

REVIEW ARTICLE

Potential photocarcinogenic effects of  
 nanoparticle sunscreens

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**ABSTRACT**

Titanium dioxide and zinc oxide nanoparticles are being increasingly formulated in sunscreens. While the same compounds, in larger particle form, work by reflecting UV radiation, in nanoparticle form, they absorb UV radiation, resulting in photocatalysis, releasing reactive oxygen species. These reactive oxygen species are known to have the capability to alter DNA. Previous studies suggest that this photocatalytic process may not be significant, because the nanoparticles do not penetrate below the level of the stratum corneum. However, some recent studies suggest that nanoparticles may, under certain circumstances, breach that barrier. The majority of those studies have used animal skin models rather than human skin.

**Key words:** barrier function, nanoparticles, penetration, photocatalysis, reactive oxygen species, sunscreens, titanium dioxide, zinc oxide.

**INTRODUCTION**

In January 2008, a paper was published in *Progress in Organic Coatings* that detailed the effect of modern sunscreen formulations on the rapid deterioration of paint surfaces on steel roofing.<sup>1</sup> Investigators in the Colorbond laboratory at Port Kembla in Wollongong, Australia, showed that sunscreens containing titanium dioxide (TiO<sub>2</sub>) and zinc dioxide (ZnO) nanoparticles (NP) were the primary cause of the corrosion, via the production of reactive oxygen species (ROS), also known as free radicals. ROS also play an integral role in photocarcinogenesis and skin aging.<sup>2</sup> It is uncertain as to when the majority of sunscreen formulations changed from large particle to NP products, as there is no current

mandatory requirement for listing the particle size on sunscreen labels. The effects on paint surfaces have been noted increasingly over the last 7 years.<sup>1</sup> Given that time period, the long-term effects on skin biology may not yet be evident. Debate continues as to whether NP penetrate the stratum corneum (SC), under certain circumstances, to cause damage to underlying keratinocytes, fibroblasts, melanocytes and Langerhans cells.

**CHARACTERISTICS OF NP**

The prefix ‘nano’ is derived from the Greek language, meaning dwarf or extremely small. NP (1–100 nm) are widespread in the environment, emanating from volcanic eruptions to man-made combustion. For comparison, the intercellular gap is 25 nm, and the average melanocyte is 7000 nm in diameter.<sup>5</sup> The health effects of carbon-derived NP are well known, particularly relating to respiratory diseases.<sup>4</sup>

**COSMESIS AND NP SUNSCREENS**

ZnO and TiO<sub>2</sub> have been used in sunscreens for decades, as they are effective broad-spectrum sunscreen agents. They are particularly effective in blocking the UVA spectrum, which may not be covered adequately by chemical sunscreens.<sup>5</sup> As large microscopic particles, ZnO and TiO<sub>2</sub> appear as white pastes. However, if particles are made to nanoscale, they become too small to scatter or reflect visible light and become transparent, whilst still absorbing UV radiation (UVR), resulting in significant aesthetic improvement.<sup>5</sup>

In 2006 the Therapeutic Goods Association of Australia estimated that 70% of TiO<sub>2</sub>-based sunscreens and 30% of ZnO-based sunscreens contained NP.<sup>6</sup>

Abbreviations:

5-ALA	5-aminolevulinic acid
NP	nanoparticles
ROS	reactive oxygen species
SC	stratum corneum
TiO <sub>2</sub>	titanium dioxide
UVR	UV radiation
ZnO	zinc oxide

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## MECHANISM OF NP PHOTOCATALYSIS

The photocatalytic properties that make ZnO and TiO<sub>2</sub> NP excellent UVR absorbers are also the very properties that make them excellent agents for industrial uses such as in water purification, solar cells and self-cleaning glass.<sup>7</sup>

The crystalline forms of TiO<sub>2</sub> and ZnO NP are semiconductors.<sup>7</sup> When a photon of UVR hits the lattice structure, an electron is displaced, ultimately finding its way to the surface. Displacement of the electron also leaves a 'positive hole' in the lattice structure. The liberated electrons and the resulting positively charged holes (h<sup>+</sup>) react with water to produce ROS, such as superoxide anion radicals (O<sub>2</sub><sup>-</sup>), hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>), free hydroxyl radicals (OH) and singlet oxygen (<sup>1</sup>O<sub>2</sub>).

