Silver, Titanium and Zirconium: Metals in Cosmetics and Personal-Care Products

Jurij J. Hostýnek and Howard I. Maibach

Department of Dermatology, School of Medicine, University of California, San Francisco, CA, USA

Howard I. Maibach, M.D., is Professor of Dermatology, University of California School of Medicine, San Francisco, California. His laboratory has been interested in and has published extensively on dermatopharmacology and dermatotoxicology.

This is the fifth article in a series reviewing the metals present in personal care products. Earlier installments appeared in January 1998, *Toxic Potential from Metals Absorbed through the Skin* (pages 33-42); March 1999, *Metals in Personal-Care Products*, (pages 47-56); August 2000, *Chromium, Cobalt, Copper and Iron: Metals in Personal-Care Products*, (pages 52-65); and August 2001, *Lead, Manganese and Mercury: Metals in Personal-Care Products*, (pages 26-36).

Silver

Toxicity: Silver and its salts pose no notable hazard upon contact with healthy, intact skin. Binding to keratin-rich, superficial layers of the skin appears to prevent absorption of the silver ion into the deeper layers, and penetration rates of water-soluble salts are considered to be toxicologically insignificant. No data are available which would allow calculation of flux or permeability coefficients. Reports of allergic reactions of the immediate and delayed type due to contact with the metal or its salts are rare.[1-4] The only toxicological hazard is presented by concentrated silver salt solutions, due to their caustic action on live tissue. Similar to other heavy metals, the highly electrophilic silver ion reacts with nucleophilic amino acid residues in proteins, attaching to sulfhydryl, amino, imidazole, phosphate and carboxyl groups of membrane or enzyme proteins, leading to protein denaturation.[5]

A practical aspect of such reactivity is their effect on microorganisms. One significant therapeutic use of silver as the nitrate or its sulfonamides[6,7] is the disinfection of the skin of thermal injury patients, where the antiseptic effect is primarily due to the metal's denaturing action on viral and bacterial proteins.[8] This makes the metal an effective sterilant for water and other beverages, an effect which has been recognized and put to use over centuries, e.g., in the use of silver drinking and storage vessels. Currently, finely divided silver metal is incorporated in commercial filters for domestic water purification, or in cosmetic formulations where in the pH range of 3-11.5 at levels of 100-5,000 ppm it is an effective preservative against microbial contamination.[9] Silver is also listed as a color additive by the US FDA Office of Cosmetics and Colors. The use of silver in coloring fingernail polish is approved by the FDA's Office of Cosmetics and Colors.

Skin absorption, elimination and reactivity: Independent of the route of entry, silver preferentially accumulates in the mucosa, nail lunulae, hair and the superficial layers of the skin.[10] Once deposited, silver particles accumulate throughout the aging process. Excretion of silver through the skin is insignificant; consequently, impregnation of dermal tissues, even due to systemic absorption through the trivial and habitual use of silver-plated tableware, potentially results in graying of the skin. This is most pronounced on the face and neck, a condition termed *argyria*. Two types of this phenomenon are described: generalized argyria, stemming mainly from chronic systemic, medicinal application, or from external occupational exposure, and localized argyria, persistent bluish macules due to the presence of silver in dental crowns or implanted needles (acupuncture).[10,11] Significant bodyburden of silver thus becomes noticeable as a permanent hyperpigmentation, particularly of sun-exposed areas of the skin. Both forms are considered to be only esthetic effects. Also, discoloration of scalp and body hair has been noted, resulting in a steel gray tint.[12]

Intentional dietary intake of silver, as practiced in certain parts of the world (in the form of extremely thin foil with some

Cosmetic Ingredient Dictionary		CAS	Uses
Ag	Silver	7440-22-4	Antimicrobial, Colorant
$AgNO_3$	Silver nitrate	7761-88-8	Sterilant
Ag_2SO_4	Silver sulfate	10294-26-5	

