Nickel Compounds in Cosmetics

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This is the seventh article in a series discussing metals in cosmetics. The series was introduced in January 1998 with a discussion of the toxic potential from metals absorbed through the skin. Subsequent articles presented quantitative data reflecting the extent to which each metal cited in the *Cosmetic Ingredient Dictionary* has a potential for skin absorption and toxicity. The present article discusses nickel.

Nickel is a micronutrient, presumably essential for the normal functioning of mammalian organisms. Critical physiological processes depend on the availability of nickel, notably the metabolism of carbohydrates. As an electrophilic transition metal, nickel avidly binds with nucleophilic functions (such as sulfur) in peptides and proteins once it reaches the living organism, thus rendering it immunogenic. While the metal was primarily an occupational health hazard in metalworking and refining in the beginnings of the industrial age, mostly due to its allergenicity,[1,2] since World War II it has become more of a general public health problem because of its widespread use in metal fabrication. Its outstanding metallurgical properties contribute to machineability and corrosion resistance in alloys, and it is incorporated in virtually all so-called white metals used in items which come in repeated, often intimate contact with the human skin, if not with the live tissues. Among these items are costume jewelry, prosthetic devices, clothes fasteners, tools and coins – all household articles used every day.

Table 1. Cosmetic Ingredient Dictionary: Nickel

		CAS	Uses
$C_8H_{14}N_4NiO_4$	Ni dimethylglyoxime	13478-93-8	pigment
$(C_7H_{13}NO_2S)_2Ni$	Ni acetylmethionate		conditioner
$C_{12}H_{22}O_{14}Ni$	Ni gluconate		

Numerous reports have been published in the dermatology literature documenting hypersensitivity reactions elicited by nickel present in certain cosmetics and particularly in eye makeup products.

General Toxicology

None of the natural nickel-containing minerals and ores are immunogenic, mainly due to their lack of solubility and thus bioavailability. Human activities such as mineral extraction, concentration and conversion into soluble compounds (salts) or alloys, however, have made the metal a health hazard. On long-term occupational exposure, nickel is recognized as genotoxic and carcinogenic. Nickel absorbed through the major exposure routes (dermal, gastrointestinal, and respiratory) has an additive effect and levels tend to increase in the aging organism.

Skin Absorption and Reactivity

Qualitative observations: Nickel shows a special affinity for keratin encountered in the stratum corneum (SC), the skin's outermost layer, which has a retarding effect on skin penetration rates. Thus absorption through the appendages (sweat ducts, follicles and sebaceous glands) appears to proceed at a faster rate than the trans-cellular route.[6] Such binding to epidermal and dermal tissue is also responsible for establishing depots of the metal in the epidermis, which functions as a local reservoir for nickel.[7,8] Sustained exposure to nickel metal dust in the industrial setting can induce dermatitis collectively described as "nickel rash" – papules, erythema and vesicles progressing to weeping eczema. These effects seen in the epidermal tissues all confirm the ability of the metal to penetrate beyond the outermost layers of the skin.

 0361-4387/02/0011-0024$05.00/0

The role of the counter ion (e.g., chloride, sulfate), concentration and occlusion on the percutaneous absorption rate and on the irritation potential of nickel salts as indicators of penetration has been demonstrated in human skin in vivo and in vitro. The irritation potential was determined by application under occlusion on healthy volunteers, and irritancy was evaluated by objective measurement with the laser Doppler technique.

Comparison of equimolal concentrations showed a clear dose-response relationship, whereby the chloride and the nitrate were more irritating than the sulfate; 0.30 M aqueous nickel chloride and nickel nitrate caused erythema, while lower concentrations (0.01-0.10 M) did not affect skin blood flow, a measure of irritation.[9] Applied as a chloride, nickel permeates at 50 times the rate of the sulfate. Occlusion may increase skin penetration up to 10-fold. Under all experimental conditions, induction times were substantial (50 to 90 hours) for either sulfate or chloride.[7,10]

In order to visualize the depth-concentration profile of nickel and other heavy metals as they transit the SC and to gain insight into the mode of penetration through the skin, the standard protocol of sequential tape stripping of the exposed skin[11,12] was implemented in our laboratory on human volunteers.[13]

Chloride, sulfate, nitrate and acetate salts of nickel at levels of 0.001-1% of the metal in methanol were presented in single open application over 30 minutes to 24 hours on the skin of volunteers. The application sites (volar forearm and intrascapular region) were tape-stripped 20 times and analyzed for metal content by inductively coupled plasma mass spectroscopy (ICP-MS).

The concentration-versus-depth profiles obtained using this method confirmed the diffusion characteristic of nickel, as described earlier by others.[7,14] The four nickel salts followed similar patterns in their SC diffusion, leading to the following conclusions:

- Accumulation of nickel in the SC increased as a function of exposure time; in other words, the concentration gradient between the superficial and deeper layers of the SC increases commensurate with duration of exposure.
- While the concentration gradients of metal retained in the SC vary with counter ion, anatomical site, dose and exposure time, for all variables tested the profiles converge towards non-detectable levels (<7 ppb) beyond the 15th tape strip, independent of these parameters. The only notable exception is the concentration profile of nickel applied as the nitrate, which remains constant at 1% of dose from the 3rd through the 20th strip.
- The steep initial concentration gradient observed for all four nickel salts confirmed earlier observations of surface reservoir formation.
- The counter ion in nickel salts plays a major role in their passive diffusion through the SC, suggestive of ion pairing.

