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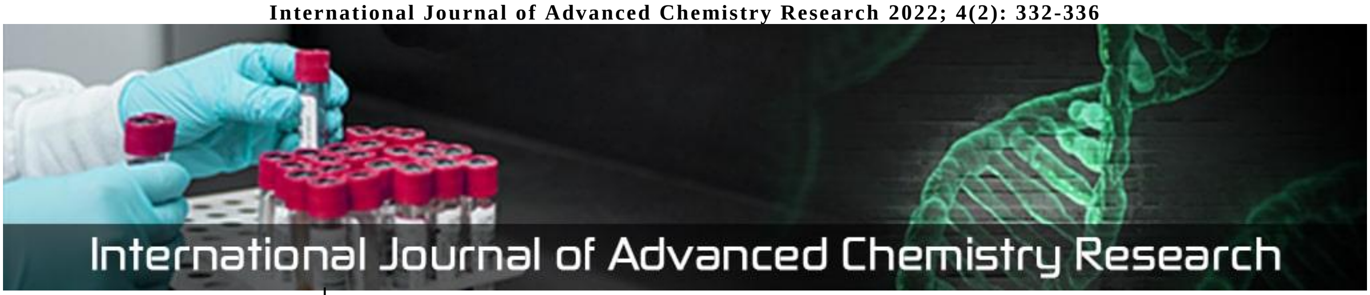

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A review on inorganic UV filter zinc oxide against keratinocyte cancer and photoaging

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Abstract

Photoprotection has become pivotal in the prevention of keratinocyte cancer and photoaging. Organic ultraviolet (UV) filters such as oxybenzone and octinoxate have become controversial due to their possible impact on the environment and their potential human health risks. As such, inorganic UV filter, zinc oxide (ZnO), has become paramount in discussions about photoprotection. ZnO is used in sunscreens as nanoparticles, which denote a size <100 nm. The smaller size of these mineral particles surges their cosmetic acceptability by users as they are much less visible after application. ZnO has a broad UVA-UVB absorption curve. Overall, the human health risks with inorganic filters are extremely low given a lack of percutaneous absorption; however, there is a possibility of 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 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-containing sunscreens are safe alternatives. Recently ZnO nanoparticles (NPs) have attracted attention owing to their unique features. There can be numerous applications of ZnO NPs due to their antibacterial, antineoplastic, wound healing, ultraviolet scattering and angiogenic properties. These have also been used to promote tissue repair, as a food preservative and as feed additive. This paper reviews the recent developments in ZnO NPs research and its potential for application in animal health and production.

Keywords: Zinc oxide, nanoparticles, keratinocyte cancer, photoaging, ultraviolet (UV) radiation

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 examined5 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 collect the reliable data on fuel wood consumption of the area and also to evaluate the impact of fuel wood collection on forest ecosystem.

There are two inorganic filters (also known as mineral filters) approved by U.S. Food and Drug Administration (FDA): zinc oxide (ZnO); is a metal oxide particles [7]. The molecule absorb, reflect and refract UV photons but function in photo protection 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. Cosmetic and patient satisfaction encouraged new formulations by decreasing particle size culminating in the usage of nanoparticles. In 2018, the EWG reported 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 zinc oxide inorganic filters in photo protection, including mechanism and safety concerns.

What are nanoparticles?

Anoparticles have wide applications in the cosmetic industry; they are a key component of inorganic sunscreens. ZnO have been used in sunscreens since the 1980s.Normally, ZnO range in size from 200-400 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.3Nanoparticles 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 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) appearance. These particles provide photo protection 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 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 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 is 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 [3, 7, 12, 13]. When used together, ZnO provide good broadband UV protection [13]. ZnO 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 have the advantages of a non-greasy formulation that is transparent, inexpensive and does not degrade with UV radiation exposure [14].

Health Concerns

As discussed earlier, smaller nanoparticles are important for the improved and ease of application, 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 15, 16]. It should be highlighted 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 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 bloodstream. 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 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 nanoparticles did penetrate into the epidermis slightly.

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 Zn2+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 nanoparticles as well as skin irritation, phototoxicity, photosensitization, and photo irritation. The risk of toxicity in humans is none to minimal [18, 27].

The risk of ZnO exposure during pregnancy and lactation has been studied. Experiments were done in mouse and rat animal models to examine the effects of ZnO in pregnancy, placental development, and fetal development. In these experiments, animals received 100-400 mg/kg/d of ZnO or 100 mg/kg body weight [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].

There are toxicity concerns when considering the manufacturing of ZnO nanoparticles for sunscreen and other cosmetic products. The lungs are unable to clear nanoparticles, which creates the potential for increased concentrations in the alveoli 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% [32]. These nanoparticles appeared to induce DNA damage in this *in vitro* model [32, 33]. An *in vivo* study with 12 human volunteers evaluated the risk of inhalation using 500 µg/m3 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].

Photo Mutagenesis

Some forms of ZnO have semi-conductor and photocatalytic activity under specific conditions. When exposed to UV radiation, ZnO can induce free radical formation *in vitro*, raising the concern for photo mutagenesis [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 photo genotoxicity should no longer be included in safety testing [37].

It has been suggested that the small amount of free radicals that may be generated on the skin's surface can be contained with the body's own antioxidants3 *In vitro*, certain microsized ZnO particles were found to be photo-stable and non-photocatalytic; [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].

Environment

The effect of nanoparticles on the environment is complicated. Because ZnO is a mineral 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 nanoparticles found in aquatic environments would be in the low 10 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 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 laboratory settings, ZnO nanoparticles caused severe and rapid bleaching of *Acropora* spp. of coral, 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].

Therefore, studies 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 higher 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].

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. A discussion regarding the advantages, approaches and limitations on the use of ZnO NPs for various applications and drug delivery has been presented. The understanding of current challenges in terms of the potential toxic effects of ZnO NPs, the possible mechanisms and cellular consequences as a result of ZnO NPs interactions with host cells is necessary to provide better delivery options for ZnO NPs. The approaches discussed to improve their safety will further make them attractive for various applications. Based on currently available data, the health risks of ZnO to humans is extremely low, primarily due to a lack of absorption across both intact and damaged (tape-stripped) skin. Patients should be counseled to seek shade when outdoors, use photo protective 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 containing sunscreens could be used.

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