Chapter 4

Titanium Dioxide in Sunscreen

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Additional information is available at the end of the chapter

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Abstract

Titanium dioxide has been used in various industrial and cosmetic applications due to its unique elemental properties. This substance has a refractive index higher than most other compounds (n = 2.6142, in comparison to water at 20°C n = 1.33). This allows titanium dioxide to have an iridescent and bright quality. It has been used in the cosmetics industry for “whitening” and “thickening” in multiple make-up brands. As titanium dioxide has the ability to greatly absorb UV light, it has been used as a physical sunscreen for many years. Over time, newer formulations, including “nanoparticle” formulations, have been marketed for ease of consumer use. We aim to discuss the evolution of titanium dioxide in sunscreens over time, discuss its mechanisms of actions, and comment on the efficacy and safety of these products.

Keywords: titanium dioxide in sunscreens, titanium dioxide, skin, allergic contact dermatitis

1. Introduction

A systematic search with the keywords “titanium dioxide” and “sunscreen” all in the title was conducted using the Google Scholar database. No restrictions on year of publication, language, full-text availability, human- or animal-based studies were applied to the initial search. The results were then manually filtered using a systematic approach. Articles that did not pertain to the topic of titanium dioxide and sunscreens were excluded. Articles which were published only in a language other than English or in which full text was not available were excluded. A similar search and systematic review was conducted using the PUBMED database with the same keywords. However, the filters “clinical trials,” “review,” “full text,” and “humans” were applied to result in 133 results which were then manually filtered excluding articles in non-English languages and not pertaining to the topic.

Titanium dioxide (TiO_2) is a Food and Drug Administration (FDA)-approved sunscreen, which is considered broad spectrum (protects against UVB radiation as well as UVA2 radiation 320–340 nm). Previously, TiO_2 had a suboptimal cosmetic profile, appearing thick and white on application. Current formulations are micronized or nanoparticle formulations, which blend in with the skin tone and attain better cosmesis. Concern about dermal penetration of these smaller particulate formulations and safety has been raised. However, current data are controversial. Several studies demonstrate negligible penetration beyond the stratum corneum, whereas other studies demonstrate cytotoxicity and oxidative stress in cell models. More studies are needed to definitively comment on long-term use of TiO_2 sunscreens and health effects. TiO_2 has interestingly been implicated in allergic contact dermatitis in gold allergic patients in recent years. We discuss a newly hypothesized mechanism of TiO_2 and gold particulate matter interaction on the surface of the skin.

2. History of photoprotection and titanium dioxide

For generations, humans have sought various methods of sun protection, extending to ancient times. Ancient Egypt, India, Greece, and indigenous American populations used physical barriers such as hats, umbrellas, cloth wrapped over the head and face, and even topical materials such as tars and oils. During those times, these efforts were mostly directed at preventing darkening effects from the sunlight as in some of these cultures, fairer complexion, especially for female members of society, was desired [1]. The more important effects of ultraviolet radiation, that is, damage to the skin's cells and subsequent cancerous/mutagenic potential from prolonged sunlight exposure were not studied until 1800s [1]. The development and use of sunscreens on a population-wide scale was initiated during and after WWII as American troops experienced high intensity sunlight exposure from spending months to years in equatorial and tropical regions [2]. Multiple products and agent have been used in sunscreens to date and the FDA has currently approved 17 active ingredients, which are allowed in sunscreens bought and sold in the USA. With the variety of sunscreen agents used in cosmetic and UV protection products, Australia, Canada, and the European Union (EU) have also developed regulatory protocols on safe sunscreen product use. Unlike the USA though, Australia has approved 34 active sunscreen ingredients and the EU has approved 28 of these ingredients. This is thought to be due to the designation of sunscreen products in the USA as over-the-counter agents unlike in other countries which designate many of these ingredients as cosmetic. The former type of designation requires greater scrutiny in the approval process by a regulatory body [2, 3]. The introduction of titanium dioxide use in sunscreens came in 1952, around which time other physical blockers such as zinc oxide and its derivatives were also being introduced. Even so, the FDA only recently approved the use of titanium dioxide in sunscreens in 1999 [4]. However, titanium dioxide along with zinc oxide, although effective in sun protection, were not popular commercially when first introduced. This is because of the large particle size of these agents and thick white, opaque appearance upon application [3]. This characteristic of the products made them cosmetically unappealing and less preferred among consumers. However, in the 1990s, micronized versions of titanium dioxide sunscreens were marketed for their cosmetic superiority to older versions. These versions along with "nanoparticle" formulations of the product quickly rose to popularity.

