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REVIEW ARTICLE

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A review of inorganic UV filters zinc oxide and titanium dioxide

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Summary

Photoprotection has become integral in the prevention of keratinocyte cancer and photoaging. Organic ultraviolet (UV) filters such as oxybenzone and octinoxate have become controversial due to their potential impact on the environmental and their potential human health risks. As such, inorganic UV filters, zinc oxide (ZnO) and titanium dioxide (TiO_2), have become paramount in discussions about photoprotection. ZnO and TiO_2 are used in sunscreens as nanoparticles, which denotes a size <100 nm. The smaller size of these mineral particles increases their cosmetic acceptability by users as they are much less visible after application. ZnO has a broad UVA-UVB absorption curve, while TiO_2 provides better UVB protection. Overall, the human health risks with inorganic filters are extremely low given a lack of percutaneous absorption; however, there is potential risk when exposed via inhalation, prompting recommendations against spray sunscreen products with nanoparticles. At this time, the known risk to the environment is low though the risk stratification may evolve with increasing usage of these filters and higher environmental concentrations. The continued practice of photoprotection is critical. The public should be counseled to seek shade, use photoprotective clothing including hats and glasses in addition to sunscreens on sun-exposed skin. For those concerned about emerging evidence of environmental impact of organic UV filters, based on current evidence, ZnO and TiO_2-containing sunscreens are safe alternatives.

1 | INTRODUCTION

Keratinocyte cancer, including basal and squamous cell carcinoma, is the most common malignancy in the United States[1] affecting up to 3 million Americans annually.[2] Ultraviolet (UV) radiation is a main risk factor for skin cancer development; it also induces erythema and photoaging. Photoprotection is utilized to protect the skin from these negative effects of UV radiation with sunscreen as an integral part of the photoprotective strategy.

In 2018, the Environmental Working Group (EWG) reported that two-thirds of the sunscreens available in the United States contained chemicals that EWG deemed to be harmful to the environment, which are predominantly organic filters.[3] This is due to the environmental effects of these filters, including an effect on coral reefs, as well as their prevalence in the water supply and in aquatic animals. Furthermore, organic filters have been reported to have negative hormonal effects in animal models.[4] While there have not been any known effects in humans, they are continuing to be examined.[5] It should be noted that although these risks are being reported, a formal environmental risk assessment, as is done for pesticides and other chemicals, has not yet been performed. On May 1, 2018, the Hawaiian state legislature passed a bill banning the sale and distribution of sunscreens containing organic filters oxybenzone and octinoxate;[6] at the time of this writing, it is anticipated that the bill will become law, effective 2021. Other states are proposing similar legislation. With the controversies of organic sunscreens, the role of inorganic sunscreens has become paramount to consider for patients.

There are two inorganic filters (also known as mineral filters) approved by U.S. Food and Drug Administration (FDA): titanium dioxide (TiO_2) and zinc oxide (ZnO); both are metal oxide particles.[7] These molecules absorb, reflect and refract UV photons but function in photoprotection primarily by absorbing UV radiation.[8] The initial formulations of mineral filter-containing sunscreens often left a white, chalky appearance on the skin, which is most noticeable in dark-skin individuals. Cosmesis and patient satisfaction encouraged new formulations by decreasing particle size culminating in the usage of nanoparticles. In 2018, the EWG reported that a large increase in these inorganic filters with ~41% of sunscreens in the United States designated as mineral only. This figure has more than doubled (from 17%) since 2007.[3]

This review article will discuss the role of inorganic filters in photoprotection, including mechanism and safety concerns. We will also evaluate their reported potential environmental impact. To conclude, we will propose photoprotection recommendations.

2 | WHAT ARE NANOPARTICLES?

Nanoparticles have wide applications in the cosmetic industry; they are a key component of inorganic sunscreens. ZnO and TiO_2 have been used in sunscreens since the 1980s.[9] Normally, ZnO and TiO_2 range in size from 200-400 nm and 150-300 nm, respectively.[7] The larger particle size accounts for the white, chalky texture on the skin's surface as these particles reflect incident visible light, which is perceived by the retina as white.[3] Nanoparticles refer to particles that are <100 nm in diameter, which are small enough to be undetectable by conventional microscopes.[10,11] These smaller particles allow most sunscreen formulations to be applied smoothly and transparently.[3]