The wavelength of UVR that is required to excite an electron from ground (valence) state to excited (conduction) state is called the band gap. This excitation can be induced either by sunlight or low-level UVR emitted from ubiquitous household fluorescent lamps.<sup>7</sup> The band gaps of ZnO and TiO<sub>2</sub> correspond to light of 380 nm and 405 nm, respectively. UVR at or below these wavelengths will be attenuated.<sup>5</sup> Photocatalysis increases as the size of the NP decreases, as smaller particles have a larger surface area to mass ratio.<sup>7</sup> As an example, the rate of H<sub>2</sub>O<sub>2</sub> production is 100–1000 times faster with ZnO NP of 4 nm to 5 nm, than with larger ZnO particles of 100 nm.<sup>8</sup>

It is important to note that NP are catalysts in the production of ROS, they are not consumed in the reaction, and once *in situ*, will continue to produce ROS indefinitely.

TiO<sub>2</sub> has two common crystalline structures, anatase and rutile; the latter is a less photoactive form and therefore more desirable for use in sunscreens. There is evidence to suggest that combining rutile and anatase into one mixture is more photoreactive than if either is used in its pure form.<sup>9</sup>

In addition to the potential photocatalytic effect on cells, ZnO and TiO<sub>2</sub> NP may cause loss of the UVR filtering efficacy of sunscreens, due to the enhanced photo-oxidative degradation of organic sunscreens and/or their non-active carrier components, such as emulsifying agents.<sup>10–12</sup>

There are various methods available by which to attempt to reduce the production of ROS caused by NP photocatalysis. These include adding manganese to the NP crystal matrix,<sup>15</sup> coating NP with aluminium-oxide or silicon oxide<sup>14</sup> or liposomal encapsulation.<sup>15,16</sup> Other methods include the addition of antioxidant compounds to the sunscreen formulation, including vitamin A, vitamin E, vitamin C and β-carotene.<sup>17</sup> Some of these additives (phenylalanine, sodium ascorbyl phosphate and ascorbyl palmitate) have been shown to inhibit the peroxidation of SC lipids in porcine skin, caused by TiO<sub>2</sub> NP.<sup>18</sup>

## DERMAL PENETRATION OF TiO<sub>2</sub> AND ZNO NP

The adverse cellular effects of TiO<sub>2</sub> and ZnO would only be of concern if NP could penetrate beyond the SC. Previous studies have shown that TiO<sub>2</sub> and ZnO NP of sunscreen grade do not penetrate beyond the SC.<sup>19–21</sup> The majority of these studies, however, were carried out over short periods

of topical application, from 24-h exposure on excised skin<sup>19</sup> to 2–6 weeks application *in vivo*.<sup>22</sup> They also used skin without significant cutaneous barrier disruption. Decreased barrier function may be caused by pathological states such as eczema, or may be induced, as in repetitive skin flexion, tape stripping or dermabrasion.

In a ZnO NP sunscreen study using excised human skin, the sunscreen was left *in situ* for 24 h and then followed by an electron microscopic examination.<sup>19</sup> This showed that less than 0.03% of the applied zinc content penetrated the epidermis, which is not significantly more than the quantity of zinc detected following application of a placebo formulation. No particles could be detected in the lower SC or viable epidermis. However, evidence of zinc penetration has been reported in a study using stable radioisotope zinc incorporated into sunscreens applied to the backs of healthy male volunteers.<sup>23,24</sup>

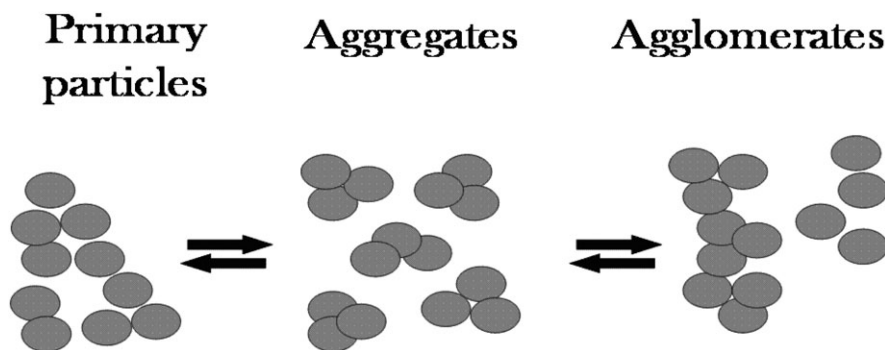
In systems attempting to maximize the percutaneous absorption of various drugs, hair follicles have been studied as an alternative route to bypass the SC barrier. An *in vivo* study using confocal scanning laser microscopy demonstrated that NP (solid nano-polystyrenes 40 nm and 200 nm) can penetrate along the follicular duct, translocate into the perifollicular tissue and be taken up by epidermal and dermal antigen-presenting cells (Langerhans cells), which then migrate to regional lymph nodes.<sup>25</sup> Hair follicles may allow deposition, aggregation and storage of NP of up to 320 nm for 10 days in humans.<sup>26</sup>