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However, the newer formulations came with their own set of troubles with questions about safety, toxicity, and efficacy arising from the consumer as well as scientific community as is discussed in the following sections.

3. Mechanism of action

Titanium dioxide is a widely used substance due to its convenient chemical properties, ease of mass production, and relatively low cost. The substance is chemically inert, which means that it rarely interacts with other chemical substances to undergo a reaction which can change its own chemical composition or the chemical milieu of the surrounding environment. This is true for biological surfaces and environments as well, thus leading to its safe use in food additives, cosmetics, and sunscreen products [4]. TiO_2 is a semiconducting material with very high refractive indices for all its crystalline forms. The high refractive index is what allows the substance to scatter visible light as well as has a significant ability to whiten substances in which it is an additive. There are three main crystalline forms in which TiO_2 can occur: rutile, anatase, and brokite. The rutile form of TiO_2 has an impressive refractive index with the average of rutile polycrystalline films being $n = 4.0$ from experimentation. This refractive index is higher than that of zinc oxide derivatives, and therefore TiO_2 has a greater whitening effect [5]. Titanium dioxide is used in sunscreens mainly due to its ability to reflect and scatter ultraviolet radiation. However, the high refractive index is not the only property that determines how well a substance blocks light. The film thickness in which the substance is suspended as well as the size of the individual particles also affects the efficacy of the sunscreen. However, the reflectant property, a numerical value often used to compare efficacies of different sunscreen agents does rely wholly on refractive index of the substance. The formula for this measure is defined by the refractive index of the substance divided by the refractive index of the surrounding medium [6]. This high refractive index of TiO_2 as discussed earlier also confers it an opaque, cosmetically unappealing appearance upon topical application. Therefore, most formulations are micronized, and the properties of these agents are more relevant to discuss. Older forms of TiO_2 products were created with particle sizes of 150–300 nm. The newer micro-formulations which are transparent upon topical application have TiO_2 particle sizes of 20–150 nm [2]. The micronized particle formula of TiO_2 does not cross the stratum corneum and confers broad spectrum UV protection against both UVB and UVA2 which includes wavelengths from 315–340 nm. However, there is no protection against UVA1 wavelength ranges [7]. The caveat when manufacturing micronized forms of inorganic particulate sunscreens is the possibility of agglomeration. This describes a phenomenon in which the TiO_2 particles have a tendency to join together and form larger clusters. This physically causes the sunscreen to appear opaque once again on application and reduces its photoprotection efficacy defeating the purpose of the micronized formula. Therefore, many manufacturers coat the TiO_2 particles with either silica or dimethicone to prevent aggregation. In addition to micronized formulas, it should be mentioned that the addition of other ingredients into TiO_2 formulations has also been tried. Iron oxide, another inorganic blocking agent, naturally has a reddish tinge which can resemble the complexion of human skin. This substance is sometimes added to TiO_2 products to reduce the white opacity of the final application. Furthermore, iron oxide, itself being an inorganic blocking agent, enhances the photoprotection of TiO_2 formulations when included [2, 3, 6].

For the sake of comprehensive discussion, the mechanism of action of organic sunscreens, also known as chemical sunscreens should also be noted. Whereas, the inorganic blockers, mainly titanium dioxide, zinc oxide, and iron oxide compounds, scatter and reflect light, the organic sunscreens actually absorb UV light which tends to be high energy in the natural environment and release it in a lower energy state that does not damage skin cells. Chemically, most of these compounds are aromatic and have a conjugated carbonyl group. These include aminobenzoates, anthralates, cinnamates, salicylates, benzophenones, dibenzoylmethane, and camphor to name a few [7].