Nanoparticles are an area of ongoing investigation and research. In 2002, there were over 22 000 articles and 1900 patents published compared to only 1000 articles 12 years prior.[10] ZnO and TiO_2 nanoparticles utilized in sunscreens reflect only a small portion of incident visible light, which allows most products to appear transparent. It is important to note that increasing inorganic filter concentrations will decrease their transparency creating a white (ZnO) or blue/white (TiO_2) appearance. These particles provide photoprotection mostly be absorbing UV radiation; a small degree of scattering may also occur.[7,8] In the United States, nanoparticles are regulated by the FDA with a broad definition that does not differentiate between variably sized particles smaller than 100 nm.[10] This inclusive definition does not discriminate amongst the different characteristics of nanoparticles of even the same molecule such as size, shape, and surface area.[3]

The nanoparticles of ZnO and TiO_2 exist in three main physical states: (a) primary particles, (b) aggregates, and (c) agglomerates. Primary particles are 5-20 nm in size. When put into suspension, these primary particles bind together through their innate chemical and physical properties forming aggregates. Aggregates range in size from 30 to 150 nm and are the most common physical manifestation of ZnO and TiO_2 in sunscreens. When aggregates clump together, agglomerates are formed. This process occurs primarily during manufacturing where aggregates are exposed to heat and drying processes. These agglomerates are much larger (>1 μm), which reflect more visible light and leave a whitish discoloration on the skin. Agglomerates are converted back to aggregates in the final stages of the manufacturing process.[9]

ZnO and TiO_2 are utilized in sunscreens since they reflect and absorb UV photons. The ability of these particles to protect against UV exposure is directly related to particle size. ZnO has a flat absorption curve across the UVA and UVB spectrum. The absorption spectrum of TiO_2 shifts to a predominantly UVB spectrum as the particle size decreases.[3,7,12,13] When used together, ZnO and TiO_2 provide good broadband UV protection.[13] ZnO and TiO_2 nanoparticles can be coated with various products. Silica is thought to be one of the most effective coatings to prevent a photocatalytic event.[13]

Nanoparticles of ZnO and TiO_2 have the advantages of a nongreasy formulation that is transparent, inexpensive and does not degrade with UV radiation exposure.[14]

3 | HEALTH CONCERNS

As previously discussed, smaller nanoparticles are critical for the improved ease of application and cosmesis while providing UV protection. However, smaller nanoparticles have larger surface areas, which could lead to unwanted consequences identified in vitro such as generation of reactive oxygen species and toxicity.[11] Neurotoxicity is a concern given in vitro and in vivo murine experiments with TiO_2 that demonstrated increased mitochondrial dysfunction, oxidative stress, and hippocampal cell apoptosis.[15,16] It should be emphasized that based on currently available data, inorganic UV filters have few to no health concerns in humans.[3,17,18]

Oxidative stress and cellular toxicity could be a concern were ZnO and TiO_2 able to penetrate the stratum corneum, enter the dermis and ultimately the blood supply. Fortunately, studies both in vivo and in vitro have found that these minerals do not permeate the skin to any significant degree.[7,13,18-22] When nanosized ZnO was examined on human volunteers with twice daily applications over five consecutive days, subjects had <0.01% identified in their blood stream. Additionally, testing was unable to determine if the minimal increase in zinc in the blood was due to the insoluble nanoparticles from the sunscreen or from minute fluctuations in the body's zinc stores.[23,24] In two studies (in vitro porcine and in vivo human volunteers), ZnO and TiO_2 depth of penetration was examined both in normal intact epidermis as well as tape-stripped skin and found a lack of penetration beyond the stratum corneum and pilosebaceous units.[19,25] In one experiment studying UVB damaged skin in a porcine model, ZnO and TiO_2 nanoparticles did penetrate into the epidermis slightly and TiO_2 did reach the superficial dermis; particles did not extend deep into the dermis or the subcutis.[26]

With most products regulated by the FDA, toxicity is examined. Given that ZnO nanoparticles do not appear to be readily absorbed, researchers examined the effects of increased Zn^{2+} ions in the body. Zinc is an important ion in the body, and its levels are tightly regulated. Increasing zinc levels can lead to oxidative stress, mitochondrial dysfunction and cell death in vitro.[7] In vitro and in vivo human and animal studies examined the toxicity of oral and cutaneous exposure to ZnO and TiO_2 nanoparticles as well as skin irritation, phototoxicity, photosensitization, and photoirritation. The risk of toxicity in humans is none to minimal.[18,27] It should be noted that TiO_2 is used as an additive in food, personal care products, and other consumer goods. It provides a white color and is seen in many candies and forms of chewing gum. It has been suggested that US children <10 years of age have been exposed to 1-2 mg TiO_2 kg body weight/d, and those older than 10 years, up to 0.2-0.72 mg TiO_2 kg body weight/d.[3,28]

