

Nanoparticles: small and mighty

Alison Wiesenthal¹, MD, Lindsey Hunter², BS, Shuguang Wang³, PhD,
Jeffrey Wickliffe³, PhD, and Michael Wilkerson¹, MD

¹University Health Science Center San Antonio, San Antonio, TX, USA,

²University of Texas Medical Branch, Galveston, TX, USA, and ³Tulane University, New Orleans, LA, USA

Correspondence

Michael Wilkerson, MD
Associate Professor
University of Texas Medical Branch
Department of Dermatology
301 University Blvd.
Galveston, TX 77555
USA
E-mail: mgwilker@utmb.edu

Conflicts of interest: None.

Introduction

Nanoparticles are particles measuring 1–100 nm in at least one dimension.¹ To put the nanoscale in perspective, 10 million nm are in 1 cm, and a human hair is about 100,000 nm in diameter. Naturally occurring nanoparticles and nanomaterials have been part of the human experience since the evolution of the species. For centuries, nanoparticles have been used in artwork and other materials manufactured by humans.² The advent of engineered nanomaterials and nanoparticles has created new opportunities and potential problems that may differ substantially from naturally occurring materials and particles. Because of the potential benefits of nanoparticles, we are currently in the midst of a nanoscience revolution.³

Nano-sized particles and materials display unique physical properties that are neither those of bulk metal nor those of molecular compounds. Nanomaterials are in extensive use in wound dressings, cosmetics, detergents, food packaging, drug delivery, therapeutics, biosensors, antimicrobial coatings, bactericidal food containers, stain-resistant clothing, high-performance sporting goods, and faster and smaller digital electronic devices.^{2–4} According to the Wilson Center's Project on Emerging Nanotechnologies, since 2006 the number of nano-products has increased by over 300%, from 212 products in 2006 to over 1000 products in 2009. Personal care products account for the largest category, with almost 200 products in the market today.⁵ In the cosmetic market, prod-

Abstract

The properties of engineered nanomaterials and nanoparticles such as zinc oxide and titanium dioxide may differ substantially from naturally occurring materials and particles. Nanoparticles have unique physical properties making them ideal for use in various skin care products currently on the market. Nano-preparations are currently under investigation as novel treatments of acne vulgaris, recurrent condyloma accuminata, atopic dermatitis, hyperpigmented skin lesions, and other non-dermatologic diseases. Because of their increased surface area, nanoparticles have increased reactivity and a small size allowing for enhanced mobility through the human body and environment. As their use becomes more prevalent, nanoparticles are being scrutinized for their safety and long-term effects. This review discusses the benefits of nanoparticles in dermatological therapies and skin care products as well as potential disadvantages and possible mechanisms of toxicity.

ucts using nanomaterials are particularly valued for their optical and tactile properties; they flow easily, may be transparent, and are pleasant to the touch.⁶ In addition, functional modifications (e.g. silanization or PEGylation) are expanding the diversity of applications for many nanoparticles. According to the National Science Foundation, nanotechnology is expected to become a \$1 trillion industry within the next decade.⁷

Metal oxide nanoparticles, specifically zinc oxide (ZnO) and titanium dioxide (TiO₂), are the primary nanomaterials used in sunscreen, skin care, and cosmetic products. In terms of the technology behind these nanoparticles, the specific aspects of most metal oxide processes are patent-protected or proprietary. Different crystalline forms of the parent materials, which often occur as oxide ores (e.g. ilmenite or FeTiO₃), exist naturally. For example, anatase, rutile, and brookite mineral forms of TiO₂ occur naturally, and anatase TiO₂ can be converted to rutile TiO₂ by heating.⁸ These different mineral forms of TiO₂ have unique optical and photocatalytic properties that change or can be modified at the nanoscale. Titanium dioxide nanoparticles may also be produced through a fuming process where TiCl₄ is hydrolyzed to TiO₂ (75% anatase, 25% rutile) in a hydrogen flame.⁹ Furthermore, metal oxide nanoparticles such as these can be doped or modified further by processes, including silanization.¹⁰ These processes are generally designed to increase the functionality or stability of the nanoparticles.

