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THE PRESENCE OF TITANIUM DIOXIDE (TiO_2) IN SUNSCREEN PREPARATIONS ON THE SERBIAN MARKET

PRISUSTVO TITAN DIOKSIDA (TIO_2) U PREPARATIMA ZA ZAŠTITU OD SUNCA NA SRPSKOM TRŽIŠTU

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Ključne reči
preparati za sunčanje, TiO_2, TiO_2 NPs, srpsko tržište

Abstract

Nowadays, sunscreens are increasingly used worldwide to protect skin from UV radiation and prevent skin cancer. TiO_2 and TiO_2 nanoparticles (NPs) are the most commonly used in these preparations as physical blockers. There are studies that indicate that TiO_2 and TiO_2 NPs from sunscreen preparations can cause production ROS *in vivo*, which can cause cytotoxicity and genotoxicity. The largest number of studies show that there is no significant penetration of TiO_2 and TiO_2 NPs through healthy skin. Therefore, in this survey, content of TiO_2 and TiO_2 NPs in sunscreens on the Serbian market, was analyzed. There is a large number of preparations with different SPF (sun protection factor), and most have a SPF higher than 30. In preparations with SPF higher than 30, most commonly are physical blockers (TiO_2 and TiO2 NPs) 63%, while in preparations with SPF less than 30, this percentage is twice as low. In the products of domestic manufacturers, the most common is TiO_2, unlike the European manufacturers, where TiO_2 NPs are mainly used. In sunscreens for children, there are at least TiO_2 NPs, which is especially important because studies have shown that resorption is increased through sensitive and damaged skin.

INTRODUCTION

Positive effects of sunlight are known for many years, as well as the negative ones. UV radiation has an ability to cause harmful effects on the skin. Partly, UVB and UVA rays can reach the human skin and cause metabolic and biological reactions such as developing skin redness (erythema), different degenerative skin changes, such as actinic keratoses and skin cancer from epidermal cells.(1) UVA rays also play an important role in the photo aging process by producing reactive oxygen species (ROS). The results are damaged collagen and other dermal proteins.(2,3)

Sunscreens should provide protection against the adverse effects of both UVB and UVA radiation. The protective effect of sunscreens has been confirmed in the cases of squamous cell carcinoma and actinic keratoses, but for basal cell carcinoma and malignant melanoma the results are inconclusive.(4,5,6)

In the United States, skin cancer is the most common form of cancer. Annually, more than one million cases are diagnosed in the form of squamous cell and basal cell, both associated with ultraviolet radiation. The incidence of melanoma is rising significantly. Compounds that have an ability to protect from UV radiation are classified into two groups: organic and inorganic blockers. Minerals zinc oxide (ZnO) and titanium dioxide (TiO_2) are often used as inorganic physical sun blockers. They are preferred above organic compounds that only absorb UV radiation.(7)

Advantages offered by sunscreens based on inorganic compounds comprise the absence of skin irritation and sensitization, high photo stability, the inertness of the ingredients, limited skin penetration, and a broad spectrum protection.(8) These inorganic blockers also prevent disruption of the endocrine system typically induced by chemical UV filters. TiO_2 and ZnO have been used as ingredients for sunscreen formulations for more than 20 years, and now they are widely used nanomaterials based on TiO_2 and ZnO. They are white non-combustible and odorless powders and widely used as a white pigment, with important optical properties.(9)

TiO_2 and ZnO complement each other, because TiO_2 is primarily UVB absorbing compound, while ZnO is more effective in UVA absorption.(10) The disadvantage of micro-

sized TiO_2 particles is poor dispersive properties, giving the white barrier that is not cosmetically appealing and user-friendly.(11)

The rapid development of nanotechnology has resulted in an increasing number of nanomaterial-based products. When particles become smaller than the optimal light scattering size, visible light is transmitted to the particles appear transparent. This solves the cosmetically undesired opaqueness of inorganic sunscreens and makes the application of nanoparticles (NPs) commercially attractive, without reducing UV blocking effectiveness.(12)

On the other hand, since the surface area to volume ratio of particles increases as the particle diameter decreases, nanoparticles may be more bioreactive than normal bulk materials. It is the reason why the safety of cosmetic products containing NPs, has been frequently discussed. Many scientists and research institutes mainly focus on various kinds of toxicological and skin penetration studies.(13) However, safety also concerns the physicochemical properties of sunscreen ingredients to be taken up by skin in both the absence and presence of light.