4. Ultraviolet radiation and its effects on human skin

It is worthwhile to briefly discuss ultraviolet radiation, its definition and categorization, and its effects on human skin. The main source of ultraviolet radiation exposure for human beings is natural sunlight. There are three main categories of ultraviolet radiation including UVA, UVB, and UVC radiation. UVC radiation (100–280 nm)[1] will not be emphasized as this form of radiation does not generally reach the earth's surface to a significant degree. The earth's atmosphere blocks most UVC rays, and therefore, they are not thought to be important contributors to the biological effects on human skin [8]. UVB radiation (280–315 nm),[1] on the other hand, has been implicated in three major adverse effects in human beings: sunburn (radiation-induced erythema and inflammation of the skin), skin cancer, and immunosuppression. However, it should be noted that UVB does play a beneficial role in human health and wellness as it is important in the conversion of vitamin D in the skin to useable forms for human metabolism. Recent evidence in the literature also suggests that it may lower the risk of certain cancers including colon, prostate, and breast cancer [8]. UVA radiation (315–400 nm)* was previously regarded as having insignificant carcinogenic potential and mainly implicated as a cause of aging and wrinkling. However, recent evidence has suggested that it too has an important role in carcinogenesis and immunosuppression [8, 9]. Although, the major source of human exposure to UVA is still natural sunlight, tanning beds have had an increasing role in UVA exposure during recent years [8].

The molecular effects of UV radiation on human skin can be broadly separated into short-term (acute) effects, and long-term, continuous effects. When the skin is acutely exposed to UV radiation, DNA damage in the form of pyrimidine dimers occur. However, most humans with normal cell functioning are able to fix these lesions through DNA repair mechanisms. Furthermore, when individual cells recognize that too much damage has ensued and normal DNA repair processes will not suffice, cells engage in active, purposeful cell death to prevent the cell from multiplying and propagating mutagenic DNA which would lead clinically to cancer. On a physical level, acute UV radiation exposure can lead to two main changes: sunburn and tanning. Sunburn describes the phenomenon thickening of the outer skin layer (stratum corneum) and swelling in the layers of the skin containing blood vessels. This clinically appears as swollen, red skin that is painful to the touch. In addition to sunburn, tanning

[1]These wavelength ranges vary depending on the source of the text. However, they are all within range of ±5 nm.

is a known side effect of UV radiation exposure as the cells in the skin responsible for pigment production (melanocytes) are stimulated to produce more pigment for unclear physiological reasons. Certain theories suggest that the hormone melanocyte-stimulating hormone and its receptor may have a role depending on individual skin type [9]. Long-term effects of sunlight exposure include both photoaging and increased risk of skin cancer including both non-melanoma type as well as melanoma. Photoaging results from thickening of outer skin layers and breakdown in the support structure proteins of the skin, mainly collagen and elastin. The clinical manifestations of photoaging include freckles, dryness, hyperpigmentation, wrinkling, and dilated blood vessels [9]. Malignancy resulting from chronic UV radiation exposure is thought to result from two major processes. Chronic UV exposure can lead to accumulating genetic mutations which can affect normal DNA repair and cell self-destruction mechanisms over time. The accumulation of genetic changes can lead to cell transformation and dysplasia which can eventually lead to clinical malignancy. In addition to genetic changes, chronic UV exposure is also thought to play a role in immune suppression in the outer layers of the skin which can make it easier for cancerous cells to escape detection and subsequent cell death as the immune system plays a role in the elimination of genetically damaged cells [9].