 0361-4387/02/0001-0026$05.00/0

foods), results in markedly elevated levels of the metal in hair. Thus, neutron activation analysis of pre-cleansed human scalp hair revealed a mean content of 1.927 µg/g silver in the Punjab population, which compares with values of 0.39 µg/g seen in other parts of India or 0.162 µg/g in Japan, where such dietary habits are not known to exist.[13]

Silver ions are not significantly absorbed through unbroken human skin, most likely due to silver reactivity with skin proteins, resulting in its accumulation in the uppermost stratum corneum layer.[14] Chemical and electron probe techniques, however, have revealed that complex silver salts do penetrate through the epidermal portion of the sweat duct, cross over into the adjacent epidermal cells and enter the papillary bodies, precipitating as silver sulfide.[15] Examination of discolored areas shows the presence of silver granules in the sweat gland membrane, on sebaceous glands and the connective tissue membrane, as well as in collagen tissue below the basal membrane of the epidermis.[16]

The antimicrobial activity of silver has been put to use by formulating a composite of silver chloride and titanium dioxide, which allows a controlled release of silver ion. The composite is active at concentrations less than 25 ppm against a wide range of micro-organisms, including Gram-negative bacteria, yeasts and moulds. Its preservative activity against bacteria and fungi falls between 50 ppm and 500 ppm.[17]

Titanium

Titanium is a light metal that imparts outstanding tensile strength and high corrosion resistance in chemical and biological environments to its alloys. No biological role has been assigned to titanium or its compounds but titanium dioxide is frequently used as white pigment in cosmetics, paints, enamels and plastics as well as a coloring agent in food. In spite of its widespread use, no quantitative penetration values have been determined through human skin. Titanium dioxide is a white pigment with considerable covering and opacifying power. It exists in three crystalline modifications: anatase, brookite, and rutile, and one amorphous form. Anatase is used in papermaking, and is the only variety approved by the US FDA for use in foods, cosmetics and colors in general, and for eye area use in particular.

In the cosmetics industry, titanium dioxide is used as a whitener in a wide variety of products including sunscreens, after shave powders, bath powders, face powders, depilatories, deodorants, fingernail coatings, beauty masks, cleansing creams, eye makeup, foundations, lipsticks, tooth paste, skin lighteners, etc.

General toxicology: Titanium compounds are poorly absorbed from the gastrointestinal tract, which is the main route of exposure for the general population. Most titanium absorbed with food is eliminated unchanged with urine. Absorbed from the air, it seems to accumulate with age in the lungs (e.g., through industrial exposure), without known adverse effects. In a bioassay of titanium dioxide for general toxicity or carcinogenicity there was no evidence of adverse effects in rodents.

Skin absorption and reactivity: No data are available on titanium absorption through the human skin. Indirect evidence was obtained in animal experiments that titanium is absorbed percutaneously from suspensions of the oxide in various liquids.[18] The use of inorganic light absorbers (pigments, insoluble minerals) such as titanium dioxide in sunscreens offers the advantage of their presumed insolubility and lack of reactivity in contact with live tissue. This sets them in contrast to organic UV-active compounds with their associated relative toxicity, which upon irradiation are converted to an "excited" state and thus absorb the sun's harmful radiation energy; thereby they are also reactive with the skin's proteins and more often than not are allergens, leading to hypersensitivity reactions.

Review of the literature, though, shows that inorganic light scatterers such as titanium dioxide are also not entirely inert when exposed to ultraviolet (sun) radiation. They appear to be subject to photochemical activation and degradation, manifest in a pronounced catalytic activity. Such activation seems to lead to the formation of reactive intermediates with spectral characteristics of hydroxyl radicals. These can react with natural unsaturated fatty acids on the skin, and can also penetrate the stratum corneum to then react with functional cells in live tissue. This finding led to the development and evaluation of titanium dioxide coated with silicones, yielding a material especially intended for use as sunscreen. This modification appears to be sufficient to prevent biologically significant damage from the reactive species formed under UV radiation.[19]

Cosmetic Ingredient Dictionary		CAS	Uses
TiO_2	Titanium dioxide	13463-67-7	Opacifier Pigment
$Ti(OH)_4$	Titanium hydroxide	20338-08-3	

