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Real Facts about Safety and Efficacy of Zinc Oxide and Titanium Dioxide in Solar Products

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Abstract

Background: Titanium dioxide and zinc oxide were often criticized over the last decade because of their supposed noxious effects on human health. Moreover, these compounds which are frequently introduced in sunscreen products as UV filter, are sometimes associated with poor UVA protection factors. So, in order to clarify the real efficacy and safety status of these products, we provide here some bibliographic and experimental data regarding 1) their "real" protective effect against UVA rays and 2) their real harmful effects on human skin notably by studying their capability to penetrate through the human cutaneous tissue. **Materials and Methods:** We studied here 4 sunscreen products containing titanium dioxide and zinc oxide for 3 of them. First, because the UVA-PF values obtained for these compounds by using the "classical" *in vitro* ISO 24443 procedure seem to be significantly different from to those obtained by using the *in vivo* method ISO 24442, we chose to develop a new *in vitro* methodology in order to more precisely define the UVA-PF of titanium and zinc oxides. This new methodology was then used to lead UVA-PF studies with the 4 selected solar products. We also provide here an evaluation of the toxicological effects of titanium and zinc oxides on human skin based on the SCCS reports and analysis of recent and relevant bibliographic studies. Moreover, as the harmful effects of this type of products are closely linked to their ability to penetrate cutaneous tissue, we tested 7 sunscreen products to precise the skin penetration profiles of titanium dioxide and zinc oxide by using human skin explants mounted on Franz cells. **Results:** We here demonstrated that our new *in vitro* methodology gave some UVA-PF values very close to those obtained with *in vivo* methods and we took advantage of it to define more realistic UVA-PF for titanium dioxide and zinc oxide. Additionally, we here evaluated the human skin permeation and resorption capacities of titanium dioxide and zinc oxide incorporated in

the 7 tested products. As it was defined by World Health Organization (WHO) in 2005, permeation consists in the ability for a compound to penetrate into different layers of a tissue, and the resorption consists in the absorption of this compound into the vascular system. In our experimental conditions, we showed 1) that zinc oxide and titanium dioxide permeations did not exceed 8.5 and 5.5 μg/cm^2 of skin respectively (*i.e.* 0.89% and 0.26% of the applied product, respectively), and 2) that their resorptions were not significantly different from zero. As a consequence, we can assume that the supposed harmful effects of titanium dioxide and zinc oxide on cutaneous tissue could not be observed following the use of the tested solar products. **Conclusion:** Regarding their efficacy, we here provide, by using a new *in vitro* methodology for UVA-PF measurements (which is also very efficient to determine SPF), new evidence showing that titanium dioxide and zinc oxide could constitute "good" UV filters. In addition, our work with Franz cells reinforces the fact these compounds can be safely used for human skin solar protection.

Keywords

TiO_2, ZnO, UV-Radiations, Human Skin, UVA-PF, Resorption, Cutaneous Penetration, Franz Cell, New *in Vitro* Methodology

1. Introduction

Sunscreen products are used over decades to protect human skin against harmful solar expositions. These products so contain compounds called UV-filters designed to significantly reduce the quantities of UVA and UVB radiations damaging the cutaneous tissue (for a review, see [1]). Mainly due to the generation of reactive oxygen species (ROS), UV radiations can for example induce a loss of skin elasticity by activating different matrix metalloproteinases, which damage collagen and other dermal matrix proteins [1] [2]. In a more dramatic way, UV radiations were also identified as the most important risk factor for skin cancer [3].

In this context, two major categories of UV filters have been developed: Organic ones and inorganic ones. As the first class can sometime induce allergic reactions (for a review, see [4]) and need about 15 to 30 minutes to be absorbed by the skin and to act as efficient decoy targets for the oxidative damages induced by UV radiations, numerous cosmetic companies choose to resort to mineral filters. These compounds, also called inorganic filters, are able to scatter light and to reflect UV rays and acts as a real physical barrier. They are less allergen than organic filters [5] and are efficient as early as they are applied at the skin surface.

However, during the last decade, some consumer's associations (notably) have suggested that inorganic filters such as zinc and titanium oxides incorporated into sunscreen products could present 1) a poor efficacy regarding their protec-

tive effect against UVA, and 2) possible harmful effects for human skin and health.