5. Efficacy of titanium dioxide sunscreens

The efficacy of sunscreens is determined by the ability to protect against both UVB radiation and UVA radiation. As discussed in previous paragraphs, titanium dioxide sunscreens are effective broad-spectrum agents, meaning that they are capable of protection against both types of radiation. A sunscreen's efficacy in protecting against UVB radiation is assessed based on two values: the sun protection factor (otherwise known as SPF) and substantivity. The SPF is calculated as a ratio of the amount of ultraviolet radiation needed to cause sunburn when the skin is protected with a certain sunscreen to the amount of ultraviolet radiation needed to cause sunburn when the skin is left unprotected. Therefore, if a product is SPF 30, then 30 times the UV radiation is needed to cause sunburn if the patient is wearing the sunscreen with that SPF value [10]. Generally, in order to be considered broad spectrum, a sunscreen must be at least SPF 30 or greater. Substantivity is another measure that sunscreens are subjected to when being evaluated for use in the United States. This measurement evaluates the ability of a sunscreen to withstand exposure to factors which can cause the physical removal of the agent off the skin (and still remain effective afterward). These factors include sweat and water, among others. By measuring the substantivity of a product, manufacturers can have insight into the product's actual usability in the real-world setting. Interestingly, until 1933, many products were being labeled as "waterproof" based on superior product stability when tested with water immersion. However, the FDA released a statement disapproving the terminology as misleading since all products lose effectiveness after a certain amount of exposure. Now, the term "water-resistant" is more commonly seen on products [2].

Efficacy of UVA radiation protection is often measured by immediate pigment darkening (IPD), persistent pigment darkening (PPD), and protection factor (PFA). Both IPD and PPD measure photo-oxidation of melanin in the skin which contributes to skin pigmentary changes.

However, PPD is seen as the better measure in most cases, as the measurement takes place 2–24 h following exposure to radiation unlike IPD which reaches peak levels within 1 min of exposure. PPD also measures the photostability of the sunscreen being tested. Protection factor measures redness and tanning 24 h after UV radiation exposure and can also be used to test UVA protection efficacy [2].

Both titanium dioxide and zinc oxide sunscreen formulations have several advantages as inorganic blockers. These agents are not only effective against UV radiation but also protect against infrared radiation and visible light. As mentioned before, titanium dioxide is chemically inert—this is useful since in most cases, titanium dioxide is combined with other organic sunscreens and does not react with other ingredients in the compound. In the past, both titanium dioxide and zinc oxide sunscreens were less preferred due to their chalky, white appearance on application. However, micronization of particles and more recently "nanoparticle" formulations have made TiO_2 sunscreens more popular in recent years [11]. Early studies comparing micronized versions of TiO_2 versus micronized versions of zinc oxide sunscreens concluded that micronized zinc oxide sunscreens were superior as they conferred better protection against longer wave UVA and had greater cosmetic outcomes [12]. However, nanoparticle formulations of TiO_2 have virtually replaced all other forms in the sunscreen market and these sunscreens have demonstrated great effectiveness. Nanoparticle TiO_2 sunscreens not only have superior cosmetic outcomes as these product are virtually invisible upon application, but they also possibly confer greater UV protection. One study published by Tyner and colleagues in 2011 demonstrated that nanoparticle TiO_2 may have greater UV radiation attenuation. The authors also commented that overall formulation of the sunscreen is important when attaining high levels of efficacy. The best TiO_2 sunscreens occur when particles are coated, stabilized, and distributed evenly on the surface of the skin. Coated nanoparticles are very effective at non-agglomeration and therefore distribute effectively on the skin surface [13]. It is also important to note that the vehicle of the sunscreen can also affect effectiveness. The best vehicles avoid significant interaction between active and inactive ingredients. Vehicle also affects the substantivity measure of the sunscreen since the vehicle is often the main determinant of how well the sunscreen resists water, sweat, and other environmental factors. The vehicle types currently available include lotions and creams, gels, sticks, and sprays. Gels are often the most sensitive to water and sweat removal [3].

6. Safety of titanium dioxide sunscreens

The safety of sunscreens has various dimensions and is assessed most commonly by toxicity studies. However, irritation and allergic sensitization as well as dermal penetration are also commonly studied when assigning safety profiles to different products [10].