Table 1 Summary of select studies

Study (reference)	Substance characteristics	Endpoints measured	Exposure	Results
Wu <i>et al.</i> ³²	TiO ₂ : 4–10 nm (100% anatase); 25–90 nm (100% rutile); Degussa P25 (21 nm: 25% rutile/75% anatase)	Penetration and toxicity of TiO ₂ NP <i>in vivo</i> (mice and pigs) and <i>in vitro</i> (porcine skin)	<i>In vivo</i> : 30 (pigs) and 60 d (mice) <i>In vitro</i> : ≤ 24 h (porcine skin)	<i>In vitro</i> , porcine skin: TiO ₂ in SC. <i>In vivo</i> , pigs: TiO ₂ in SC, SG, PrC, and BC (4 nm TiO ₂) layers; pathological changes in cellular structures <i>In vivo</i> , mice: nanoparticles (10–60 nm) pass through skin and enter organs; adverse growth effects (10, 25 nm; P25)
Sharma <i>et al.</i> ³³	ZnO: DLS = 165 nm; TEM = 30 nm; BET = 50–70 nm	Genotoxicity <i>in vitro</i> (A431, human epidermal cell line)	≤ 48 h	+Genotoxic potential, concentration and time-dependent
Uchino <i>et al.</i> ³⁷	TiO ₂ : Anatase: 30 nm; Rutile: 90 nm; Amorphous	OH radicals and <i>in vitro</i> (CHO cells) cytotoxicity from TiO ₂ ⁻ UVA exposure	24 h	+ROS production and cytotoxicity: anatase > rutile, amorphous forms
Baroli <i>et al.</i> ⁴³	TMAOH-stabilized Maghemite NP: 6.97 ± 0.9 nm (by TEM); AOT-stabilized Iron NP: 4.97 ± 1.3 nm to 23.37 ± 3.6 (by TEM)	Penetration of NPs using ex vivo full-thickness skin pieces	≤ 24 h	NPs (<10 nm) penetrate hair follicles and SC; occasionally viable epidermis

AOT, sodium bis (2-ethylhexyl) sulfosuccinate; BC, basal cell; BET, Brunauer–Emmett–Teller method; CHO, Chinese hamster ovary cells; DLS, dynamic light scattering; NP, nanoparticle; PrC, prickle cell; ROS, reactive oxygen species; SC, stratum corneum; SG, stratum granulosum; TEM, transmission electron microscopy; TiO₂, titanium dioxide; TMAOH, tetramethylammonium hydroxide; ZnO, zinc oxide.

Most recently, nanoparticles are being used in the medical field to create innovative ways to detect and treat diseases as their size scale is similar to that of biological molecules (e.g. proteins and DNA) and structures (e.g. viruses). Nanoparticle products are currently being developed to treat methicillin-resistant *Staphylococcus aureus*, Alzheimer's disease, lung and liver carcinoma, and coronary artery disease to name a few.^{11–15} As their use becomes more prevalent, nanoparticles are being scrutinized for their safety and long-term effects. This review will discuss the benefits of nanoparticles in dermatological therapies and skin care products, as well as potential disadvantages and possible mechanisms of toxicity.

Nanoparticles in dermatology

Topically applied nanoparticles are utilized in over 200 commercially available skin products, including sunscreens, cosmetics, and personal care products. Older formulations of sunscreens using ZnO or TiO₂ did not

use nanoscaled material but rather micron-sized material. The optical properties of micron-sized materials increase reflection and have a fairly low refractive index compared with nano-sized materials. Therefore, contemporary sunscreens using nano-sized ZnO or TiO₂ are relatively opaque and clear compared with older formulations that remained bright white after application. This dramatically increased the cosmetic appeal of these products without sacrificing their effectiveness. Nanoparticle preparations are also currently under investigation for novel treatments of dermatological conditions such as acne vulgaris, recurrent condyloma accuminata, atopic dermatitis, and hyperpigmented skin lesions.

Acne vulgaris treatment

Acne vulgaris afflicts millions of people, and treatment is often inadequate secondary to poor patient compliance.¹⁶ Use of topical retinoids, one of the mainstays of acne treatment, is limited by a high incidence of side effects,

including photosensitivity, eczematous irritation, dryness, and scaling.¹⁷ Nanopreparations of acne medication, including formulations containing retinoic acid, offer similar efficacy and decreased side effects, possibly improving patient compliance and treatment outcomes.