The risk of ZnO and TiO_2 exposure during pregnancy and lactation has been studied. Experiments were done in mouse and rat animal models to examine the effects of ZnO and TiO_2 on pregnancy, placental development, and fetal development. In these experiments, animals received 100-400 mg/kg/d of ZnO or 100 mg/kg body weight TiO_2 via gavage.[29,30] Pregnant rats exposed to ZnO had decreased body and liver weight; however, no issues related to their pregnancy or offspring.[29] An additional hen animal study found that liver dysfunction identified in pregnant mothers was transferred to offspring.[31] Offspring of pregnant rats exposed to TiO_2 had increased apoptotic cells in the hippocampus and decreased overall neurogenesis.[30] A mouse model study demonstrated pre-mature ovarian failure from TiO_2 nanoparticles ingested via gavage.[32] The placenta had significantly impaired growth and development with dysregulation of vascular proliferation and apoptosis in another mouse model.[33] These studies in animal models demonstrate that TiO_2 has negative impact on pregnancy and fetal development; however, there is no known reported risk in humans, most likely due to the lack of percutaneous absorption.

There are toxicity concerns when considering the manufacturing of ZnO and TiO_2 nanoparticles for sunscreen and other cosmetic products. The lungs are unable to clear nanoparticles, which creates the potential for increased concentrations in the alveolae and possible absorption into the bloodstream. If this were to occur, there is potential for damage to internal organs.[3] In a study of human nasal mucosa cells in vitro, ZnO was detected in the cytoplasm in up to 10% of cells, and in the nucleus in 1.5%.[34] These nanoparticles appeared to induce DNA damage in this in vitro model.[34,35] An in vivo study with 12 human volunteers evaluated the risk of inhalation using 500 $\mu g/m^3$ of ZnO nanoparticles for 2 hours; no acute systemic effect was detected when examining patient symptoms, leukocyte antigen markers, hemostasis, cardiac electrophysiology, and sputum.[20,36] The International Agency for Research on Carcinogens has, however, classified TiO_2 as a possible carcinogen when inhaled in large doses due to an increase in cancer in a rat model.[3,11,13,28] Those most at risk for inhalation of these products are thought to be the workers directly involved in manufacturing. Due to the potential risk with inhalation, the EWG has recommended against powdered products or spray sunscreens containing ZnO and TiO_2.[3,20]

4 | PHOTOMUTAGENESIS

Some forms of ZnO and TiO_2 have semi-conductor and photocatalytic activity under specific conditions. When exposed to UV radiation, TiO_2 > ZnO can induce free radical formation *in vitro*, raising the concern for photomutagenesis.[3,7] Nanoparticles appear to be even more effective free radical generators than larger particles.[3] However, it is interesting that a separate in vitro study with murine cells found ZnO particles protected against UVR induced oxidative stress when used in large enough concentrations.[7] It is likely these discordant in vitro studies that encouraged the International Workshop on Genotoxicity in Test Procedures working group to conclude that photogenotoxicity should no longer be included in safety testing.[37]

It has been suggested than the small amount of free radicals that may be generated on the skin's surface can be contained with the body's own antioxidants.[3] In vitro, certain microsized ZnO particles were found to be photo-stable and non-photocatalytic;[7,38] however, pharmaceutical companies are not required to divulge their different formulations; thus, there may be products that are at higher risk. Because these agents are not readily absorbed, the risk of free radicals affecting cells beyond the superficial stratum corneum and desquamating skin cells is exceedingly low.[20]

5 | ENVIRONMENT

The effect of nanoparticles on the environment is complicated. Because ZnO and TiO_2 are minerals found in the environment, it is difficult to differentiate the effect of the nanoparticles from naturally occurring particles.[39] It has been estimated that the concentration of ZnO and TiO_2 nanoparticles found in aquatic environments would be in the low 10s μg/L, which is very low.[14,39] A group out of Austria evaluated the concentration of nanoparticles in Old Danube Lake in Vienna from suspended particulate matter (SPM). This group used multiple methodologies to identify concentrations of nanoparticles in the environment and found that they could not differentiate sunscreen nanoparticles from natural titanium-bearing nanoparticles but did find a slight overall increase in titanium particles in the summertime that were transient in the SPM. Additionally, using electron microscopy, they found that the nanoparticles do not remain suspended freely in the water for a prolonged period of time but instead aggregate and fall to the sediment.[39] The same process is thought to occur in seawater.[40]

