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# Photoprotection in the Era of Nanotechnology

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**Commercial sunscreen based on nano-sized titanium dioxide ($TiO_2$) and zinc oxide (ZnO) delivers superior UV protection and reduces whitening on skin compared to the older generations of inorganic sunscreens. This review discusses the historical use of nano-sized $TiO_2$ and ZnO in sunscreen and the relationship between UV attenuation and the primary particles, aggregates and agglomerates that make up these inorganic oxides. In addition we reviewed the recent safety concerns surrounding these materials, specifically, percutaneous penetration of $TiO_2$ and ZnO nanoparticles through human skin and their potential to cause phototoxicity.**
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Excessive exposure of skin to ultraviolet (UV) radiation induces a wide range of adverse effects, such as sunburn, photoaging, photoimmunosuppression, and photocarcinogenesis.[1-11] Although wearing hats and seeking shade is the most effective method of reducing UV damage, sunscreen is the most widely used form of photoprotection by the public.

Inorganic-based sunscreen composed of mineral UV filters, such as titanium dioxide ($TiO_2$) and zinc oxide (ZnO), have long been regarded as safe and effective. They are especially preferred by individuals with a high propensity for skin irritation over sunscreen containing organic UV filters, such as avobenozone and oxybenzone. Despite these benefits, the use of older generations of sunscreen based on inorganic UV filters was limited because of poor cosmetic elegance. The large particle size of $TiO_2$ and ZnO left a white film on the skin. In addition, the inorganic filters had poor dispersive qualities, leaving users with a grainy after-feel.

Nanotechnology involves the design, production, and application of materials in the size range of 1-100 nm. In the last decade, the wide-reaching impact of this branch of science is becoming more apparent as industry and researchers begin to use nanotechnology to solve a range of challenging problems. The rapid adoption of nanotechnology by different disciplines centers on the fact that researchers can take advantage of a new set of physical, chemical, mechanical, and electrical properties as existing materials are reduced in size <100 nm.

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In the late 1990s, nanosized $TiO_2$ and ZnO were integrated into commercial sunscreen products on a large scale. At the same time there was growing concern, mainly from consumer and environmental groups, regarding the potential safety implications associated with these products penetrating through human skin.

## History of Nanosized $TiO_2$ and ZnO

The public's interest and awareness of the use of nanosized $TiO_2$ and ZnO in sunscreen has rapidly developed during the last few years. The interest is largely driven by alleged safety concerns surrounding these materials. When one reviews the history of metal oxides in sunscreen products, it may be surprising to many that nanoparticles have been used in sunscreens since the early 1980s. Nanosize $TiO_2$ and ZnO are essential to achieve effective sun protection; the issue with older-generation sunscreen products is the board distribution of particle sizes in the products. The oversized particles caused excessive whitening on the skin, resulting in reluctance by consumers to use the products.

Patents on nanosized $TiO_2$ and ZnO with average size <100 nm were filed in the 1980s detailing the benefits of these products to provide superior UV protection and improved cosmetic appearance. In addition, engineering and technical breakthroughs allowed mass production of nanosized metal oxides with narrow size distribution and permitted the incorporation of these materials into sunscreen formulations. Since the 1990s, the use of nanosized $TiO_2$ has increased dramatically followed by the exploitation of nanosized ZnO in the later part of the decade.

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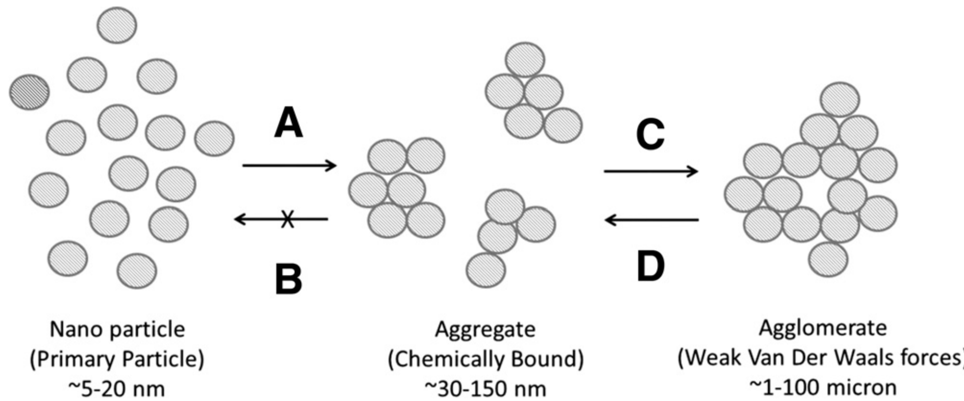