Currently, populations with skin highly sensitive to sunlight, such as Australians and New Zealanders, are advised to use titanium dioxide-based sunscreens every day of their lives. This potentially leads to massive cumulative exposures and has prompted several investigations. Human skin penetration studies with micronized, ultra-fine titanium dioxide (size 20-50 nm) show that hair follicles will be penetrated up to a size of 50 micron (50,000 nm), and the stratum corneum up to a size of 5 micron (5,000 nm), to a depth of ca. 10 skin tape strips (approx. 10 micron depth).[20-23] Those data were generated by moderate massage of the applied particles into the skin. It is reasonable to assume that a consumer will apply sunscreens with moderate rubbing onto the skin also. In another study conducted in Australia, volunteers were asked to apply titanium dioxide sunscreen to the skin daily for 2-6 weeks. After removal of the superficial stratum corneum by stripping, biopsy of epidermis and dermis, and analysis by inductively coupled plasma mass, spectroscopy showed that levels of titanium there were higher than the levels of titanium found in the tissues of controls.[24]

Also the penetration of silicone-coated titanium dioxide microparticles into the horny layer and the follicular orifices from sunscreen applications was investigated by tape-stripping the treated skin.[25] Coated TiO_2 was localized mainly in the corneocytes in the upper part of the stratum corneum and in the pilosebaceous orifices.

In certain countries a product similar to mascara, named "kohl," is popular as eyeliner, also used to prevent sun glare. Such eyeliner pencils of various origins, used not only to darken eyelids but also applied in the conjunctival surfaces, have been analyzed for presence of heavy metals.[26] Besides the usual content of antimony trisulfide, some were found to contain up to 30% titanium, as determined by dispersive X-ray analysis.

Zirconium

Zirconium compounds as they occur as minerals in nature pose no toxicological threat, in part due to their lack of solubility, which makes them biologically unavailable. In the past, use of certain synthetic zirconium salts in personal care and medicinal products resulted in granulomatous hypersensitivity if they became embedded in tissue underlying damaged skin or were applied in soluble form for the treatment of Rhus (e.g., poison oak) dermatitis. Their use in personal care products is now restricted. Zirconium silicate is still used in creams and powders in Europe.

Cosmetic Ingredient Dictionary		CAS	Uses
$ZrSiO_4$	Zirconium silicate	10101-52-7	Pigment
Cl_2OZr	Zirconyl chloride	7699-43-6	Antiperspirant
O_2Zr	Zirconium dioxide	1314-23-4	Pigment

General toxicology: Zirconium mainly occurs in the environment as a constituent of mineral deposits. These deposits are abundant and widespread, but are not known to pose an environmental or human health threat, because of their lack of solubility. Furthermore, zirconium cannot form covalent bonds with carbon, an important condition for interaction with biological systems, and in fact the metal has no known biological significance.

Although deodorants are considered cosmetics, both deodorants and antiperspirants are regulated as over-the-counter (OTC) drugs. Formerly, zirconium compounds were widely used in antiperspirant formulations. The FDA-OTC Antiperspirant Review Panel however recommended their removal as components of aerosol antiperspirants because of the potential for formation of granulomata in the lung when inhaled. Sodium zirconium lactate, which had caused granulomatous lesions in the skin of the axilla, also had to be removed from commercial products.

Skin absorption and reactivity: The widest commercial use of zirconium complexes was in deodorants and antiperspirants, often together with aluminum compounds. Most commonly used was zirconium oxychloride hydrate. Zirconium compounds are among the agents that cause closure of the sweat duct (emphraxis) due to protein precipitation or hydroxide gel formation, or both.[27]

Once they penetrate the skin, such as through abrasions, zirconium salts are likely to form granulomas, which prompted their removal from cosmetics. The granulomatogenic agent in such cases may be either the soluble salt as it was used in antiperspirants,[28] or the insoluble hydroxide or acetate, used in topical preparations to treat Rhus plant dermatitis.[29] Such granulomata are benign growths that envelop the irritating agent and, thereby, remove it from further tissue contact. Granuloma, such as induced by zirconium, is transitory if caused by soluble salts, but permanent if in-

duced by insoluble particles which remain imbedded indefinitely in tissue. In this latter case, they are refractory to therapy and require surgical removal.