The rising awareness regarding the importance of sun protection is followed by the expansion of the global market for sun care products. The global sun care market is estimated to expand at a 5.8% CAGR (compound annual growth rate) during the following period, rising from a value of US$14.8 bn in 2015 to US$24.9 bn by 2024.

Almost all the major cosmetic manufacturers use nanotechnology in many products. More than a decade ago Cosmetics giant Estee Lauder entered the NanoMarket with a range of products containing nanoparticles. L'Oreal, the largest cosmetics company on the world, is devoting about $600 million dollars, to the project Nano patents. It ranks number 6 in nanotech patent holders in the U.S. (14)

A 2007 survey by iVillage found that 11% of respondents used some type of sunscreen every day, whereas 59% used a sunscreen occasionally. (15) Extrapolation of this data suggests that 33 million people in the United States use a sunscreen product daily and 177 million apply sunscreen occasionally. With this widespread use and the potential for TiO_2 or ZnO NP exposure, concerns have focused on their possible resorption. Occasions for application of sunscreen products must be considered (sunburned skin or water-soaked).(16)

International Cooperation on Cosmetic Regulation defines a nanomaterial in cosmetics as an insoluble intentionally manufactured ingredient with one or more dimensions ranging from 1 nm to 100 nm in the final formulation. In addition, the nanomaterial must be sufficiently stable and persistent in biological media to enable potential interactions with biosystems.(17)

In 2012, the International Organization for Standardization underlined that the physicochemical characterization of nanomaterials was critical for the identification of test materials before toxicological assessment.(18)

Physico-chemical parameters important for characterization are particle composition, size/particle size distribution, surface charge, solubility/dispersibility, aggregation/agglomeration state, shape, surface area and surface chemistry.(19)

Consumers become more and more informed about potential toxic effects of nanoparticles, so it is one of the problems for manufacturers using nanotechnology. British scientific body Royal Society and the US Food and Drug Administration warn that the health risks of nanocosmetics require an investigation before product commercialization.

In European Union Cosmetic products notification portal (CPNP) is the portal for registration of the cosmetic products. The notification must emphasize if the product contains nanomaterials, with their identification and the foreseeable exposure conditions.

Nanomaterials must be authorised by the European Commission prior to their use in cosmetic products. Up until now, the Commission has authorized three UV-filters as nanomaterials: titanium dioxide, zinc oxide and tris-biphenyl triazine.

Nanomaterials must be labeled in the list of ingredients with the word 'nano' in brackets following the name of the substance.(20)

In Serbia, cosmetic products are regulated by the Law on the healthfulness of the products for general use; Rulebook on the conditions regarding the health suitability of the products for general use, "*Sl. glasnik RS*", br. 92/201. It is released in 2011. Transposition of the Regulation on the safety of cosmetic products of the European Union is obligatory after signing Stabilization and association agreement.

MATERIALS AND METHODS

Research was conducted in Niš, during July 2018. Sunscreen preparations from five community pharmacies are included in research. We analyzed data on the content of physical blockers based on TiO_2 in sunscreen preparations. Results are statistically analyzed using Microsoft Office Excel 2007.

RESULTS

We analyzed data on the content of physical blockers in eighty four sunscreens.