**Figure 1** Formation of $TiO_2$ aggregates and agglomerates from nanoparticle building blocks.

## Three States of Nano $TiO_2$ and ZnO

Nanosized $TiO_2$ and ZnO exist in 3 different states: (1) primary particles, (2) aggregates, and (3) agglomerates. Manufacturing primary particles is the first stage in producing $TiO_2$ and ZnO nanoparticles. The size of primary particles typically ranges from 5 to 20 nm. Because of the strong attraction forces between individual crystals, primary particles cluster together and form tightly bound aggregates, which have a larger size than their primary building blocks (Fig. 1, sequence a).[12] The sizes of these aggregates are typically between 30 and 150 nm and represent the smallest units that actually occur in a final sunscreen formulation. The forces required to break apart the aggregates into individual primary particles (Fig. 1, sequence b) are far greater than those encountered during production of sunscreen formulations or application of these products onto skin.

The situation is complicated further because the aggregates form loosely-bound agglomerates (Fig. 1, sequence c) because of the drying and heat treatment processes encountered during manufacturing. The agglomerates have particle sizes $>1$ $\mu$m, which is typical of the size of nano $TiO_2$ and ZnO powder. The large agglomerates are not effective at providing the desired UV attenuation; hence, the agglomerates must be broken down into aggregates (Fig. 1, sequence d).

The UV absorption profiles of $TiO_2$ and ZnO are largely dependent on the aggregate size of the metal oxides. Sun protection factor (SPF) varies significantly if sunscreen formulations are made with the same concentration of inorganic particles, but the size of the particles in formulation varies. In contrast, the UV absorption profiles of organic UV filters are more closely related to the concentration of the filters. Figure 2 shows the UV-visible properties of titanium dioxide for 3 different aggregate sizes.

## The Relationship Between UV Attenuation and Particle Size

$TiO_2$ particles with an average aggregate size of approximately 100 nm (red curve) offers effective UVA and UVB protection. Significant scattering is noted in the visible region of the spectrum, but the resulting whitening effect is much less than sun creams produced by older grades of TiO2. In comparison, $TiO_2$ particles with an average aggregate size of approximately 50 nm (green curve) offer higher UVB but lower UVA protection. At the same time, there is also significantly less scattering in the visible region. Hence, aggregated $TiO_2$ in the 50 nm size range is more transparent but has to be combined with other UVA filters to achieve a formulation with broad spectrum protection. $TiO_2$ particles with an average aggregate size of 20 nm (blue curve) offers significantly lower protection from UVA and UVB radiation compared with 50- and 100-nm aggregates.

Aside from choosing the optimal size of inorganic particles, it is crucial to maintain the particle size in the final sunscreen formulation. As discussed previously, primary particles of nano $TiO_2$ and ZnO cluster to form aggregates and agglomerates. To obtain the desired UV absorption profile and hence the target SPF, treatment of nano metal oxides is required to maintain the optimum aggregate size in final formulation. Nanosized $TiO_2$ and ZnO are usually stabilized

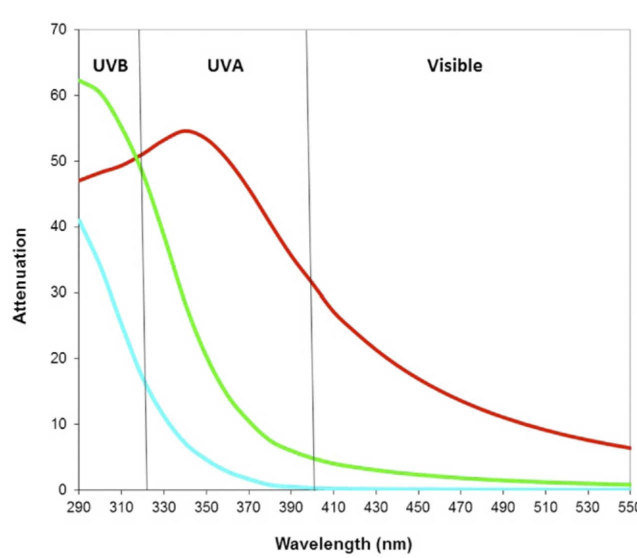


**Figure 2** UV-visible attenuation versus wavelength for spherical titanium dioxide of varying particle size. Blue line, 20 nm; green line, 50 nm; and red line, 100 nm.

by dispersing agents to maintain the fine aggregate size and prevent the reformation of agglomerates.