Titanium dioxide and zinc oxide have always been considered safe alternatives to their organic counterparts because of their chemically inert status. However, with the introduction of micro and nanoparticulate formulations, titanium dioxide sunscreens have fallen under greater scrutiny. The two most important concerns noted have been the potential of TiO_2 nanoparticles to generate reactive oxygen species when exposed to UV radiation which can cause DNA damage within skin cells and the dermal penetration of TiO_2 nanoparticles themselves.

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Other concerns related to the size of the particles themselves include greater surface reactivity due to the fact that nanoparticles have a greater proportional surface area compared to their larger particle counterparts. Catalytic reactions with proteins and translocation into tissues, which may lead to autoimmune consequences, and evasion of regular immune surveillance mechanisms have also been discussed [14].

Since the 1990s, there have been several studies with evidence supporting the claim that TiO_2 nanoparticles can generate potentially dangerous free radicals. In 2001, Serpone and colleagues demonstrated that TiO_2 particles absorbed significant UV radiation to generate hydroxyl-radical species. These free radicals can cause DNA strand breaks and lead to increased susceptibility to genetic aberrations [15]. In 2006, Hidaka and colleagues published similar results describing specific damage to DNA induced by titanium dioxide and zinc oxide which had absorbed UV radiation. This led the subsequent production of free radicals, mainly hydroxyl species which then caused conformational changes in DNA at a rapid rate [16]. However, even though there was ample evidence for reactive oxygen species forming from irradiation of titanium oxide and zinc oxide nanoparticles, Newman and colleagues aptly noted in a recent review that the true biological consequences on humans was not truly known. In order for the reactive oxygen species to be concerning, they would have to penetrate deeper levels of skin. The question of whether nanoparticles penetrate the outer layer of skin to any significant degree is controversial, but there have been several published studies in recent years which provide evidence against such a phenomenon [14].

In 1999, Lademan and colleagues conducted a study in which penetration of coated titanium dioxide microparticles into the horny layer of the skin and orifice of the hair follicle was evaluated. They took biopsies of relevant skin areas and noted that penetration of particles had occurred in the open segments of the hair follicles, but this was less than one percent of the total sunscreen applied. They also noted that no particles were found in the viable sections of skin tissue [17]. Pflucker and colleagues published a study in 2001 which used electron and light microscopy to evaluate whether dermal penetration of micronized titanium dioxide particles occurred to any measurable degree. Their results suggested that particles could only be found in the top most layer of the stratum corneum and further penetration into deeper layers of stratum corneum, epidermis, or dermis was not noted [18]. Sadrieh and colleagues conducted a similar more recent study in 2010 using electron microscopy-energy dispersive x-ray analysis and again noted that there was no significant penetration of particles past the intact epidermis [19]. A general review of the toxicology of titanium dioxide nanoparticles by Shi and colleagues was published in 2013. They concluded that most dermal exposure studies with TiO_2 had not found significant penetration of particles into deeper layers of skin. However, the review noted that long term studies of TiO_2 inhalation were associated with lung tumors in rats. Several reviewed studies also suggested that intravenous injection of TiO_2 nanoparticles could potentially result in pathological lesions to a variety of internal organs [20].

The current opinion and recommendation on nanoparticles is controversial with the data that has been presented in recent years. The European Union's Scientific Committee on Emerging and Newly Identified Health Risks notes that TiO_2 nanoparticle use in sunscreens and cosmetics appears to be safe, but they advise caution when using such products on areas of impaired barrier function until more data can be obtained [21].

Another potential health and safety concern with the general use of sunscreens is the potential of vitamin D deficiency. Appropriate vitamin D synthesis necessitates certain levels of UVB exposure and the American Academy of Dermatology has recently revised its position on sunscreen effects on adequate vitamin levels. They note several populations are at higher risk for vitamin D deficiency including the elderly, darker skinned those who live in areas of low sunlight exposure, the obese, and the photosensitive. It is generally recommended that individuals obtain 1000 international units of vitamin D daily and some may have to supplement this through oral formulations [3].

