The 2011 Nanodermatology Society Position Statement on Sunscreens

Introduction

The harmful effects of both short-term and long-term sun exposure have been well described and range from accelerated skin aging to skin cancer, a potentially fatal condition. One of the most common approaches to prevent this damage or harm is with the application of sunscreens, which contain a variety of chemicals and minerals that act to block or reflect ultraviolet (UV) radiation, the component of sunlight that is responsible for many of its harmful effects. For years, titanium dioxide (TiO_2) and zinc oxide (ZnO) have been used in sunscreens since they serve as a physical barrier to both short (UVB) and long wave (UVA) UV radiation and thus decrease the amount of radiation to which the skin is exposed. However, these ingredients in their native state are not water soluble, but are opaque and coat the skin when applied with an oily and cosmetically displeasing white residue, resulting in limited consumer use. In recent years, there has been a revival of TiO_2 and ZnO use in sunscreens as the science of nanotechnology has allowed for improved versions of these products.

Nanotechnology involves the design, production, and application of materials that are extremely small, (1 nanometer = one billionth of a meter)[1]. When this technology is applied to sunscreens, specifically nano-sized TiO_2 and ZnO, these products do not have the thick feel or unsightly chalky film as compared to their predecessors. Even more importantly, sunscreens with these nanomaterials offer superior UV protection when compared to conventional formulations[2,3]. However, many organizations and regulatory bodies have raised concerns regarding the safety of nanoparticle sunscreens.

These concerns are based on the unique properties of materials at the "nano" level, which include increased surface area to weight ratio (provides more surface to interact with the environment) and enhanced skin and organ penetration capabilities. As such, agencies wonder if these nanoparticles are toxic to living cells and if they are capable of being absorbed through the skin into the bloodstream. Regulatory agencies have reviewed studies that have focused on the safety of nanoparticle formulations. These results have been presented by the Environmental Protection Agency (EPA), Environmental Working Group (EWG), European Union (EU) and Australia's Therapeutic Goods Administration (TGA), among other groups. This paper reviews important questions regarding titanium and zinc nanoparticles and sunscreen safety.

Are TiO_2 and ZnO nanoparticles toxic to cells?

Recently, it was discovered that nanosized titanium and zinc generate free radicals or reactive oxygen species (ROS) when exposed to UV radiation. ROS are chemically-reactive molecules that have the potential to significantly damage proteins, DNA, RNA, and fats within cells. The actual toxicity of the nanoparticles depends on a variety of factors including their size, structure, surface properties (coating), and ability to aggregate. For example, several crystal forms of nanosized TiO_2 exist, and differ in the amount of damage they exert on cells. In addition, coating with manganese[4] or other materials[5-7] has been shown to limit the formation of free radicals.

Damage associated with free radical formation is dependent on their ability to interact with living cells. Two barriers must be surmounted for nanoparticle toxicity to occur: penetration in the body via the skin, and host defenses against ROS by neutralizing enzymes and small molecules. It is important to remember that the evidence implicating nanoparticles as a skin toxin has been generated from *in vitro,* studies[4,7-14], meaning they were performed outside the living body[15]. In contrast, topical application studies performed within living organisms (*in vivo*) have not yielded the same results[1,16]. This is largely due to the protective barrier of the skin, which defends animals/humans from this interaction with ROS. Therefore, the major safety concern depends on the ability of nanoparticles to penetrate the initial layers of the skin[17,18].

Do nanoparticles penetrate through the skin?

The skin is divided into three major components, including the outermost epidermis, the dermis beneath, and subcutaneous tissues deeper still. Each component has several layers. The outermost layer of the epidermis, the stratum corneum, is composed of a wall of dead skin cells and is the rate-limiting barrier against absorption or penetration of substances applied to the skin[16]. Furthermore, the stratum corneum is constantly shed, and any matter attached to it sloughs away from the body accordingly. Many studies have investigated the ability of nano-titanium and zinc to penetrate the skin[11,16,19-35] with the majority demonstrating an inability of the particles to pass through the stratum corneum and reach living cells.