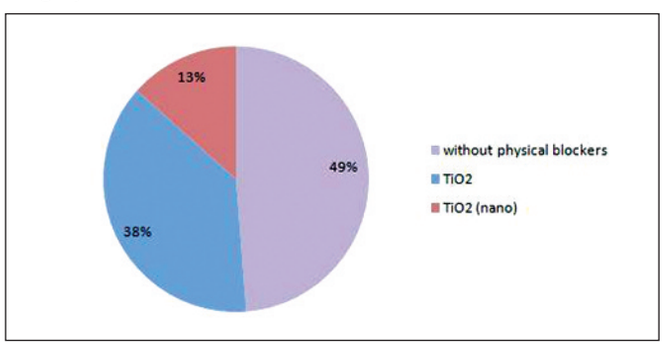

Figure 1. Percentage of sunscreens on market that contain TiO_2, TiO_2 NPs and do not contain any physical blocker

The results show that half of the preparations do not contain any physical blockers. There is a significant difference between number of sunscreen that contain conventional TiO_2 and TiO_2 NPs. Sunscreens with conventional form of TiO_2 triple more than TiO_2 NPs .

Special attention has been paid to the analysis of the content of physical blockers in sunscreen preparations for children, since their skin is more sensitive.

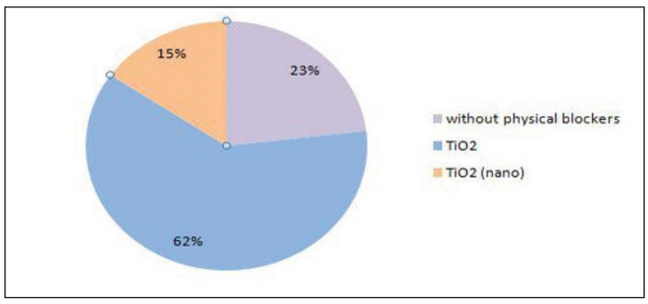

Figure. 2. Percentage of the sunscreens for children on the market that contain TiO_2, TiO_2 NPs or do not contain any physical blocker

The most of the sunscreens for children contain conventional form of TiO_2, one quarter do not contain any physical blocker. Insignificant number of sunscreens for children contain TiO_2 NPs.

Domestic and foreign sunscreen preparations can be found in Serbian markets. An analysis of data on the content of physical blockers from the aspect of product origin was also done.

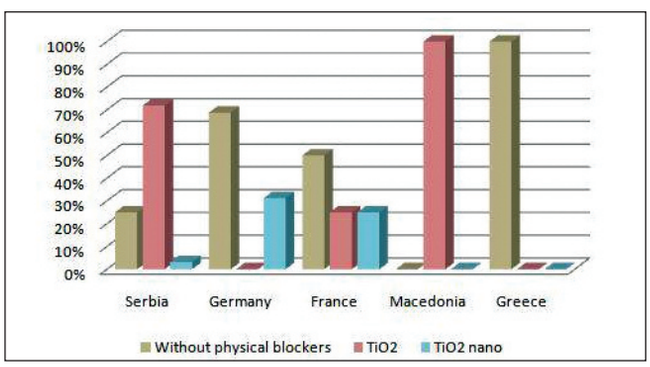

***Figure 3**. Percentage of sunscreens from different countries and presence of physical blockers in those products*

Results have shown that one quarter of sunscreens produced in Serbia do not contain any physical blocker. The most number of sunscreens containing conventional TiO_2. Only one sunscreen contain TiO_2 NPs. Sunscreens produced in Germany contain only TiO_2 NPs , or do not contain any physical blocker. Two sunscreens from France contain both the conventional and TiO_2 NPs. All sunscreens from Macedonia contain conventional TiO_2 and all sunscreens from Greece no contain physical blockers.

On the market, sunscreens with different SPF, but the most of them have SPF 30, and more.