Unlike other organic sunscreens, the inert nature of titanium dioxide sunscreens makes it one of the least likely compounds to cause irritation and sensitization of the skin. In fact, because of its chemical inertness and lack of photoreactivity, it is often the preferred sunscreen for individuals with sunscreen allergies and children [3]. However, in recent years an interesting interaction between gold allergic patients and titanium dioxide has been proposed and studied. In 2005, Nedorost and Wagman hypothesized that patients with facial and eyelid dermatitis may be experiencing reactions due to an interaction between their gold jewelry (earrings, bracelets, etc.) and the titanium dioxide in their cosmetic products. Mechanistically, titanium dioxide was thought to adsorb gold particulate matter which then caused contact dermatitis in the locations of makeup application. Their results demonstrated a subgroup of individuals who used TiO_2 containing makeup on areas then affected by contact dermatitis, benefiting from gold jewelry avoidance, lending credence to the interaction theory [22]. In 2015, Danesh and Murase published a clinical pearl in the Journal of the American Academy of Dermatology regarding a trial of gold avoidance in patients presenting with eyelid allergic contact dermatitis. They noted that the North American Contact Dermatitis Group implicated gold as the most common allergen to cause eyelid dermatitis most likely through a mechanism in which eyelid cosmetics containing titanium dioxide particles adsorbed gold particles from elsewhere on the body [23].

7. General recommendations on appropriate sunscreen use

The American Academy of Dermatology has set forth guidelines for appropriate sunscreen use and sun protection. They recommend using sunscreen with broad-spectrum properties (protection against both UVA and UVB radiation) daily. These include sunscreens with sun protection factors greater than 30. Sunscreen should be applied 15–30 min prior to sun exposure and be reapplied as needed when environmental factors (swimming and sweating) cause sunscreen removal [3].

8. Conclusions

In conclusion, titanium dioxide sunscreens are effective agents against UV radiation. They also have an advantage as they protect against multiple wavelengths of energy

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including UV radiation, visible light, and infrared radiation. Furthermore, unlike organic compounds, titanium dioxide, like its zinc counterpart, is a chemically inert substance, and therefore, there is less concern about reactivity in terms of toxicity profiles and allergic reactions. Although these agents were not heavily marketed in previous decades due to their thick, chalky appearance on the skin, the development of nanoparticle formulas improved their cosmetic profile. Nanoparticle formulations are considered effective sun protection agents as well as cosmetically acceptable. Concerns about safety with induction of radical oxygen species on the skin as well as absorption have been discussed. However, current evidence does not support claims of nanoparticle toxicity to humans. With this said, a greater number of studies with longitudinal data will be helpful in further informing this topic.

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References

[1] Urbach F. The historical aspects of sunscreens. Journal of Photochemistry and Photobiology B: Biology. 2001;**64**(2-3): 99-104.

[2] Palm MD, O'Donoghue MN. Update on photoprotection. Dermatologic Therapy. 2007;**5**:360-376

[3] Sambandan DR, Ratner D. Sunscreens: An overview and update. Journal of the American Academy of Dermatology. 2011;**64**:748-758

[4] Skocaj M, Filipic M, Petkovic J, Novak S. Titanium dioxide in our everyday life; is it safe? Radiology and Oncology. 2011;**45**(4):227-247

[5] Smijs TG, Pavel S. Titanium dioxide and zinc oxide nanoparticles in sunscreens: Focus on their safety and effectiveness. Nanotechnology, Science and Applications. 2011;**4**:95-112

[6] Murphy GM. Sunblocks: Mechanisms of action. Photodermatology, Photoimmunology & Photomedicine. 1999;**15**(1):34-36

[7] Rai R, Shanmuga SC, Srinivas CR. Update on photoprotection. Indian Journal of Dermatology. 2012; **57**(5):335