The efficacy of solar filters regarding their protective effect against UVA can today be evaluated by two different validated methods, an *in vitro* one, *i.e.* the ISO 24443 procedure, and an *in vivo* one, *i.e.* the ISO 24442 procedure. However, Hedayat *et al.* in 2020 [6] reported that these two methods can often lead to significantly different results. In line with this work, we also observed in our laboratory that solar products only containing titanium dioxide and/or zinc oxide displayed lower UVA-PFs when they were measured by using the *in vitro* procedure. As a consequence, we decided to develop a new method allowing a better prediction of their *in vivo* efficacy and we tested 7 formulations containing titanium dioxide and zinc oxide for 3 of them.

In a second part of this work, we have also examined the safety status of titanium dioxide and zinc oxide as they are described by official international organizations [7] [8]. To sum up, titanium dioxide notably, seems to be hazardous for alimentary purposes [7]. Concerning its use and the use of zinc oxide as UV-filters and their possible harmful effects for human health, the situation remains unclear and the legislator has chosen to alert the consumers regarding a too "massive" exposition to these products [7] [8].

Anyways, we have chosen to realize cutaneous penetration studies in order to evaluate the real capabilities of titanium dioxide and zinc oxide to go through the human skin and to penetrate into blood and/or lymphatic circulations. For these studies, we have chosen to evaluate the "permeation" and the "resorption" parameters as they are defined by the World Health Organization (WHO); "permeation" consisting in the ability for a compound to penetrate into different layers of a tissue, and "resorption" consisting in the absorption of this compound into the vascular systems [9].

2. Materials and Methods

2.1. Tested Products Composition (INCI LISTS)

Formula 1/P1

Glycine Soja (soybean) Oil, Dicaprylyl Carbonate, Titanium Dioxide, Zinc Oxide, Alcohol Denat., Caprylic/Capric Triglyceride, Dicaprylyl Ether, Stearic Acid, Polyglyceryl-3 Diisostearate, Aluminum Hydroxide, Alumina, Polyhydroxystearic Acid, Tocopherol.

Formula 2/P2

Caprylic/Capric Triglyceride, Coconut Alkanes, Zinc Oxide, Titanium Dioxide, Helianthus Annuus Seed Oil, Cocos Nucifera Oil, Polyglyceryl-2 Dipolyhydroxystearate, Alumina, Polyglyceryl-3 Diisostearate, Stearic Acid, CocoCaprylate/Caprate, Glyceryl Caprylate, GelidiumSesquipedale Extract, Propanediol, Tocopherol, Aqua, Polyglyceryl-4 Caprate.

Formula 3/P3

Dicaprylyl Carbonate, Aloe Barbadensis Leaf Juice, Zinc Oxide, Titanium Dioxide, PongamiaGlabra Seed Oil, Diethyl Sebacate, Polyglyceryl-2 Dipolyhy-

droxystearate, Propanediol, Stearic Acid, Polyglyceryl-3 Diisostearate, Aluminum hydroxide, Brassica Campestris Oil, Talc, Benzyl Alcohol, Bisabolol, Sodium Chloride, Dehydroacetic Acid, Tocopherol, Aqua.

Formula 4/P4

Dicaprylyl Carbonate, Titanium Dioxide, PongamiaGlabra Seed Oil, Dicaprylyl Ether, Alcohol Denat., Glycine Soja (soybean) Oil, Polyglyceryl-3 Diisostearate, AluminiumHodroxide, Stearic Acid, Rubus (raspberry) Idaeus Seed Oil, Helianthus Annuus (sunflower) Hybrid Oil, Olea (olive) Europaea Fruit Oil, Tocopherol, Propolis Extract, Pollen Extract, Curcuma Longa (tumeric) Root Extract.

Formula 5/P5

Titanium Dioxide, Dicaprylyl Carbonate, CarthamusTinctorius Seed Oil, Caprylic/Capric Triglyceride, OleylErucate, C15-19 Alkane, Stearic Acid, Camellia Oleifera Seed Oil, Parfum, Aluminum Hydroxide, Polyglyceryl-3 Diisostearate, Polyhydroxystearic Acid, LinumUsitatissimum Seed Oil, Polyglyceryl-2 Dipolyhydroxystearate, Alumina, Glycine Soja Oil, Passiflora Edulis Seed OiL, PhysalisAngulata Extract, Tocopherol, Benzyl Salicylate, Geraniol, Linalool.