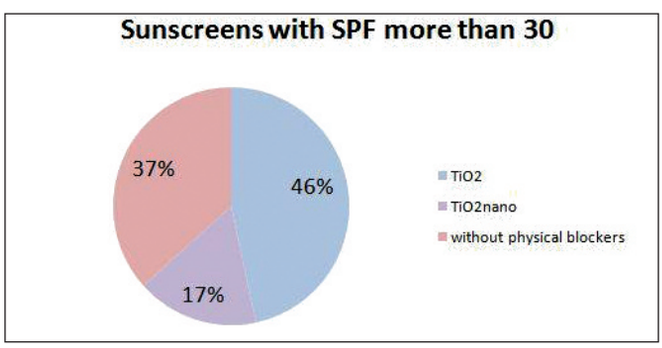

***Figure 4.** Percentage of sunscreens with SPF more than 30 that contain TiO_2, TiO_2 NPs or do not contain any physical blocker.*

Considering SPF, the most of sunscreens (63%) with SPF 30 or more, contain TiO_2 conventional or nanoform.

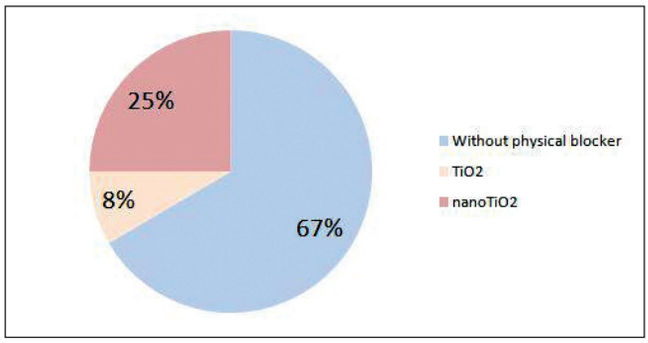

Figure 5. Percentage of sunscreens with SPF less than 30 that contain TiO_2, TiO_2 Np or do not contain any physical blocker.

Focusing on sunscreens with low SPF, the most of them do not contain physical blockers. There are insignificant number of sunscreens with TiO_2 NPs.

DISCUSSION

There are conclusive results that titanium can cause lung cancer after inhalation, so it is the reason for increased concerns about potential toxicity after dermal applications. Titanium is classified into group 2B of carcinogens.

Organized, accurately and detailed studies must be conducted in order to give an information about dermal permeation, local effects, and eventually generalized effects. It is necessary because sunscreens are applied to the skin in some countries during the whole year, in large amounts, on almost whole skin area. There are few factors that must be considered during research of dermal permeation of TiO_2: characteristics of the studied substance, skin, ingedients of sunscreen formulation.

Different experimental approaches are used for investigating dermal absorption: in vitro models, human skin, animal skin, damaged and intact skin. Many researchers have examined potential resorption of nanoparticles from sunscreens and their potential to interact with important structures in organism.

The stratum corneum represents the outermost layer of the skin and plays an important role in protecting the human organism against penetration by xenobiotics. The ingredients of sunscreen formulation also must be known. The biopharmaceutical characteristics are not the same comparing O/W, W/O emulsions, emulsions silicone-based or aerosol sprays. Researchers investigating dermal absorption should underline all properties and circumstances of the experiment.

Results of the recent studies provided the information that TiO_2 NPs can generate, reactive oxygen species (ROS): superoxide anions and hydroxyl radicals. [21,22]

The mechanism of the reaction is UV-induced photo catalysis. ROS can damage cellular components and macromolecules, ultimately cause cell death if produced in excess or if they are not neutralized by antioxidant defenses. ROS derived from the photo catalysis of NPs are cytotoxic to a variety of cell types.[23]

This is the reason why skin penetration studies of TiO_2 particles are usually investigated *in vivo* and *in vitro* with both intact skins and stripped skin which mimics an injured skin.[21]