[8] Gallagher RP, Lee TK. Adverse effects of ultraviolet radiation: A brief review. Progress in Biophysics and Molecular Biology. 2006;**92**:119-131

[9] Matsumura Y, Ananthaswamy HN. Toxic effects of ultraviolet radiation on the skin. Toxicology and Applied Pharmacology. 2004;**195**:298-308

[10] Latha MS, Martis J, Shobha V, Shinde RS, Bangera S, Krishnankutty B, et al. Sunscreening agents: A review. Journal of Clinical and Aesthetic Dermatology. 2013;**6**(1):16-26

[11] Fathi-Azarbayjani A, Tan PL, Chan YY, Chan SY. Ascorbic acid for the safe use of a sunscreen agent: Accumulation of nano zinc oxide and titanium dioxide on the skin. Scientia Pharmaceutica. 2013; **81**(4):1141-1150

[12] Pinnell SR, Fairhurst D, Gillies R, Mitchnick MA, Kollias N. Microfine zinc oxide is a superior sunscreen ingredient to microfine titanium dioxide. Dermatologic Surgery. 2000;**26**(4):309-314

[13] Tyner KM, Wokovich AM, Godar DE, Doub WH, Sadrieh N. The state of nano-sized titanium dioxide (TiO_2) may affect sunscreen performance. International Journal of Cosmetic Science. 2011;**33**(3):234-244

[14] Newman MD, Stotland M, Ellis JI. The safety of nanosized particles in titanium dioxide- and zinc oxide-based sunscreens. Journal of the American Academy of Dermatology. 2009;**61**(4):685-692

[15] Serpone N, Salinaro A, Emeline A. Deleterious effects of sunscreen titanium dioxide nanoparticles on DNA: Efforts to limit DNA damage by particle surface modification. In: BiOS 2001 The International Symposium on Biomedical Optics. Proceedings of SPIE, 2001;**4258**:86-98

[16] Hidaka H, Kobayashi H, Koike T, Serpone N. DNA damage photoinduced by cosmetic pigments and sunscreen agents under solar exposure and artificial UV illumination. Journal of Oleo Science. 2006;**55**(5):249-261

[17] Lademann J, Weigmann HJ, Rickmeyer C, Barthelmes H, Schaefer H, Mueller G, Sterry W. Penetration of titanium dioxide microparticles in a sunscreen formulation into the horny layer and the follicular orifice. Skin Pharmacology and Physiology. 1999;**12**(5):247-256

[18] Pflücker F, Wendel V, Hohenberg H, Gärtner E, Will T, Pfeiffer S, et. al. The human stratum corneum layer: An effective barrier against dermal uptake of different forms of topically applied micronised titanium dioxide. Skin Pharmacology and Physiology. 2001;**14**(Suppl. 1):92-97

[19] Sadrieh N, Wokovich AM, Gopee NV, Zheng J, Haines D, Parmiter D, Siitonen PH, Cozart CR, Patri AK, McNeil SE, Howard PC. Lack of significant dermal penetration of titanium dioxide (TiO_2) from sunscreen formulations containing nano-and sub-micron-size TiO_2 particles. Toxicological Sciences. 2010;**115**(1):156-166

[20] Shi H, Magaye R, Castranova V, Zhao J. Titanium dioxide nanoparticles: A review of current toxicological data. Particle and fibre toxicology. 2013;**10**(1):15

[21] Jansen R, Osterwalder U, Wang SQ, Burnett M, Lim HW. Photoprotection: Part II. Sunscreen: Development, efficacy, and controversies. Journal of the American Academy of Dermatology. 2013;**69**(6):867-e1.

[22] Nedorost S, Wagman A. Positive patch-test reactions to gold: Patients' perception of relevance and the role of titanium dioxide in cosmetics. Dermatitis. 2005;**16**(2):67-70

[23] Danesh M, Murase JE. Titanium dioxide induces eyelid dermatitis in patients allergic to gold. Journal of the American Academy of Dermatology. Pearls. 2015;**73**(1):e21

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