While the etiology of acne is multifactorial, increased sebum production due to androgens acting at the sebaceous follicle is seen in all patients with acne.¹⁸ In the past, oral anti-androgenic therapies have been limited by their systemic effects, including teratogenicity in women and gynecomastia in men. With the latest nanopreparation, cyproterone acetate-loaded solid lipid nanoparticles (SLN), researchers have observed enhanced skin absorption with reduced systemic side effects compared with the oral administration.¹⁹

Condyloma acuminata treatment

The most common sexually transmitted infections seen by dermatologists are due to mucosal human papillomavirus (HPV) infections. Of those infected with HPV, up to 1% of sexually active individuals between 15 and 19 years of age will develop condyloma acuminata within several months.²⁰ Once an individual contracts HPV, there is no way to eradicate the virus from the body. Podophyllotoxin (POD) has been shown to decrease HPV-infected epithelial cell growth delaying the development of condyloma acuminata but has been linked to severe skin irritation after its systemic absorption.

Research has shown that POD-loaded SLN may avoid the systemic uptake of POD through its strong epidermal localization, unlike the ordinary topical cream and tincture preparations of POD. Furthermore, POD-loaded SLN increased the accumulation of POD in the stratum corneum (SC) of pig skin nearly 3.5 times that of a 0.15% tincture. This finding was thought to be due in part to the small diameters of the SLN and the enhancement of SC permeability by the soybean lecithin incorporated into the SLN preparation.²¹

Skin hyperpigmentation treatment

Melasma, post-inflammatory hyperpigmentation, and senile lentigines are all common examples of benign forms of skin hyperpigmentation. Hyperpigmentation results from an overproduction of melanin by melanocytes and is typically treated by sun avoidance, sunscreen, and a combination of topical all-trans retinoic acid (atRA) with hydroquinone.²² The atRA accelerates epidermal turnover, which in turn causes an acceleration of melanin granule discharge, while hydroquinone suppresses the formation of new melanin.²³ This epidermal turnover replaces a hyperpigmented epidermis with a less-

pigmented one within weeks of treatment. Although it is an effective treatment, the use of atRA and hydroquinone are known to cause irritation and erythema.

Nano-atRA preparations have a similar bleaching efficacy to standard preparations, but they have improved permeation into the SC and may allow for slow release. Retinoid dermatitis is a side effect of nano-atRA but to a lesser degree.²⁴

Another concern with atRA is its poor stability in heat, air, and light, as it contains conjugated double bonds, which are easily isomerized or oxidized creating altered products.^{24,25} Nano-atRA preparations can have colloidal structures, such as micelles and liposomes, and other modifications influencing its physical stability.²⁶ As a result, the solid matrix of SLN offers protection from hydrolysis and oxidation of active pharmaceutical ingredients such as atRA. Thus, these nanopreparations have a longer shelf life, allowing many to be stored for six months to three years without losing their chemical activity.^{22,26}

Atopic dermatitis treatment

The prevalence of atopic dermatitis is increasing in industrialized countries, where 10–20% of children and 1–3% of adults are affected.²⁷ These patients characteristically present with dry skin and pruritus, with failed attempts at alleviation by scratching or rubbing leading to additional inflammation and lichenification. Acute, subacute, and chronic atopic dermatitis are effectively managed by topical glucocorticoids. However, prolonged or excessive use of glucocorticoids has been shown to cause osteoporosis, pituitary–adrenal axis suppression, growth retardation in children, and the inhibition of fibroblasts leading to skin atrophy.^{28,29}

During an atopic dermatitis flare, glucocorticoids can reach the dermis after bypassing the compromised and inflamed epidermis, leading to irreversible skin atrophy.²⁶ In one study, the topical glucocorticoid, prednicarbate (PC), was incorporated into SLN and found to induce a localized effect in the epidermal layer particularly pronounced at 6 h, exceeding that of the standard cream and ointment nearly fourfold. Furthermore, with the use of PC-loaded SLN, PC levels were not enhanced in the deeper dermis, and there was no increase in the concentrations of PC or toxic PC metabolites.²⁹ Nanopreparations of these traditional treatments may enhance drug efficacy and decrease drug toxicity leading to greater patient satisfaction.

Toxicity and adverse effects

Penetration: just skin deep?

Nanoparticles' increased surface area creates increased reactivity, and their small size allows for great mobility

through the human body and the environment.³⁰ Concern exists as to the extent of penetration of nanopreparations of topical medications. According to Rastogia *et al.* in their 2009 study on transdermal penetration, polymer vesicles accumulate in the epidermis with minimal concentration in the deeper layers. They postulate that the site-specific nanoparticle accumulation in the epidermis can be used for sustained delivery of potent topical agents in the treatment of psoriasis.³¹

Still, others disagree with this observed level of penetration and argue that nanoparticles are able to infiltrate beyond the superficial layers of the dermis and possibly into the bloodstream.