Formula 6/P6

Dicaprylyl Carbonate, Titanium Dioxide, Aloe Barbadensis Leaf Juice, Dicaprylyl Ether, Polyglyceryl-6 Stearate, Caprylic/Capric Triglyceride, ArganiaSpinosa (argan) Kernel Oil, SesamumIndicum (sesame) Seed Oil, Polyglyceryl-3 Polyricinoleate, SorbitanIsostearate, Stearic Acid, Polyglyceryl-3 Diisostearate, Aluminium Hydroxide, Aqua (water), CI 77492 (iron oxides), CandelillaCera (candelilla wax), Parfum (fragrance), Silica Polyhydrostearic Acid, Simmo, dsiaChinensis (jojoba) Seed Oil, Polyglyceryl-6 Behenate, Glycerin, Sodium Benzoate, Water, Alumina, Potassium Sorbate, Sodium Levulinate, CI 77491 (ironoxides), Cetyl Alcohol, CI 77499 (iron oxides), Sodium Anisate, Sodium Lauroyl Glutamate, Tocopherol, Lysine, Helianthus Annuus (sunflower) Seed, Magnesium Chloride.

Formula 7/P7

Aqua, Dicaprylyl Carbonate, Titanium Dioxide, Glycerin, Caprylic/Capric Triglyceride, Simmondsia Chinensis Seed Oil, Polyglyceryl-3 Diisostearate, Coconut Alkanes, Polyglyceryl-2 Dipolyhydroxystearate, Polyhydroxystearic Acid, Stearic Acid, CalophyllumInophyllum Seed Oil, Magnesium Sulfate, Sodium Chloride, Xanthan Gum, Aluminum Hydroxide, Aloe Barbadensis Leaf Juice Powder, Sodium Levulinate, Glyceryl Caprylate, Alumina, Coco-Caprylate/Caprate, Sodium Anisate, Citric Acid, Tocopherol.

2.2. UVA-PF Determination (for the Formulas P2 to P4 and P6)

The *in vivo* method used in this study follows protocols given by the International Organization for Standardization (ISO 24442, provided by European Union at May 2013).

Two *in vitro* methods were used for the UVA-PF determination of the tested products: The first one corresponded to the ISO 24443 procedure (provided by

European Union in 2012), the second one to a modified version of the ISO 24443 procedure in which the calculation of the UVA-PF is realized by using the solar spectrum value instead of the spectrum value of the xenon lamp used to irradiate the samples.

Briefly for the *in vitro* measurments, 1.3 mg/cm^2 of the tested products were spread on the rough side of sandblasted Polymethyl metacrylate (PMMA) plates. The transmission of PMMA plates was measured with a UV spectrophotometer equipped with a UV source and a monochromator capable of delivering UV energy between 290 and 400 nm. PMMA plates were then exposed to UV radiation for 30 minutes, using a sun simulator with an irradiance of 550 W/m^2. In this way, the tested product received two Minimal Erythemal Dose (MED). Transmission of PMMA plates was measured again with a UV spectrophotometer equipped with a UV source and a monochromator capable of delivering UV energy between 290 and 400 nm. The SPF and UVA-PF were expressed from the entire residual UVB and UVA spectrum that has passed through the layer of cream spread on the PMMA plate. However, this wave function $T(\lambda)$ must be multiplied by:

1) A first wave function which expresses the spectral characteristic of the sun $S(\lambda)$.

2) A second wave function which expresses the reactivity of the skin as a function of the wavelength (and therefore of the dissipated energy): this is the erythematous function $E(\lambda)$.

$$\text{SPF } in\ vitro = \frac{\sum_{290\text{ nm}}^{400\text{ nm}} E(\lambda)\cdot S(\lambda)\mathrm{d}\lambda}{\sum_{290\text{ nm}}^{400\text{ nm}} E(\lambda)\cdot S(\lambda)\cdot T(\lambda)\mathrm{d}\lambda}$$

$$\text{UVA}_\text{e}\ in\ vitro = \frac{\sum_{320\text{ nm}}^{400\text{ nm}} E(\lambda)\cdot S(\lambda)\mathrm{d}\lambda}{\sum_{320\text{ nm}}^{400\text{ nm}} E(\lambda)\cdot S(\lambda)\cdot T(\lambda)\mathrm{d}\lambda}$$

The mean SPF and UVA-PF of the studied products were obtained by calculating the arithmetic mean of the protection indices of each test. Calculations were obtained by using a dedicated software.