The lack of penetration through the epidermis is considered as the main reason for the absence of skin carcinogenesis-promoting effects. The cytotoxicity of TiO_2 NPs was demonstrated in keratinocytes in vitro, [24, 25] but , no genotoxicity was observed. [26] Currently, only a few studies have been conducted with TiO_2 NPs applied to the damaged skin what normally occurs when sunscreens are reapplied to sunburned skin. UVB-damaged skin slightly enhanced TiO_2 NPs penetration in sunscreen formulations. [27]

In psoriatic skin, the fragility of stratum corneum seemed to facilitate the penetration of the nanoparticles. [28]

Investigation using *in vitro* 3D human skin models (KeraSkinTM) provide the evidence that ZnO NPs and TiO_2 NPs and their mixture are 'non-irritant' and 'non-corrosive' to the human skin by a globally harmonized classification system.[29]

On the market there are many sunscreens with different SPF. The largest number has a SPF higher than 30. There is a significant difference in the content of physical blockers (TiO_2 and TiO_2 NPs) in preparations with different SPF. With more than 30, the most common are physical blockers, 63%, while in preparations with less than 30, this percentage is double lower. Titanium dioxide is important for SPF and efficacy of sunscreens, but its toxicological properties and safety must be carefully considered. The preparations combine physical and chemical factors to increase the protection. The aim is to achieve as much effective protection as possible with fewer harmful effects.

CONCLUSION

There are many studies of harmful effects of TiO_2 and TiO_2 NPs from sunscreen preparation. The highest number of studies shows their no significant penetration trough healthy skin. However, there are studies that indicate the risk of harmful effects of TiO_2 NPs, which can induce ROS in vitro that can cause cytotoxicity and genotoxicity. The results of these studies in vivo, in vitro, and on animals should be carefully extrapolated. It is therefore very important to correctly evaluate the benefits of using TIO_2 NPs in sunscreen preparation and potential risks. Particular attention should be paid when treating children skin, damaged and diseased skin, because penetration is higher. Considering the results of available sunscreen preparations on the market, we can conclude that in Serbia a small number of preparations contain TiO_2 NPs. In countries in western Europe, preparations with TiO_2 NPs are predominantly represented. It is interesting that the number of the preparations for children with TiO_2 NPs is a very small. This is especially important for sunscreen preparations for children, as studies have shown that nanoparticle resorption has been increased through sensory, damaged and diseased skin, and it is known that children skin are not an effective barrier in the first years of life.

Sažetak

Danas se u svetu sve više koriste preparati za sunčanje koji štite kožu od UV zračenja i njegovih eventualnih štetnih posledica. U tim preparatima od fizičkih blokatora najzastupljeniji su TiO_2 i TiO_2 u obliku nanočestica (nanoparticles-NPs). Postoje studije koje ukazuju da TiO_2 i TiO_2 NPs iz preparata za sunčanje, mogu izazvati produkciju oksidativnih radikala *in vitro*, a oni mogu uzrokovati citotoksičnost i genotoksičnost. Najveći broj studija pokazuje da nema značajne resorpcije TiO_2 i TiO_2 NPs kroz zdravu kožu. Izvršena je analiza podataka o njihovom sadržaju u preparatima za sunčanje na tržištu Srbije. Postoji veliki broj preparata za sunčanje sa različitim SPF (sun protection factor), a najveći broj ima SPF veći od 30. Kod preparata sa SPF većim od 30, najčešći su fizički blokatori (TiO_2 i TiO_2 NPs) 63%, dok je u preparatima sa SPF manjim od 30, ovaj procenat dvostruko manji.

U proizvodima domaćih proizvođača najčešće se nalazi TiO_2, za razliku od proizvođača iz Evrope, gde se uglavnom koriste TiO_2 NPs. U sredstvima za sunčanje za decu ima najmanje preparata koji sadrže TiO_2 NP, što je posebno važno, jer su studije pokazale da je resorpcija nanočestica povećana kroz osetljivu, oštećenu i obolelu kožu.

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