Nanoparticles in sunscreen: safe or hazardous?

Sunscreens are one of the most common products utilizing nanotechnology. Traditional inorganic particles in sunscreens, such as ZnO and TiO₂, are larger in size, scatter visible light, and appear white when applied to the skin. Though ZnO and TiO₂ are effective in filtering ultraviolet (UV) A and UVB, the conventional preparations are cosmetically unattractive, leaving an obvious white film on the skin. The cosmetic industry solved this problem by decreasing the size of these inorganic particles down to the nano-scale, which enabled their products to scatter less visible light, creating more transparent and aesthetically-appealing topical products. However, the use of these nano-sized particles, such as nano-TiO₂ and nano-ZnO, has created concern about health risks due to the increased potential for penetration and reactivity in the presence of UV light. While several studies suggest little if any epidermal or dermal penetration of these nanoparticles, recent work in live mice and pigs indicates that topically applied nano-sized TiO₂ particles (<10 nm) may indeed pass through the SC.³²

In a study by Sharma *et al.*,³³ ZnO nanoparticle-induced genotoxicity was investigated using a human epidermal cell line (A431) and a variety of cytotoxicity parameters. A431 cells were exposed to different concentrations of ZnO nanoparticles (0.008–20 µg/ml) for 3–48 hours. The resulting cytotoxicity was determined by assessing lactate dehydrogenase release, mitochondrial activity (MTT assay), and neutral red uptake assay for assessing cell viability, all of which showed evidence of a time-dependent cell compromise. DNA damage was assessed using the Comet assay, which showed a significant amount of DNA damage in the cells exposed to the ZnO nanoparticles for 6 hours at 5 and 0.8 µg/ml concentrations. More damage was found with higher ZnO nanoparticle concentrations. There was also an increase in lipid peroxidation with ZnO nanoparticles at concentrations > 0.08 µg/ml, dose-dependent levels of glutathione depletion (59% at 0.8 µg/ml and 51% at 0.08 µg/ml), decreased catalase activity, and reduced

superoxide dismutase activity after 24 h of exposure to the ZnO nanoparticles. These data provide evidence that even low concentrations of ZnO nanoparticles may have genotoxic effects in human epidermal cells, likely due to lipid peroxidation and oxidative stress.³³

Titanium dioxide + ultraviolet A yields reactive oxygen species

TiO₂ has different crystal forms, including rutile, anatase, and amorphous. The rutile form, or a mixture of rutile and anatase, is generally used in cosmetic sunscreens.³⁴ Studies have found that UV irradiation of the anatase form of TiO₂ can lead to reactive oxygen species (e.g. hydroxyl radical, hydrogen peroxide) formation.^{35–37}

In a 2002 study by Uchino *et al.*, TiO₂ + UV treatment (0–36 mJ/cm²)-induced cytotoxicity was assessed using various sizes (15–400 nm), crystal forms (anatase, rutile, and amorphous), and quantities of TiO₂ (0–100 µg/ml). Results of this study showed that the amount of OH radical formation depended on the anatase crystal form and size in both a dose and exposure-related manner, while the rutile and amorphous forms were less capable of generating OH radicals. They also used Chinese hamster ovary (CHO) cells to examine the OH radicals' cytotoxicity from the first experiment. Uchino *et al.*³⁷ found that cytotoxicity was influenced more by the anatase concentration, while there was no significant change in CHO cell viability with the rutile form. In short, the CHO cells were sensitive to the amount of OH radical formed.

In 2007, Consumer Reports analyzed eight different sunscreens, and although there was not any identification on the bottle, both titanium and zinc nanoparticles were found.³⁸ In their study of sunscreens, Barker and Branch³⁹ found that several of the sunscreens they sampled contained the anatase crystal form of TiO₂. The risks and benefits of using the anatase crystal form of TiO₂ in sunscreens and other cosmetics should be carefully considered, as the risk of OH radical production and cytotoxicity appear to increase in the presence of UV irradiation.