2.3. Cutaneous Penetration Studies (for the Formulas P1 to P7)

Human normal cell explants were mounted on Franz cells. Receptor compartment of each cell was then filled up with physiologic serum (NaCl 0.9%) and after a period of 1 hour corresponding to the stabilization of the system, tested products were applied at the surface of the skin at the rate of 10 mg/cm^2 (in order to reach roughly 5 applications of the tested products, corresponding to a normal human behavior during a sunny day). Before and after a 12 hours' incubation period, titanium dioxide and zinc oxide (when necessary) were quantified in the receptor compartment of the Franz cell; they were also quantified in the

skin.

2.4. Quantification of Titanium Dioxide and Zinc Oxide

Inductively Coupled Plasma associated to a mass spectrometer (ICP-MS) was used to detect and quantify titanium dioxide and zinc oxide following their electric charge and their mass. Briefly, after a mineralization step corresponding to the solubilization of the sample by using strong acids and/or microwaves, the samples were vaporized by using argon plasma before to be characterized and quantified by the mass spectrometer (for more details, see [10]).

2.5. Statistics

In vitro data are expressed as means ± S.E. of experiments realized in quadruplicate (n = 4). *In vivo* data are expressed as means ± S.E. of experiments realized with 10 healthy volunteers. The statistical significances between the different experimental conditions were assessed (as indicated) by using Student t-tests or by using one way analysis of variance (one way ANOVA) followed by Holm-Sidak's tests when necessary.

3. Results and Discussion

As shown in **Figure 1**, *in vivo* and *in vitro* methods ISO 24442 and ISO 24443 gave significantly different results for the UVA-PF of the 4 tested products. These findings are in line with the work of Hedayat *et al.* in 2020 [6] which also concluded that the *in vivo* method is often preferred to assess UVA-PF owing to its precision and repeatability.

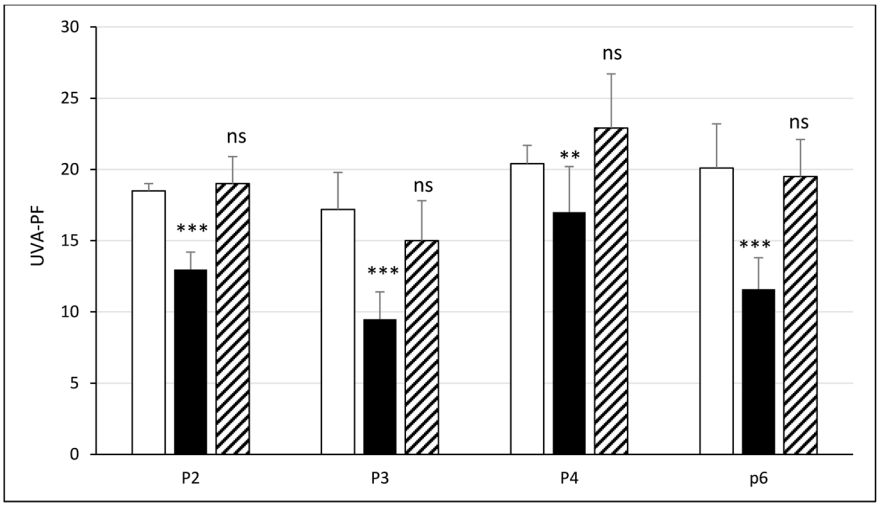

Figure 1. UVA-PF of the 4 tested products. White bars: UVA-PF determined *in vivo* on 10 healthy subjects by using the ISO 24442 procedure; black bars: UVA-PF determined *in vitro* by using the ISO 24443 procedure (n = 4); hatched bars: UVA-PF determined *in vitro* by using a modified version of the ISO 24443 procedure (n = 4). ns: Non-significantly different from the UVA-PF measured *in vivo* (Student *t-tests*), **: Significantly different from the UVA-PF measured *in vivo* ($p < 0.01$; Student *t-tests*), ***: Significantly different from the UVA-PF measured *in vivo* ($p < 0.001$; Student *t-tests*).