A recent experiment compared *in vitro* and *in vivo* cutaneous penetration of TiO<sub>2</sub> NP, using up to 8 weeks application.<sup>27</sup> The study used mouse and pig skin. Results showed that, when applied topically to pig ears for 30 days, TiO<sub>2</sub> NP can penetrate the SC and enter the deeper layers of the epidermis. Application to mouse skin for 60 consecutive days showed that TiO<sub>2</sub> (10–60 nm) can pass through the skin and enter the systemic circulation, with pathological changes to the heart, spleen, liver and skin, mirroring TiO<sub>2</sub> NP tissue distribution when injected intravenously.<sup>28</sup> It was thought that mice housed together, and licking each other, might contribute to gastrointestinal absorption. However this could not have happened with the individually housed pigs. The cutaneous effects reported in the study were excessive keratinization and wrinkling of the epidermis, and atrophy of the dermis. The 10-nm and 25-nm NP treatment groups showed more severe damage, while the control group and 90-nm NP treatment group did not show similar changes.

It is worth noting that normal skin permeability in different species varies, mostly due to the skin thickness and the lipid content of the SC. Porcine skin shows the closest resemblance to human skin with regard to percutaneous absorption of topically applied drugs. It is approximately four-fold more permeable than human skin.<sup>29</sup>

## COMPOUNDING MODES OF PENETRATION

There are several compounding modes of entry by which NP may penetrate the skin. As an example, a day at the beach for a person with altered skin barrier function, such



**Figure 1** A primary nanoparticle is an individually detached particle. An aggregate is a heterogeneous particle cluster in which the primary particles are grown or fused together by strong covalent bonds. High-energy forces are required to disrupt those bonds. A particle agglomerate is a group of particles held together loosely by relatively weak forces, including Van Der Waals forces, electrostatic forces and surface tension. They are relatively easily broken by weak physical forces or surfactants. Agglomerates can be groups of primary particles, or aggregates, or combinations of both.

as that seen in atopic eczema, may adversely induce further barrier damage by sunburn, super-hydrating the epidermis when swimming, dehydration, abrading the skin in the sand, and flexing the joints. Such compound damage may greatly enhance the movement of TiO<sub>2</sub> and ZnO NP into the skin.<sup>50–52</sup>

Abrading, massaging and flexing thin and creased skin around joints may allow large particles (0.5–1.0 μm) to penetrate the skin and enter the systemic circulation. This has been documented with large rigid beryllium particles of up to 1 μm (1000 nm).<sup>50</sup> Beryllium microparticles are responsible for the disease podoconiosis, seen in individuals who walk barefoot in the African rift valleys. In this condition there is percutaneous penetration of the microparticles, which ultimately lodge in the femoral and inguinal lymph nodes, causing a granulomatous response that leads to lymphoedema of the lower limbs.<sup>53</sup>

### PARTICLE SIZE AND PENETRATION

Although most studies showing epidermal penetration of NP have been carried out with particles other than TiO<sub>2</sub> and ZnO, the principle of size and penetration may still be relevant, as TiO<sub>2</sub> NP as small as 10 nm may be found in sunscreens.<sup>54</sup> A study using hydrated quantum dots, a form of experimental NP of 35-nm diameter, showed that they may passively diffuse across the SC and localize in the epidermal and dermal layers.<sup>55</sup> This passive diffusion to the epidermis with small NP has also been observed with iron NP (10 nm).<sup>56</sup>