Most of these studies were performed in intact, healthy skin. However, penetration may be influenced by other factors such as the presence of hair follicles, skin disease such as eczema, or if the skin is damaged[18,36,37]. It is well known that nanoparticles are capable of entering open hair follicles[29,30,34] which is concerning since hair follicles originate in the dermis and therefore act as portals to deeper skin layers. One mitigating factor is the architecture of the hair follicle, which is constantly changing over due to growing hair strands, likely pushing trapped nanoparticles towards the skin surface. Furthermore, hair follicles are lined by a tough, thick shell that would make it difficult for particles to exit the area and reach the surrounding dermis[29]. Mechanical stressors may also increase the rate at which nanoparticles penetrate the dermis. For example, skin overlying joint surfaces is constantly flexed or stretched, and, as a result, is more susceptible to particle penetration. Similarly, damage to the skin surface from disease or injury results in a loss of its protective barrier function[16,38]. Although more research must be conducted to understand the potential penetration of nanoparticles through damaged and diseased skin, one study found no change or a minimal increase in nanoparticle penetration in both flexed and scraped skin, respectively[39].

The stratum corneum has two defenses against nanoparticle penetration: it is a physical barrier; and it is constantly shed and renewed. Nanoparticle penetration is also limited by their size. In solution, nanoparticles rarely exist as individual particles, but instead group together to form larger clusters, that are often tens or hundreds of times larger than individual particles, essentially functioning as microparticles, well outside the nano range [15]. Therefore nano-based sunscreens may not behave as true nanoparticles, both in their ability to penetrate the skin, or to demonstrate the high surface to weight ration associated with increased toxicity.

Are there other health concerns?

Although nano-titanium and zinc sunscreens have been deemed safe by several regulatory bodies with respect to skin penetration, there are still concerns regarding the occupational and environmental hazards that nanomaterials may pose. Inhalation may be the most harmful route of nanoparticle exposure, and while this is a small concern for consumers of skin care products, it poses a significant risk for workers handling the product before it reaches store shelves[40]. Several studies have shown that inhaled TiO_2 particles induce a harmful inflammatory response in the lungs[41,42], and these exposed workers may not be receiving adequate protection[43].

TiO_2 and ZnO particles may also impact the environment in several ways. Depending on manufacturing techniques, nanoparticles can be released into the air or water. Consumers may also contribute to water contamination, as residual nanoparticles run off their skin while bathing or swimming. Ultimately, nanoparticles could contaminate water, soil, and food products[44]. The EPA has acknowledge these potential risks and is planning to conduct a comprehensive environmental assessment of the potential risks related to nano-titanium and nano-zinc[41].

What's the bottom line?

Recently, a study from Australia reported that daily sunscreen use reduces the risk of melanoma by 50%, and reduces the risk of squamous cell carcinoma, another type of skin cancer, by 39%[45]. Therefore, the importance of sun protection is unquestionable. Although more research is needed to solidify the environmental and occupational risks, the Nanodermatology Society believes that nano-based sunscreens do not pose serious health risks to consumers and agrees with non-profit agencies like the Environmental Working Group, which states: "Zinc and titanium-based formulations are among the safest, most effective, sunscreens on the market"[40]. This statement is based on the current evidence showing:

- Consumers using zinc and titanium sunscreen products are exposed to 20% less UVA radiation than those using sunscreens without these products[40].
- Nano-titanium and zinc do not penetrate the outer layer of human skin, even through hair follicles.
- Nano-titanium and zinc do not reach living cells, and therefore pose no risk of toxicity.

As the summer months approach, we encourage all individuals to protect themselves from the damaging effects of the sun. In concurrence with the American Academy of Dermatology (AAD)[46] we suggest:

- Wear protective clothing including a wide-brimmed hat and sunglasses
- For areas that are exposed, apply a water-resistant sunscreen with a Sun Protection Factor (SPF) of 30 or above that provides both UVA and UVB protection.
- Reapply sunscreen every 2 hours, regardless of activity (swimming, sweating)
- Seek shade, especially when the sun's rays are strongest between 10am and 4pm.

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