Quantitative data on nickel absorption: Despite the prominent role of nickel as an allergen, reports on quantitative percutaneous absorption are infrequent, and in vivo experiments in humans involve few subjects. Also, skin reactions due to the irritancy of nickel salts are common, which leads to gradual and uncontrollable changes in barrier properties when diffusion is examined experimentally in vivo. It therefore appears more relevant and reproducible to measure nickel salt diffusivity through isolated human stratum corneum in vitro.

Advanced diffusion systems and analytical techniques are now available to make possible a better measurement of permeant flux, as compared to earlier experiments. The permeability coefficient Kp serves to describe the penetration of individual chemical compounds through biological membranes.[15] The best "number" for the in vitro Kps of nickel compounds gleaned from the literature is on the order of 10^{-6} cm/h (compared with a Kp for water of 10^{-3} cm/h). The Kps for the four nickel salts through isolated human stratum corneum, measured under steady state conditions, ranged from 5.2 to 8.5 x 10^{-7} cm/h.[16]

A major factor affecting reliability of percutaneous absorption data is the methodology used. Different methods expectedly lead to different results (see sidebar). In data reported in the literature, rarely have two investigators used the same approach.

In view of the slow diffusion process measured experimentally, a different penetration pathway and mechanism of diffusion than the transcellular pathway (measured in vitro) needs to be invoked to explain the facile and widespread sensitization reactions in humans, reported from contact with the metal and its salts.

Measuring Permeability Coefficients for Nickel Salts

When measuring percutaneous absorption of nickel salts, different methods produce different results.

Through heat-separated human skin: Diffusion of 2 µCi of $NiSO_4$ (0.001, 0.01, 0.1 M) measured by Samitz through heat-separated human epidermis was slow.[10] After 17 hours, only one of the six diffusion cells yielded measurable nickel. After 90 hours spanning two more sampling periods, two of the six cells showed no measurable nickel at any time in the receptor chamber.

Through full-thickness human skin: The in vitro percutaneous fluxes of 1.32 mg nickel and the chloride and sulfate through full-thickness human skin were compared in 1986 by Fullerton et al.[7] After lag times of about 50 hours in experiments lasting 144-239 hours, occluded $NiCl_2$ entered the receptor fluid about 5-40 times more rapidly than (a) $NiS0_4$, (b) $NiC1_2$ with added Na_2S0_4 or (c) $NiS0_4$ with added NaCl. Solutions (b) and (c) had identical ionic activities, and the Ni^{++} and Cl^- concentrations were the same as for the $NiC1_2$ solution.

Without occlusion, the permeation of nickel decreased by more than 90%. Nickel in the skin tissue at the end of the experiments (calculated as the difference between the applied nickel and sum of the nickel in the receptor solution plus the nickel recovered by washing the skin) was also greater after exposure to pure $NiC1_2$ than to sulfate-containing solutions. These results are in agreement with cited patch test results wherein occlusion and the use of nickel chloride rather than nickel sulfate are more likely to produce positive reactions in patients.

Estimated permeability coefficients after the lag time were the following:

- Between 0.5×10^{-4} and 15×10^{-4} cm/hr for pure $NiC1_2$;
- Between 0.03×10^{-4} and 0.2×10^{-4} cm/hr in the presence of sulfate.

Nickel in Cosmetics

The consumer cannot determine the presence of metals in cosmetic products by reading the label, since in most countries there is no obligation to list their presence. In addition, they can easily escape consumers' attention because metal salts may be used as materials in synthesis, leaving undetermined residues; or their occurrence may be unintentional as contaminants of raw materials such as talcs and powders. As part of good manufacturing practices, manufacturers should be held to verify the quality (purity) of the raw materials they incorporate in the finished product.

Several transition metal salts are components used in synthesizing so-called metallic hair dyes. Salts of nickel (as well as copper, cobalt, molybdenum, chromium and other transition metals) are complexed with certain organic ligands to yield such dyes, which are insoluble coatings adhering to the outside of the hair shaft.[17] Chemical analyses of 20 commercial body powders and talcums detected levels of several hundred ppm of nickel. Similar concentrations of the allergens cobalt and chromium were also present in a number of such products.[18]

Eczema of the eyelids is common and may be due to application of mascara, eyeliner, eye shadow or eyebrow pencil contaminated with immunogenic metals present in the pigments. Eighty-eight eye colorants from a number of manufacturers were analyzed for the presence of nickel and other immunogenic metals. Levels determined there reached values of 49 ppm (µg/g), high enough to cause allergic symptoms in those previously sensitized, since concentrations as low as 1 ppm of nickel may elicit an allergic reaction.[19] Potentially these levels may even induce allergy de novo on long-term application.[20] Goh et al. analyzed 10 eyeshadows from three different manufacturers and discovered nickel in eight of the samples at levels ranging from 13 to 71 ppm.[21] Analysis of eye pencils for nickel content revealed levels of 0.38 to 1.4 ppm of the metal.[22] van Ketel and Liem detected 76 and 102 ppm in two such products.[23]

Immunology

On skin contact, metallic nickel is likely to be solubilized by fatty acids present on the skin surface. The lipid-soluble deriva-

tives formed there appear to readily diffuse into the skin in amounts sufficient to elicit an allergic reaction in an organism that has been pre-sensitized to nickel. It has cumulative properties imparted by its reactivity with proteins and its tendency to form depots. Inhalation magnifies the effects of GI exposure, and oral intake with nickel-rich foods will exacerbate a cutaneous sensitization response (such as eczema). Currently the most frequent allergen in industrialized countries, nickel can cause delayed as well as immediate-type allergy following exposure by iatrogenic, respiratory, gastrointestinal or dermal routes.[24-32]

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