While passive diffusion may be effective for smaller particles, large particles may penetrate the skin when applied to wounded epidermis, as has been shown in the rat skin model following medium-depth dermabrasion.<sup>51</sup> Minor dermabrasion with sandpaper and repetitive flexing, in the rat skin model, will allow greater penetration of NP (4.6–12 nm) into the epidermis. With skin flexion, the rate of NP penetration into hair follicles was also enhanced.<sup>52</sup> Larger rigid NP may not freely penetrate the skin, but coating them

with liposomes may enhance penetration.<sup>57</sup> When elastic and rigid particles of 100–130 nm are compared, elastic particles are able to reach the SC-viable epidermis junction, whereas rigid particles were found only in the superficial layers of the SC.

### SKIN PENETRATION AND FORMULATIONS

Although TiO<sub>2</sub> NP have a very small primary particle size, the particles may form much larger aggregates and agglomerates (Fig. 1),<sup>58</sup> reducing their photocatalytic effect.<sup>59</sup> The tendency for primary NP to form these larger particles might suggest that there would be fewer individual NP available for skin penetration.<sup>58</sup> The use of surfactants, dispersants and particle surface coatings may help prevent this process by altering the equilibrium in favour of individual NP, so imparting the characteristic transparent appearance of modern NP formulations. Sunscreens with a TiO<sub>2</sub> NP content of greater than 1% without any of these ingredients can result in a white appearance.<sup>15,40</sup> For example, the presence of hydrous alumina lowers Van Der Waals forces between pigment-grade TiO<sub>2</sub> particles by several orders of magnitude.<sup>14</sup>

### PENETRATION ENHANCERS

Penetration enhancers increase the passage of drugs through the SC. These agents may have the ability to interact with some components of the skin, causing increased lipid fluidity, swelling of the SC, and leaching of certain structural components.<sup>41</sup> Ingredients found in sunscreens, such as oleic acid, ethanol, octylpalmitate, castor oil, propylene glycol and phospholipids have all been seen to act as penetration enhancers for NP across the SC.<sup>15,42,43</sup>

Other compounds found in cosmetic and therapeutic formulations, such as salicylic acid, retinoids and benzyl peroxide, are known to alter SC barrier function, as do oral retinoids.<sup>44,45</sup> To date, no studies researching the effect of these compounds on NP penetration have been carried out.

TiO<sub>2</sub> itself may act as a penetration enhancer. In the presence of TiO<sub>2</sub>, the penetration of ZnO into the SC has been observed to be greatly enhanced.<sup>45</sup> This effect is possibly due to the possibility that the TiO<sub>2</sub> may act in synergy with ZnO, producing a greater amount of ROS and consequent barrier disruption. In comparable conditions with TiO<sub>2</sub> NP, greater percutaneous absorption of pesticides into the systemic circulation has also been documented.<sup>46</sup>

## MECHANISM OF CELLULAR INJURY

### ROS production with and without UVR

The ideal amount of applied sunscreen preparation for adequate protection is 2 mg/cm<sup>2</sup>.<sup>47</sup> However, this amount is rarely achieved in daily practice and sunscreens may be applied after the skin is already sunburnt. Exposure of skin to excessive UVR may result in SC lipid disruption and a decrease in intercellular adhesion.<sup>48</sup> The penetration of NP of up to 45 nm to deep dermis has been demonstrated following delivery of a sub-erythral dose of UVR to mice (UVB 270 mJ/cm<sup>2</sup>), within 24 h of exposure.<sup>49</sup>

TiO<sub>2</sub> and ZnO NP may also induce cellular damage even in the absence of UVR, with one possible mechanism being the catalysis of lysosomal-released H<sub>2</sub>O<sub>2</sub> to <sup>•</sup>OH during the phagocytosis and attempted degradation of NP.<sup>50,51</sup>

### Effects on DNA

The ability of TiO<sub>2</sub> and ZnO NP to cause cytotoxicity, including DNA damage via ROS generation, is well documented. They are utilized for their antibacterial effect in water and air purification.<sup>7</sup> However, in sub-lethal concentrations, ROS may induce other unwanted effects, such as malignant tumour production.<sup>52</sup> A recent *in vivo* study in mice showed that subcutaneous placement of coated TiO<sub>2</sub> NP can convert clones of regressive mouse fibrosarcoma cells with no metastatic potential, into aggressive tumour cells with metastatic ability. It was thought that sub-lethal exposure to TiO<sub>2</sub> NP may allow the surviving tumour cell population to be transformed into more aggressive fibrosarcoma cells.