Background on metallic nanoparticle penetration

A major function of the skin, especially the SC, is to provide a protective barrier against the hazardous external environment. The skin is relatively impenetrable to lipophilic particles larger than 600 Daltons in size, whereas lipophilic particles any smaller than this may passively penetrate the skin (See Table 1).⁴⁰ Because some nanoparticles have the capacity to create reactive oxygen species upon UV irradiation, much of the debate regarding the safety of nanoparticles centers around the question of skin penetrability.^{41,42}

Baroli *et al.*⁴³ investigated whether nanoparticles <10 nm (modified iron-based nanoparticles with dimensions similar to those of skin penetration routes), which were not created for skin absorption were capable of penetrating or even permeating the skin. Two different types of nanoparticle dispersions, sodium bis(2-ethyl-hexyl) sulfosuccinate and tetramethylammonium hydroxide, were applied to human skin samples with the use of vertical diffusion cells for 3–24 hours and then quantified for nanoparticle concentration. When comparing back-scattered electron images and chemical analyses, it was found that the nanoparticle-treated skin contained iron aggregates in the SC, sometimes in the epidermis, but rarely below the SC–epidermal junction. The hair infundibulum and skin grooves also had a predilection for nanoparticle penetration. This study supports the possibility of nanoparticles being able to reach the epidermis by way of the SC.⁴³

Recently, Wu *et al.*³² examined both *in vivo* and *in vitro* skin absorption and toxicity of various forms and sizes of nano-TiO₂ (anatase, rutile, and Degussa P25, anatase/rutile) using porcine ear skin and pathogen-free mutant hairless mice. The authors found that *in vitro* exposure of isolated pig skin to TiO₂ for 24 hours led to the detection of nanoparticles in the outermost surface of the SC without any evidence of penetration into epidermis or dermis. However, after exposing live pigs to 5% nano-TiO₂ for 30 days, the nanoparticles had penetrated the SC into the deeper layers of the epidermis, prickly cell layer, and basal cell layer. The authors noted that there was deeper skin penetration with smaller nanoparticle size, leading to a higher likelihood of damaging the various skin support and structures.³²

Wu *et al.* also exposed BALB/c hairless mice for a prolonged period of time (60 days) and found that all of the test nanopigments could penetrate through skin and enter the liver, lung, heart, and various other organs. Dermal exposure to these nanoparticles induced excessive keratinization, atrophy of the dermis, and skin wrinkling due to lipid peroxidation and a reduction in collagen contents in the mouse skin. Because of these findings, the authors suggest that skin penetration studies may have more accurate results when using *in vivo* porcine skin model, and that nanoparticle penetration into the skin following dermal exposure appears to be time-dependent in nature. Further, topical nano-TiO₂ exposure probably leads to dermal toxicity by way of free radical formation, oxidative stress, and collagen depletion, which lead to skin aging and a potential risk to human health over an extended period of time.³²

It is important to note that the majority of studies addressing nanoparticle skin penetration use different animals such as mice, rabbits, and pigs in an attempt to find

an animal model that is best able to predict topical absorption in humans. Each of these animals has varying skin thicknesses, making results difficult to generalize to humans. For example, studies have shown that rabbit skin has greater penetration than rodent skin, which has greater penetration than pig skin, which in turn has greater penetration than human skin.^{41,44} Studies using larger domestic animals are few in number and should be considered in future studies. Additionally, the amount of percutaneous absorption of nanoparticles in short-term studies may be relatively small. Therefore, the long-term accumulation may be of greater relevance and consequence. The inadvertent transference and absorption of topically applied substances containing nanoparticles via the gastrointestinal, ocular, and respiratory systems has not been closely examined. These other routes of entry may prove to be more concerning than percutaneous absorption.

Conclusions

Over the millennia, organisms have developed methods for handling small amounts of naturally occurring nanoparticles. Concern exists over the potential for illnesses associated with accumulating an overwhelming concentration of nanoparticles within an organism that is not equipped to dispose of such excess. Concern increases when considering the array of engineered nanomaterials that are presently under development or in production. Toxicology frequently lags behind technological advances, and it is difficult to say which specific diseases we may see associated with “nanoparticle overloading” due to their increased use and unintentional ingestion from a variety of sources.⁴⁵ For example, 10 years ago no one would have predicted that organic chelated gadolinium complexes (i.e. nanoparticle-sized gadolinium) used in magnetic resonance imaging could cause nephrogenic systemic fibrosis.^{46,47} Nephrogenic systemic fibrosis appears to be a dose–response to gadolinium, as even normal rats develop the disease when given sufficient quantities of gadolinium.⁴⁶ The lungs’ response to inhaled particles can lead to fibrosis and chronic obstructive pulmonary disease.⁴⁵ The effects of nanoparticles on the gastrointestinal tract, including the liver, are unclear at this time.