Immunology: Zirconium does produce a hypersensitivity reaction, and patch and intradermal injections are used in diagnosis of allergy. Use of zirconium-based stick deodorants or antiperspirants, or topical preparations containing zirconium oxide or carbonate for urushiol hypersensitivity, induced either non-allergic foreign body inflammations which will heal over a period of one month, or granulomatous hypersensitivity, characterized as epithelioid cells that organize into tubercles which do not phagocytize zirconium. Due to such adverse reactions the original zirconium personal care formulations had to be removed from the market. A zirconium oxychloride-aluminum chlorohydrate complex, however, also proved to be effective as a deodorant; it is one that does not release zirconium into the skin and now can be used without the risk of granuloma formation, even in persons with granulomatous hypersensitivity to zirconium.[30] Allergic hypersensitivity to zirconium as secondary reaction to granulomatous hypersensitivity is still possible, but is rarely seen any more.[28-31] Certain zirconium compounds can also elicit sarcoidal granulomas when introduced into the skin, which can persist for a year or longer.[32,33]

References

Address correspondence to Jurij J. Hostýnek, c/o Editor, *Cosmetics & Toiletries* magazine, 362 South Schmale Road, Carol Stream, IL 60188-2787 USA.

1. PO Lind, B Hurlen, T Lyberg and E Aas, Amalgam-related oral lichenoid reaction, *Scandinavian Journal of Dental Research* 94 448-451 (1986)
2. J Laine, K Kalimo and R-P Happonen, Contact allergy to dental restorative materials in patients with oral lichenoid lesions, *Contact Dermatitis* 36 141-146 (1997)
3. LE Gaul, Incidence of sensitivity to chromium, nickel, gold, silver, and copper compared to reactions to their aqueous salts including cobalt sulfate, *Ann Allergy* 12 429-444 (1954)
4. R Marks, Contact dermatitis due to silver, *Br J Dermatol* 78 606-607 (1966)
5. HG Petering, Pharmacology and toxicology of heavy metals: Silver, *Pharmacolog and Therapeutics* 1 127-130 (1976)
6. CLJ Fox, S Modak, JW Stanford and PL Fox, Metal sulfonamides as antibacterial agents in topical therapy, *Scand J Plast Reconstr Surg* 13 89-94 (1979)
7. MG Boosalis, JT McCall, DH Ahrenholz, LD Solem and CJ McClain, Serum and urinary silver levels in thermal injury patients, *Surgery* 101 40-43 (1987)
8. KF Bader, Organ deposition of silver following silver nitrate therapy of burns, *Plast Reconstr Surg* 37 550-551 (1966)
9. N Simonetti, G Simonetti, F Bougnol and M Scalzo, Electrochemical Ag+ for preservative use, *Applied and Environmental Microbiology* 58 3834-3836 (1992)
10. Y Tanita, T Kato and K Hanada, Blue macules of localized argyria caused by implanted acupuncture needles; Electron microscopic and roentgenographic microanalysis of deposited metal., *Arch Dermatol* 121 1550-1562 (1985)
11. T Matsumura, M Kumakiri, A Ohkawara, H Himeno, T Numata and R Adachi, Detection of selenium in generalized and localized argyria: Report of four cases with X-ray microanalysis, *J Dermatol* 19 87-93 (1992)
12. WR Hill and DM Pillsbury. *The diagnosis and treatment of argyria. Analysis of reported cases of argyria: Its production and prevention.* Baltimore: Williams and Wilkins, 1939:60. Argyria. The Pharmacology of Silver