Damage caused by NP sunscreens was first noted in 1997.<sup>53</sup> TiO<sub>2</sub> and ZnO extracted from sunscreen, when illuminated by UVR, caused DNA strand breaks in both supercoiled plasmids and human fibroblasts via the generation of ROS. This effect has also been documented in human epithelial cells,<sup>51</sup> as well as on human genes.<sup>54</sup> Photo-irradiated TiO<sub>2</sub> anatase NP can damage DNA at every nucleotide with little site specificity, via hydroxyl free radicals. In addition, they can catalyze copper-mediated site-specific DNA damage via the formation of hydrogen peroxide.<sup>54</sup>

### Effects on cellular lipids

The degrading effect of UVR on skin lipids is established,<sup>55</sup> and the presence of TiO<sub>2</sub> and ZnO NP may accelerate the lipid oxidative process through the production of ROS, causing enhanced disruption of cellular membranes.<sup>56</sup> Organic photosensitizers such as 5-aminolevulinic acid

(5-ALA), used in photodynamic therapy to treat non-melanoma skin cancers, work via a similar mechanism, that is, production of ROS.<sup>57</sup> The most significant difference is that 5-ALA is rapidly biodegradable, but TiO<sub>2</sub> and ZnO NP may persist indefinitely.

## THE EFFECT OF TiO<sub>2</sub> NP ON CELLS IN CULTURE

When human skin cells are cultured with TiO<sub>2</sub> NP (anatase 9 nm) they are observed to: (i) be preferentially phagocytised by melanocytes, fibroblasts and dendritic cells;<sup>58</sup> (ii) induce alterations in the cellular calcium homeostasis in melanocytes and fibroblasts, a key regulator of most cellular mechanisms;<sup>58</sup> (iii) reduce cell growth in keratinocytes, sebocytes, melanocytes and fibroblasts;<sup>58</sup> (iv) selectively induce apoptosis in dermal fibroblasts and dendritic cells;<sup>58,59</sup> and (v) inhibit the proliferation and differentiation of keratinocytes.<sup>58</sup>

Collectively, these observations (ROS formation, internalization and altered gene expression) argue that if TiO<sub>2</sub> NP are absorbed into the skin, they may deregulate cell behaviour, particularly when further photo-irradiated. With weakened barrier function, this may set up a cycle of epidermal damage and further penetration of TiO<sub>2</sub> and ZnO NP, leading to: (i) promotion of less aggressive tumours into more aggressive malignant ones;<sup>52</sup> (ii) enhanced dermal elastosis, leading to premature aging of the skin;<sup>27</sup> (iii) modification of cellular mechanics, such those as observed in human hair follicle culture, where altered hair shaft elongation, proliferation, apoptosis, and melanogenesis have been observed;<sup>59</sup> and (iv) worsening of pre-existing cutaneous pathology such as eczema in the NC/Nga and DS-Nh mouse model.<sup>60,61</sup>

## DISCUSSION

A succinct summary of the conclusions that can be drawn from the studies referenced above comes from the European Union Scientific Committee on Consumer Products. It stated in December 2007 that: 'There are large data gaps in risk assessment methodologies with respect to NP in cosmetic products . . . It is necessary to review the safety of nanonized TiO<sub>2</sub> in the light of recent information and to consider the influence of physically abnormal skin and the possible impact of mechanical action on skin penetration.'<sup>62</sup>

Current evidence indicates that sunscreens do reduce premature skin aging and the number of solar keratoses and squamous cell carcinomas.<sup>65-66</sup> However, the randomized controlled trials referenced were carried out using chemical sunscreens. No such data exists for TiO<sub>2</sub> and ZnO NP sunscreens.

The authors feel that the following points are important for disclosure and well-informed debate on the subject: (i) labelling of all sunscreen and cosmetic products containing NP; (ii) re-evaluation of the use of anatase, and uncoated NP in sunscreen and cosmetic formulations, until proven safe; and (iii) further research into the long-term biological

effects of topical preparations containing NP, particularly with respect to the stability of particle coatings *in vivo*, and the effect of these products on skin with compromised barrier function.

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