Studies have evaluated the risk to aquatic animals from nanoparticles. In vitro, Zebrafish embryos were bathed in solutions of ZnO and TiO_2 nanoparticles (extracted from sunscreens) at >1 mg/L, which is much higher than current environmental estimates. These Zebrafish demonstrated abnormal embryogenesis and even mortality, which was thought to be due to elevated Zn^+ concentrations but not specifically to the nanoparticles.[14] Another in vitro study found that ZnO nanoparticles were more toxic to zebrafish than Zn^{2+} alone. They concluded that the combination of Zn^{2+} in combination with ZnO nanoparticles is the most toxic to these animals. Interestingly, these effects were mitigated when the study was performed with ZnO particles in the sediment of the cultured zebrafish embryos.[7,41,42] ZnO was found to be detrimental to other living creatures, including roaches, algae, daphnia, earthworms, and other fish embryos.[43-45]

In the laboratory, caribbean coral (*Montastraea faveolata*) were exposed to TiO_2 nanoparticles at concentrations of 0.1 and 10 mg/L for 17 days to better understand coral reef bleaching. During the experiment, the coral expelled its algae culminating in bleaching; however, over time, it appeared to adapt to the stress and possibly recover.[46] In laboratory settings, ZnO nanoparticles caused severe and rapid bleaching of *Acrospora* spp. of coral, whereas TiO_2 only caused mineral alterations. This early study suggested that TiO_2 may be more environmentally friendly though there must be more studies before any conclusions are made.[47]

The effects of nanoparticles on vegetation have been studied. A number of species of agricultural plants exposed to ZnO had decreased seed germination and poor root growth.[7,48] Algae exposed to TiO_2 nanoparticles had decreased growth as well.[28]

The question regarding free radical generation in the environment has been raised. It was found that 1-10 parts per million of nanoparticles on surface water could generate free radicals when exposed to sunlight.[14] In the laboratory, methylene blue was used as a marker of photo-initiated reactions. It was added to water with ZnO or TiO_2 nanoparticles and the solution was exposed to UV light. TiO_2 nanoparticles caused 10 times the breakdown in methylene blue compared to ZnO. In nature, it is known that sunlight would not extend deep enough into the water where these nanoparticles have settled into sediment. Additionally, the concentrations of nanoparticles estimated in the environment (10-100 μg/L of TiO_2) is much lower than what was tested in this experiment.[14]

Therefore, studies have had conflicting results regarding the risk of nanoparticles in the environment.[49-52] At this time, the overall risk to the environment is considered extremely low. Zinc ions present in sunscreens contribute to the concentrations of zinc in the environment. As such, in the European Union, environmental concentrations of zinc are tightly regulated due to potential environmental concerns.[27] Whether the risks to the environment could increase with increasing concentrations of inorganic filters leaching into the environment remain to be observed.[14]

6 | CONCLUSION

With increasing rates of keratinocyte cancer and patient concerns regarding photoaging, photoprotection has become an important part of preventative medicine. Organic sunscreen filters such as oxybenzone and octinoxate have become controversial due to their potential environmental risks, prompting the Hawaiian legislature to pass a bill banning the sale and distribution of sunscreens containing these two filters, which has been signed into law in July 2018.[6] Since the U.S. FDA has not approved any new broad spectrum filters available in many parts of the world, this has resulted in a more prominent role of inorganic filters in photoprotection. ZnO and TiO_2 are the only U.S. FDA approved inorganic filters; they are used in sunscreen formulations as nanoparticles (<100 nm in size).[10,11]

Based on currently available data, the health risks of ZnO and TiO_2 to humans is extremely low, primarily due to a lack of absorption across both intact and damaged (tape-stripped) skin.[3,7,13,17-22] Based on studies in animal models, there is potential risk of carcinogenesis with inhalation.[3,11,13,28] Based on currently available data, the risk to the environment is considered quite low.[14] ZnO and TiO_2 are most often used in combination to provide broadband UV protection.[13]

Due to the known side effects of excessive sun exposure, the continued practice of photoprotection is paramount. Patients should be counseled to seek shade when outdoors, use photoprotective clothing including hats and sunglasses, and for exposed areas, to apply sunscreens by hand. For those concerned about the environmental impact of organic UV filters, ZnO and TiO_2 containing sunscreens could be used.

CONFLICT OF INTEREST

Dr. Samantha Schneider has no conflicts of interest to disclose. Dr. Henry Lim is an investigator/co-investigator for Ferndale, Estee Lauder, Unigen and Incyte.

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