According to these results, we have so decided to develop a new *in vitro* method for UVA-PF determination of solar products focusing our efforts to the acquisition of values in line with those obtained by using the *in vivo* method ISO 24442.

As showed in **Figure 1**, our new *in vitro* method gave results very close to those obtained with the ISO 24442 procedure for all the tested products. As a consequence, the common assertion stating that titanium dioxide and zinc oxide present low UVA-PF seems to be interpreted cautiously notably regarding the method used to define it. In a very interesting way, as this new *in vitro* method could also give also "pertinent" results to define solar products' SPFs (not only regarding UVA protection but also the UVB one, studies are currently in progress in our laboratory to precise this point), it could constitute a rapid and efficient way to score SPF and UVA-PF of new solar products containing titanium dioxide and/or zinc oxide before to test them through *in vivo* studies implicating healthy volunteers.

Concerning the supposed toxic effects of titanium dioxide and zinc oxide on human health, a lot of scientific articles have been published these last decades (for reviews, see [11] [12] [13]) and they often led to very different conclusions depending on the exposition mode to these compounds (oral administration or topical application on skin), the composition of the products containing them, and so on. We so chosen to particularly consider here the conclusion of the Scientific Committee of Consumer Safety (SCCS) concerning the possible hazardous effects of titanium dioxide and zinc oxide and human health. In fact, as reported in the SCCS document of 2012 [8], zinc oxide-containing cosmetic formulations are likely to contain a small proportion of solubilized zinc, a further small proportion of which may be absorbed through skin and other routes but the rate and amount of the absorbed zinc is, however, likely to be insignificantly small compared to the large zinc pool already present in the body.

Concerning titanium dioxide, the SCCS report is a little bit more nuanced [14] since the International Agency for Research on Cancer have classified titanium oxides as a possible carcinogenic product when it is incorporated at high concentration (25 mg/kg of body weight) in food products. So concerning the use of this product in cosmetic formulas, the SCCS recommendations mainly consist in "case by case" evaluations regarding the capabilities of titanium dioxide to penetrate the skin and particularly to reach to blood and/or lymphatic circulations.

As a consequence, we have here chosen to realize cutaneous penetration studies aiming to evaluate the "permeation" and the "resorption" parameters as they are defined by the World Health Organization (WHO); "permeation" consisting in the ability for a compound to penetrate into different layers of a tissue, and "resorption" consisting in the absorption of this compound into the vascular systems [9].

As show in **Figure 2**, permeation values obtained for the 3 tested products containing zinc oxide varied between 6.02 ± 0.69 and 8.27 ± 4.59 μg/cm^2 of skin (*i.e.* between 0.26% and 0.39% of the deposed quantity of zinc oxide on the skin

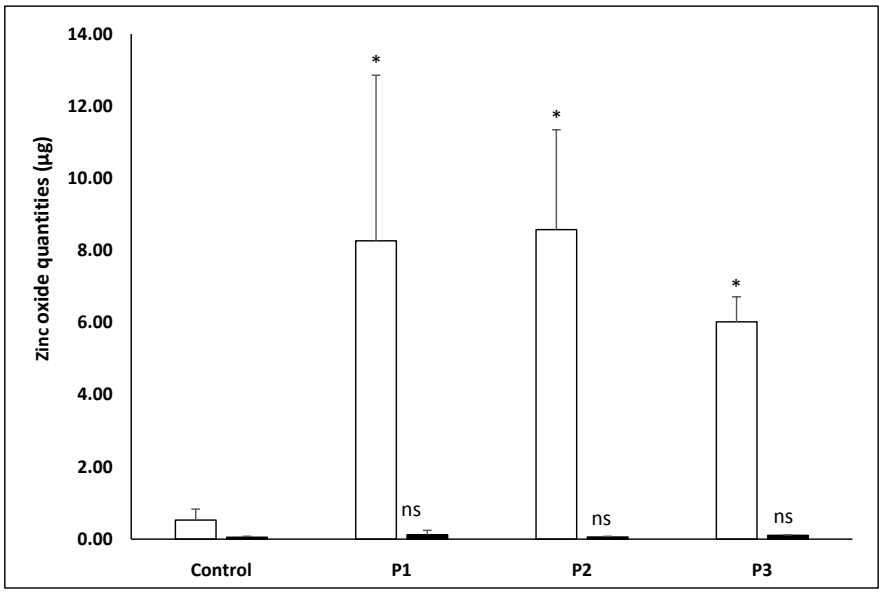

Figure 2. Permeation (white bars) and resorption. (black bars) of zinc oxide incorporated in the 3 tested products (P1 to P3). ns: No significantly different from the "Control" value (one way ANOVA), *: Significantly different from the "Control" value ($p < 0.05$) (one way ANOWA + Holm-Sidak's test).