Sunscreen use is a cost-effective means to reduce the incidence of skin cancer.⁴⁸ Still, studies have shown a causal relationship between nanoparticles (e.g. TiO₂) and dermal toxicity, though most have been short-term and used non-human cells. While the health-protective benefits of sunscreen use are well known, possible adverse health risks associated with the recently developed nanoscale ZnO and TiO₂ formulations are not yet fully resolved.

According to Newman *et al.*⁴¹ in their 2009 analysis of data from 1980 to 2008, there is no evidence to suggest that TiO₂ and ZnO nano-sized particles reach significantly beyond the SC. This suggests that proper and careful application, as directed, does not result in detectable internal exposure. Still, with daily or regular application of nanoparticle sunscreens, the long-term effects of chronic, repeated exposure are largely unknown. Whether toxicity exists from incidental ingestion and inhalation, trace amounts being absorbed dermally, or from direct reactive oxygen species formation in the skin itself, much is still unknown about the safety of these products.

Questions

- Which of the following is one of the primary nano-materials found in skincare products?
 - FeTiO₃
 - TiO₂
 - Zn₂O₃
 - TiO₃
- Cyproterone acetate-loaded solid lipid nanoparticles have enhanced skin absorption with increased systemic side effects compared with the oral administration.
 - True
 - False
- Topical podophyllotoxin-loaded solid lipid nanoparticles are thought to be less irritating due to
 - Increased systemic uptake
 - Decreased epidermal localization
 - Strong epidermal localization
 - Decreased efficacy
- Nanopreparations of all-trans retinoic acid with hydroquinone have a longer shelf life.
 - True
 - False
- Studies have shown which form of TiO₂ leads to increased formation of the most reactive oxygen species?
 - Rutile
 - Amorphous
 - Degussa P25
 - Anatase
- Lipophilic particles larger than 1000 Daltons can penetrate the skin.
 - True
 - False
- Dermal exposure to nanoparticles in hairless mice has not shown which of the following?
 - Excessive keratinization
 - Atrophy of the dermis
 - Skin wrinkling
 - Reduced lipid peroxidation
 - Reduced collagen
- Topical nanopreparations are not currently used to treat
 - Atopic dermatitis
 - Post-inflammatory hyperpigmentation
 - Scabies
 - Acne vulgaris
- The anatase crystal form of TiO₂ has been found in sunscreen on the market.
 - True
 - False
- Topical nanoparticles have been found to penetrate
 - Subcutaneous tissue
 - Hair infundibulum
 - Nail
 - Fascia

Answers on page 254.

References

- National Nanotechnology Initiative. <http://www.nano.gov/index.html> (accessed February 2nd, 2010).
- Nanotechnology: Big Things from a Tiny World. http://www.nano.gov/Nanotechnology_BigThingsfromaTinyWorld-print.pdf (accessed September 9th, 2009).
- Bawa R. Patents and nanomedicine. *Nanomedicine* 2007; 2: 351–374.
- Kahan DM, Slovic P, Braman D, *et al.* Nanotechnology risk perceptions: the influence of affect and values. In: *Woodrow Wilson International Center for Scholars*, 2009. http://www.nanoaction.org/doc/Kimbrell_CTA_Nano_FDA_Public%20Meeting_10_06.pdf
- Wilson Center and the Pew Charitable Trusts. *Nanotechnology-enabled Consumer Products Top the 1,000 Mark*. http://www.pewtrusts.org/news_room_detail.aspx?id=54793&WT.rss_ev=f&WT.rss_f=Science&WT.rss_a=Nanotechnology-enabled%20Consumer%20Products%20Top%20the%201,000%20Mark&WT.z_contenttype=PressRelease: Wilson Center and the Pew Charitable Trusts, 2009.
- Nohynek GJ, Lademann J, Ribaud C, *et al.* Grey goo on the skin? Nanotechnology, cosmetic and sunscreen safety. *Crit Rev Toxicol* 2007; 37: 251–277.
- Roco MC. Environmentally responsible development of nanotechnology. *Environ Sci Technol* 2005; 39: 106A–112A.
- Greenwood NN, Earnshaw A. *Chemistry of the Elements*. Oxford: Pergamon, 1984, 1117–1119.
- Datye AK, Riegel G, Bolton JR, *et al.* Microstructural characterization of a fumed titanium dioxide photocatalyst. *J Solid State Chem* 1995; 115: 236–239.