To illustrate the effect of particle dispersion on SPF performance, 2 sunscreen products were produced containing aggregates and agglomerates of the same base titanium dioxide. Formulation A, was produced from agglomerated $TiO_2$ powder added to the oil phase of the sunscreen. Formulation B, was based on the same agglomerated $TiO_2$ used in formulation A; however, the powder was predispersed in $C_{12}$–$C_{15}$ alkyl benzoate in the presence of a dispersing agent to produce stable aggregates before it was added to the oil phase of the formulation. In vitro SPF measurements were conducted to assess the SPF of the formulations. The SPF value of formulation B (ie, predispersed $TiO_2$ containing aggregates) was 5 times greater than that of formulation A prepared from agglomerated $TiO_2$ powder.

## Safety Concerns for Nano $TiO_2$ and ZnO

The safety concerns associated with nanosized $TiO_2$- and ZnO-based sunscreens are centered on 2 issues: potential toxicity and percutaneous penetration of nano-materials through skin. In toxicity, the issue is related to the potential of micro and nanosized $TiO_2$ and ZnO to generate free radicals and reactive oxygen species (ROS) during exposure to UV radiation.[13-16-22] ROS have the potential to damage DNA, leading to point mutation, single-strand breakage, and sister chromatin exchange. Collectively this conglomeration of damage can potentially alter the integrity of the genetic code of living tissue. In addition, ROS can also damage proteins and lipids, causing irreversible injury to cells and tissue.

The potential damage of nanosized $TiO_2$ and ZnO was demonstrated by in vitro studies in which data were generated using cell culture models.[17-20] However, the results from these data are not as conclusive as other in vitro studies[23]; they fail to demonstrate similar toxic effects on mammalian cells. When considering the biological implication of these in vitro experiments, it is important to take into account other factors that can eliminate or reduce these potential risks. First, techniques are available to coat the surface of nanosize $TiO_2$ and ZnO to reduce formation of free radicals at the surface of the oxides, even after UV exposure.[24-27] In view of the potential for free radical production, suppliers of nanosized $TiO_2$ and ZnO provide an extra layer of protection during the manufacturing process. Second, the skin has in place an elaborate antioxidant mechanism, composed of both enzymes and nonenzymatic molecules, to quench ROS. As a result, ROS generated by $TiO_2$ and ZnO nanoparticles during UV exposure can be neutralized by the body's natural defense mechanism. Finally, it is important to remember the overall safety record of both $TiO_2$ and ZnO. Both metal oxides have been widely used in various consumer products for decades. $TiO_2$ can be found in toothpaste, lotion, skimmed milk, and cottage cheese, and ZnO is a major component in many baby powders, antidandruff shampoos, as well as barrier creams.

Another critical part in evaluating the safety profile is predicated on whether $TiO_2$ and ZnO nanoparticles penetrate the human skin. A large body of studies from government, industry, and academia has shown that nanosized $TiO_2$ and ZnO do not appear to penetrate the intact stratum corneum of healthy human skin in adults.[28-44]

Although some nanomaterials can be found in the pilosebaceous openings and superficial portion of the follicles, the likelihood of nanomaterials entering living skin tissue via the transfollicular route is considered negligible, mainly because growing hair shafts tend to push materials to the surface of the skin.

A number of factors may explain poor penetration through the stratum corneum in intact and healthy human skin. The stratum corneum serves as an effective physical barrier in preventing the penetration of nanomaterials. The nanoparticles may be deposited within the stratum corneum, but the constant shedding and renewal process of the epidermis prevents long-term accumulation and penetration of nanoparticles into the viable components of skin tissue. Secondly, as mentioned above, nanosized $TiO_2$ and ZnO exist as aggregates, and agglomerates in sunscreen products.

In summary, overwhelming evidence suggests that nanosized $TiO_2$ and ZnO are safe when applied to intact human skin. However, much more research is needed to assess the penetration of nanomaterials through compromised and diseased skin. To date, a review of literature shows no conclusive evidence that compromised skin should always lead to greater penetration. In some cases, psoriasis, hyperkeratosis and thickening of the stratum corneum can reduce penetration. Aside from topical penetration, studies on the effect of systemic absorption via oral ingestion and inhalation are needed. Several studies have demonstrated that inhaled $TiO_2$powder leads to an inflammatory reaction in the lungs, which is a potential risk for workers handling nanomaterials during the manufacturing process.

## Conclusions

Sunscreen is and will continue to be a vital part of photoprotective measures for the public. The advancement in nanotechnology and subsequent incorporation of nanosized $TiO_2$ and ZnO into sunscreen has allowed formulators to create more effective and cosmetically elegant products. In developing modern inorganic sunscreens based on nanoparticles, formulators need to understand the UV-visible properties of $TiO_2$ and ZnO nanomaterials in relation to their particle size. A systemic and methodical approach is required to maintain the optimal size of these nanoparticles in the final sunscreen formulation. Although the debate regarding the safety issue of these nanomaterials is not likely to abate soon, current research strongly argues in favor of their overall safety profiles when applied to intact human skin.

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