of skin tolerance can be given to extremely sensitive individuals (21).

In conclusion, the bioavailability of the trace amounts of nickel in the particles was below the level needed to elicit an eczematous reaction in any of the nickel-sensitized individuals. Furthermore, no other skin reactions were detected, which support the innocuous nature of the investigated fine particles used in mineral cosmetics. However, as mineral powders also may contain other ingredients, such as fragrances, botanicals, and preservatives, they cannot, as a group of cosmetics, be considered as harmless to the skin of sensitive people.

Acknowledgement

Letsfaceit Nordic AB (Sweden) sponsored the study.

References

- 1 Lindberg M, Tammela M, Bostrom A, Fischer T, Inerot A, Sundberg K, Berne B. Are adverse skin reactions to cosmetics underestimated in the clinical assessment of contact dermatitis? A prospective study among 1075 patients attending Swedish patch test clinics. *Acta Derm Venereol* 2004; **84**: 291–295.
- 2 Berne B, Bostrom A, Grahnen A F, Tammela M. Adverse effects of cosmetics and toiletries reported to the Swedish Medical Products Agency 1989–1994. *Contact Dermatitis* 1996; **34**: 359–362.
- 3 Lodén M, Wessman C. Mascaras may cause contact dermatitis. *Int J Cosmet Sci* 2002; **24**: 1–4.
- 4 Thyssen J P, Menné T. Metal allergy – a review on exposures, penetration, genetics, prevalence, and clinical implications. *Chem Res Toxicol* 2010; **23**: 309–318.
- 5 Sainio E L, Jolanki R, Hakala E, Kanerva L. Metals and arsenic in eye shadows. *Contact Dermatitis* 2000; **42**: 5–10.
- 6 Basketter D A, Angelini G, Ingber A, Kern P S, Menné T. Nickel, chromium and cobalt in consumer products: revisiting safe levels in the new millennium. *Contact Dermatitis* 2003; **49**: 1–7.
- 7 Kuzima N, Nyrén M, Lodén M, Edlund F, Emtestam L. Effects of pretreatment with a urea-containing emollient on

- nickel allergic skin reactions. *Acta Derm Venereol* 2004; **84**: 9–12.
- 8 O'Doherty J, Henricson J, Anderson C, Leahy M J, Nilsson G E, Sjöberg F. Sub-epidermal imaging using polarized light spectroscopy for assessment of skin microcirculation. *Skin Res Technol* 2007; **13**: 472–484.
 - 9 Wiren K, Frithiof H, Sjöqvist C, Lodén M. Enhancement of bioavailability by lowering of fat content in topical formulations. *Br J Dermatol* 2008; **160**: 552–556.
 - 10 Ross-Hansen K, Menné T, Johansen J D et al. Nickel reactivity and filaggrin null mutations – evaluation of the filaggrin bypass theory in a general population. *Contact Dermatitis* 2011; **64**: 24–31.
 - 11 Tanojo H, Hostynek J J, Mountford H S, Maibach H I. In vitro permeation of nickel salts through human stratum corneum. *Acta Derm Venereol Suppl (Stockh)* 2001; **212**: 19–23.
 - 12 Scheuplein R J, Blank I H. Permeability of the skin. *Phys Rev* 1971; **51**: 702–747.
 - 13 Lodén M, Faijerson Y. The synthetic peptide GRF (1–29)-NH₂ with growth hormone releasing activity penetrates human epidermis in vitro. *Acta Pharm Suec* 1988; **25**: 27–30.
 - 14 Menné T, Calvin G. Concentration threshold of non-occluded nickel exposure in nickel-sensitive individuals and controls with and without surfactant. *Contact Dermatitis* 1993; **29**: 180–184.
 - 15 Wells G C. Effects of nickel on the skin. *J Dermatol* 1956; **68**: 237–241.
 - 16 Lammintausta K, Maibach H I. Clinical concepts in nickel testing. In: *Nickel and the Skin: Immunology and Toxicology*, Maibach H I, Menné T (eds): Boca Raton, FL, CRC Press, 1989: pp. 91–99.
 - 17 Nohynek G J, Lademann J, Ribaud C, Roberts M S. Grey goo on the skin? Nanotechnology, cosmetic and sunscreen safety. *Crit Rev Toxicol* 2007; **37**: 251–277.
 - 18 Fischer L A, Johansen J D, Menné T. Nickel allergy: relationship between patch test and repeated open application test thresholds. *Br J Dermatol* 2007; **157**: 723–729.
 - 19 Nilsson G E. Influence of skin pigmentation in polarization spectroscopy imaging for assessment of erythema and blanching. In: *ISBS Symposium*, Tampa, FL, 6–9 April 2011.
 - 20 Thyssen J P, Linneberg A, Menné T, Nielsen N H, Johansen J D. No association between nickel allergy and reporting cosmetic dermatitis from mascara or eye shadow: a cross-sectional general population study. *J Eur Acad Dermatol Venereol* 2010; **24**: 722–725.
 - 21 Thyssen J P, Johansen J D, Lidén C, Möller P, Jellesen M S, Menné T. Clinical work-up of a highly reactive nickel-allergic patient. *Contact Dermatitis* 2011; **65**: 51–53.