- 10 Liang S-S, Makamba H, Huang S-Y, *et al.* Nano-titanium dioxide composites for the enrichment of phosphopeptides. *J Chromatogr A* 2006; **1116**: 38–45.
- 11 Nakano K, Egashira K, Masuda S, *et al.* Formulation of nanoparticle-eluting stents by a cationic electrodeposition coating technology: efficient nano-drug delivery via bioabsorbable polymeric nanoparticle-eluting stents in porcine coronary arteries. *JACC Cardiovasc Interv* 2009; **2**(4): 277–283.
- 12 Rolland A. Clinical pharmacokinetics of doxorubicin in hepatoma patients after a single intravenous injection of free or nanoparticle-bound anthracycline. *Int J Pharm* 1989; **54**: 113–121.
- 13 Tseng C, Su W, Yen K, *et al.* The use of biotinylated-EGF-modified gelatin nanoparticle carrier to enhance cisplatin accumulation in cancerous lungs via inhalation. *Biomaterials* 2009; **30**: 3476–3485.
- 14 Liu G, Men P, Kudo W, *et al.* Nanoparticle-chelator conjugates as inhibitors of amyloid- β aggregation and neurotoxicity: a novel therapeutic approach for Alzheimer's disease. *Neurosci Lett* 2009; **455**: 187–190.
- 15 Turosa E, Shima JY, Wang Y, *et al.* Antibiotic-conjugated polyacrylate nanoparticles: new opportunities for development of anti-MRSA agents. *Bioorg Med Chem Lett* 2007; **17**: 53–56.
- 16 Katsambas AD. Why and when the treatment of acne fails. What to do. *Dermatology* 1998; **196**: 158–161.
- 17 Webster GF. Topical tretinoin in acne therapy. *J Am Acad Dermatol* 1998; **39**: S38–S44.
- 18 Gollnick H, Cunliffe W, Berson D, *et al.* Management of acne: a report from a global alliance to improve outcomes in acne. *J Am Acad Dermatol* 2003; **49**: S1–S38.
- 19 Pardeike J, Hommoss A, Müller RH. Lipid nanoparticles (SLN, NLC) in cosmetic and pharmaceutical dermal products. *Int J Pharm* 2009; **366**: 170–184.
- 20 Wolff K, Johnson RA. *Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology*, 6th edn. Part III—Diseases due to microbial agents; Section 30: Sexually transmitted infections. New York: McGraw-Hill, 2009. pp. 896–941.
- 21 Chen H, Chang X, Du D, *et al.* Podophyllotoxin-loaded solid lipid nanoparticles for epidermal targeting. *J Control Release* 2006; **110**: 296–306.
- 22 Sato K, Matsumoto D, Iizuka F, *et al.* A clinical trial of topical bleaching treatment with nanoscale tretinoin particles and hydroquinone for hyperpigmented skin lesions. *Dermatol Surg* 2007; **33**: 937–944.
- 23 Yoshimura K, Tsukamoto K, Okazaki M, *et al.* Effects of all-trans retinoic acid on melanogenesis in pigmented skin equivalents and monolayer culture of melanocytes. *J Dermatol Sci* 2001; **27**(Suppl. 1): S68–S75.
- 24 Gatti R, Gioia MG, Cavrini V. Analysis and stability study of retinoids in pharmaceuticals by LC with fluorescence detection. *J Pharm Biomed Anal* 2000; **23**: 147–159.
- 25 Alam M, Kundu RV, Bhatia AC, *et al.* *Cosmetic Dermatology for Skin of Color*. New York: McGraw-Hill, 2008.
- 26 Schäfer-Korting M, Mehnert W, Korting H. Lipid nanoparticles for improved topical application of drugs for skin diseases. *Adv Drug Deliv Rev* 2007; **59**: 427–443.
- 27 Saito H. Much atopy about the skin: genome-wide molecular analysis of atopic eczema. *Int Arch Allergy Immunol* 2005; **137**: 319–325.
- 28 Wolff K, Johnson RA. *Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology*. 6th edn. Part I—Disorders presenting in the skin and mucous membranes; Section 2: Eczema/Dermatitis. 2009. New York: McGraw-Hill, 2009. pp. 20–52.
- 29 Maia CS, Mehnert W, Schaller M, *et al.* Drug targeting by solid lipid nanoparticles for dermal use. *J Drug Target* 2002; **10**: 489–495.
- 30 Kimbrell G. Nanotechnology and nanomaterials in consumer products: regulatory challenges and necessary amendments. FDA Public Meeting on Nanotechnology, 2006. http://www.nanoaction.org/doc/Kimbrell_CTA_Nano_FDA_Public%20Meeting_10_06.pdf.
- 31 Rastogia R, Ananda S, Koula V. Flexible polyerosomes—an alternative vehicle for topical delivery. *Colloids Surf B* 2009; **72**: 161–166.
- 32 Wu J, Liu W, Xue C, *et al.* Toxicity and penetration of TiO₂ nanoparticles in hairless mice and porcine skin after subchronic dermal exposure. *Toxicol Lett* 2009; **191**: 1–8.
- 33 Sharma V, Shukla RK, Saxena N, *et al.* DNA damaging potential of zinc oxide nanoparticles in human epidermal cells. *Toxicol Lett* 2009; **185**: 211–218.
- 34 Dussert AS, Gooris E. Characterization of the mineral content of a physical sunscreen emulsion and its distribution onto human stratum corneum. *Int J Cosmet Sci* 1997; **19**: 119–129.
- 35 Jaroenworarluck A, Sunsaneeyametha W, Kosachan N, *et al.* Characteristics of silica-coated TiO₂ and its UV absorption for sunscreen cosmetic. *Surf Interface Anal* 2006; **38**: 473–477.
- 36 Cai R, Kubota Y, Shuin T, *et al.* Induction of cytotoxicity by photoexcited TiO₂ particles. *Cancer Res* 1992; **52**(8): 2346–2348.
- 37 Uchino T, Tokunaga H, Ando M, *et al.* Quantitative determination of OH radical generation and its cytotoxicity induced by TiO₂-UVA treatment. *Toxicol In Vitro* 2002; **16**: 629–635.
- 38 Consumer-Union. 2007 Sunscreens: some are short on protection. *Consum Rep* 2007; **72**: 6.
- 39 Barker P, Branch A. The interaction of modern sunscreen formulations with surface coatings. *Prog Org Coat* 2008; **62**: 313–320.
- 40 Barry B. Novel mechanisms and devices to enable successful transdermal drug delivery. *Eur J Pharm Sci* 2001; **14**: 101–114.
- 41 Newman MD, Stotland M, Ellis JI. The safety of nanosized particles in titanium dioxide- and zinc