13. G Lal, NPS Sidhu, I Singh, VK Mittal and HS Sahota, Neutron activation analysis of trace elements in human hair: Effect of dietary and environmental factors., *Nucl Med Biol* 14 499-501 (1987)
14. E Skog and JE Wahlberg, A comparative investigation of the percutaneous absorption of metal compounds in the guinea pig by means of the radioactive isotopes: ^{51}Cr, ^{58}Co, ^{65}Zn, ^{110m}Ag, ^{115m}Cd, ^{203}Hg, *J Invest Dermatol* 43 187-192 (1964)
15. WR Buckley, CF Oster and DW Fassett, Localized argyria, *Arch Dermatol* 92 697-705 (1965)
16. L Conde-Salazar, A Cannavo, B Meza, D Guimaraens and ES Yus, Occupational argyrosis and platinosis, *Am J Contact Dermat* 3 44-47 (1992)
17. RJ Corbett, An inorganic biocide using a novel presentation of silver, *Int J Cos Sci* 18 151-165 (1996)
18. ABG Lansdown and A Taylor, Zinc and titanium oxides: Promising UV-absorbers but what influence do they have on the intact skin?, *International Journal of Cosmetic Science* 19 167-172 (1997)
19. HM Swartz, KJ Liu, T Walczak, T Panz, M Kobayashi and W Zavadoski, Effects of coatings on the reactivity of inorganic sunscreen agents to light, *J Cosm Sci* 38 125-135 (1998)
20. B Illel, Formulation for transfollicular drug administration: Some recent advances, *Crit Rev Ther Drug Carrier Syst* 14 207-219 (1997)
21. B Illel and H Schaefer, Transfollicular percutaneous absorption, *Acta Derm Venereol (Stockh)* 68 427-430 (1988)
22. A Rolland, A Wagner, A Chatelus, B Shroot and H Schaefer, Site-specific drug delivery to pilosebaceous structures using polymeric microspheres, *J Pharm Res* 10 1738-1744 (1993)
23. H Schaefer, F Watts, J Brod and B Illel, Follicular penetration, In *Prediction of Percutaneous Penetration*, RC Scott, Guy RH, Hadgraft J, ed., (1990) London: IBC, 163
24. M-H Tan, CA Commens, L Burnett and PJ Snitch, A pilot study on the percutaneous absorption of microfine titanium dioxide from sunscreens, *Australasian Journal of Dermatology* 37 185-187 (1996)
25. J Lademann, H-J Weigmann, C Rickmeyer, et al., Penetration of titanium dioxide microparticles in a sunscreen formulation into the horny layer and the follicular orifice, *Skin Pharmacology and Applied Skin Physiology* 12 247-256 (1999)
26. AF Al-Hazzaa and PM Krahn, Kohl: a hazardous eyeliner, *International Ophthalmology* 19 83-88 (1995)
27. HH Reller and WL Luedders, Mechanism of action of metal salt antiperspirants. Part 2, In *Dermatotoxicology and Pharmacology*, FN Marzulli, Maibach HI, eds., (1977) London: Hemisphere Publishing Corporation, 18-54.
28. WB Shelley and HJ Hurley, The allergic origin of zirconium deodorant granulomas, *Br J Dermatol* 70 75-101 (1958)
29. WL Epstein and JR Allen, Granulomatous hypersensitivity after use of zirconium-containing poison oak lotions, *JAMA* 190 162-164 (1964)
30. WL Epstein, Granulomatous inflammation of the skin, in *Pathology of Granulomas*, HL Ioachim, ed., (1983) New York: Raven Press, pp 21-59
31. WL Epstein, JR Skahen and H Krasnobrod, Organized epithelioid cell granuloma: Differentiation of allergic (zirconium) from colloidal (silica) types, *Am J Pathol* 43 391-405 (1963)
32. L Rublin, AH Slepyan, LF Weber and I Neuhauser, Granulomas of axillas caused by deodorants, *JAMA* 162 953-955 (1956)
33. WL Epstein, JL Skahen and H Krasnobrod, Granulomatous hypersensitivity to zirconium: Localization of allergen in tissue and its role in formation of epitheloid cells, *J Invest Dermatol* 38 223-232 (1962) C&T