explants). Zinc oxide can so be fixed by skin structures and protect them from UV by scattering and reflecting these radiations. Concerning the resorption values, they are negligible (non-statistically different from zero) and insignificantly small compared to the zinc large pool already present in the human body. As a consequence, solar products containing zinc oxide couldn't obviously constitute any danger for human health.

As shown in **Figure 3**, permeation values obtained for the 7 tested products containing titanium dioxide varied between 2.49 ± 1.15 and 6.48 ± 1.85 µg/cm^2 of skin which represent in all the examined cases, less than 0.35% of the applied quantity of product on skin. In the same way than zinc oxide, titanium dioxide is so able to be fixed by skin structures and protect them from UV by scattering and reflecting these radiations.

Concerning the resorption parameter measured for titanium dioxide and reflecting its ability to penetrate blood and lymphatic circulations (as specified by the WHO), the quantified values are not statistically different from zero. As a consequence, we can assume that in our experimental conditions, titanium dioxide is not able to penetrate human circulatory systems and so, that this compound couldn't display any harmful effect for human health.

To conclude, in our experimental conditions, all the tested products can be considered as "good" inorganic UV-filters displaying a powerful efficacy in front of UVA. In addition, they all seem totally safe for human health as defined by the WHO recommendations since they are not able to penetrate blood and/or lymphatic circulations. Finally, 1) we here provide a new *in vitro* method to evaluate UVA-PF of solar products notably allowing more rapid and efficient

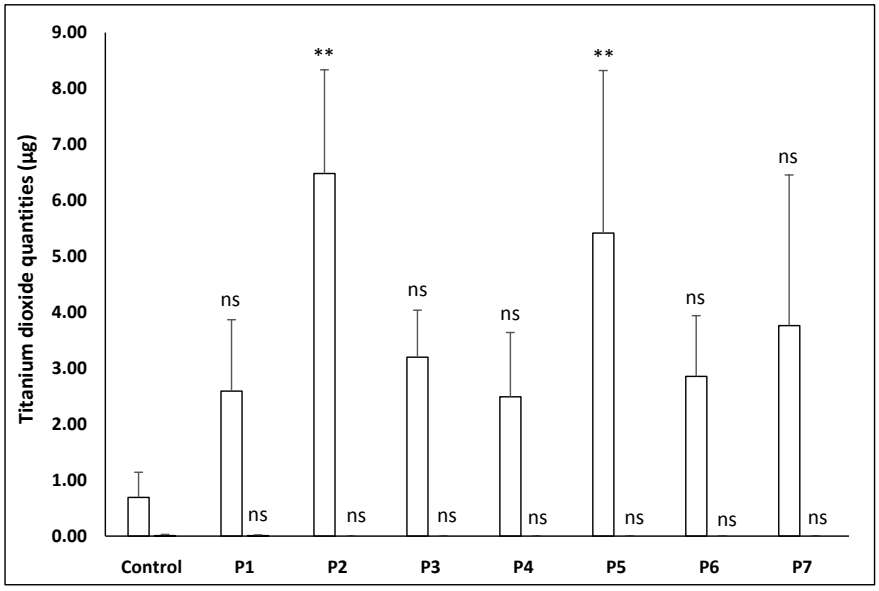

Figure 3. Permeation (white bars) and resorption. (black bars) of titanium dioxide incorporated in the 7 tested products (P1 to P7). ns: No significantly different from the "Control" value (one way ANOVA), **: Significantly different from the "Control" value ($p < 0.01$) (one way ANOVA = Holm-Sidak's test.

screenings of new compounds before to evaluate them through *in vivo* tests (some works are currently in development in our laboratory to achieve the complete characterization of this new methodology, also concerning the SPF of the tested products) and 2) we also strongly suggest that it remains possible to develop safe solar products containing titanium dioxide and/or zinc oxide according to the actual regulatory recommendations.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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