- oxide-based sunscreens. *J Am Acad Dermatol* 2009; 61: 685–692.
- 42 Nohynek GJ, Dufour EK, Roberts MS. Nanotechnology, cosmetics and the skin: is there a health risk? *Skin Pharmacol Physiol* 2008; 21(3): 136–149.
 - 43 Baroli B, Ennas MG, Loffredo F, et al. Penetration of metallic nanoparticles in human full-thickness skin. *J Invest Dermatol* 2007; 127: 1701–1712.
 - 44 Magnusson BM, Walters KA, Roberts MS. Veterinary drug delivery: potential for skin penetration enhancement. *Adv Drug Deliv Rev* 2001; 50: 205–227.
 - 45 Warheit D, Sayes C, Reed K, et al. Health effects related to nanoparticle exposures: environmental, health and safety considerations for assessing hazards and risks. *Pharmacol Ther* 2008; 120: 35–42.
 - 46 Sieber M, Pietsch H, Walter J, et al. A preclinical study to investigate the development of nephrogenic systemic fibrosis: a possible role for gadolinium-based contrast media. *Invest Radiol* 2008; 43: 65–75.
 - 47 Boyd A, Zic J, Abraham J. Gadolinium deposition in nephrogenic fibrosing dermopathy. *J Am Acad Dermatol* 2007; 56: 27–30.
 - 48 Gordon LG, Scuffham PA, van der Pols JC, et al. Regular sunscreen use is a cost-effective approach to skin cancer prevention in subtropical settings. *J Invest Dermatol* 2009; 129: 12.

Answers to questions

1. (b)
2. (b)
3. (c)
4. (a)
5. (d)
6. (b)
7. (d)
8. (c)
9. (a)
10. (b)