

LITERATURE REVIEW OF INORGANIC ULTRAVIOLET RADIATION FILTERS

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B.S., University of Pittsburgh, 2005

A REPORT

submitted in partial fulfillment of the requirements for the degree

MASTER OF SCIENCE

Department of Chemical Engineering
College of Engineering

KANSAS STATE UNIVERSITY
Manhattan, Kansas

2012

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2012

Abstract

The damage that can be inflicted by ultraviolet radiation has gained widespread interest. Traditionally sunscreens are made of organic and inorganic components that block two of the three types of ultraviolet radiation, UVA and UVB. This report is a literature review of several articles that have investigated the effects of inorganic UV filters; specifically titanium dioxide and cerium dioxide. There are concerns about absorption of titanium dioxide into the skin and the adverse reactions that could occur, but it was found that there is little to no absorption. Similarly the photostability of titanium dioxide is a concern; this was found to be remedied in part by a surface treatment to the titanium dioxide. The combination of titanium dioxide and carnauba wax was also studied and found to enhance the properties of both the organic and inorganic filters. Ceria was studied as a possible replacement for titanium dioxide. It was found to have similar ultraviolet shielding properties while minimizing the photocatalytic activity and photocytotoxicity seen in titanium dioxide.

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Chapter 1 - Introduction

In the early 1930's three scientists ventured into the field of sunscreen; Milton Blake, Eugene Schueller, and Franz Greiter. Milton Blake experimented unsuccessfully while Eugene Schueller had more success and is often credited as the inventor of sunscreen (1). Around the same time Franz Greiter also created a sunscreen called Gletscher Crème leading some to credit him as the father of modern sunscreen (1). In the 1940's Benjamin Greene created 'red vet pet' for red veterinary petroleum which was a sticky red petroleum jelly-like substance that was supplied to soldiers in World War II (1). Greene later created a more consumer friendly product and founded Coppertone (1). Franz Greiter later went on to develop the sun protection factor (SPF) scale we use now. SPF is a measurement of the effectiveness of sunscreens; the higher the SPF the more protection the formula affords. These first steps into sun protection are barely a shadow of what we know today. Up until recently the damage inflicted by ultraviolet radiation was not understood by many people. But in recent years sunscreen and sun protection has become a popular topic (1-16). Think back just a few years and one can remember how being tan was promoted as a symbol of health and beauty. As more research is done showing the negative effects of ultraviolet radiation, protection from these effects becomes more important. The American Academy of Dermatology recommends on their website that everyone wear sunscreen everyday that has broad spectrum protection (UVA and UVB protection) and a sun protection factor (SPF) of at least 30. The dangers of ultraviolet radiation are becoming commonly known, from minor issues such as wrinkles or sun spots to the much more serious issue of skin cancer. It has been found that more than 3.5 million skin cancers in more than 2 million people are diagnosed annually; many of these skin cancers could have been prevented with protection from the sun's rays (2). Its statistics like this that are making people realize how important UV protection is.

Ultraviolet (UV) radiation is broken up into three types of radiation based on wavelength. UVC is made up of the shortest wavelengths and normally doesn't make it through the atmosphere except for high elevations. UVB radiation is mainly responsible for the most severe damage: acute damage such as sunburn and long term damage including cancer (4). UVA penetrates deeper into skin than UVB, particularly affecting connective tissue producing

detrimental reactive oxygen species. UVA is a strong inducer of immune suppression and is suspected to contribute to photocarcinogenesis. UVA is involved in idiopathic photodermatosis such as most cases of polymorphous light eruption (4). Using a broad spectrum sunscreen protects you from both the UVB which affects the top layers of the skin and the UVA which penetrates more deeply. As a result there has been a movement toward sunscreens that have broad spectrum protection; protection against both UVA and UVB radiation.

Ideally sunscreens are developed to filter both the UVA and UVB range. Sunscreens typically contain 'chemical filters', that is organic compounds that absorb strongly in the UV (most often UVB) and 'physical filters', such as TiO₂ and ZnO, that block UVB and UVA sunlight through reflection and scattering (5). In most sunscreens, at least two organic filters are used in formulations displaying high SPF numbers, one with optimal screening in the UVB region and the other in the UVA region in addition to, in many instances, a 'physical filter' (inorganic) (5). This allows for the broad spectrum protection (UVA and UVB) desired. Ideally, the UVB/UVA filters should be photostable; that is, they should degrade light to heat when they absorb UV radiation, or simply reflect and scatter the radiation when a metal-oxide physical filter is used (5). Unfortunately not all filters are photostable either in given quantities or in combination with other filters. For this reason limits have been set on the safe amounts of filters that can be used in sunscreens. This list of maximum allowed concentrations is established by each country, for example, European Union, USA, Japan, and Brazil (6). As research is done the list is modified to reflect the changes. The increased awareness and potential safety concerns leads to a great deal of research being done to explore the safest and most effective combination of filters possible. As mentioned above the most effective sunscreens offer broad spectrum protection; to do this multiple UV filters may be used. UVB filters mainly absorb wavelengths between 290 and 320 nm whereas UVA filters essentially absorb wavelengths between 320 and 400 nm (4).

Organic filters are used to block wavelengths in both the UVA and UVB ranges whereas inorganic filters are more effective blocking UVB. Organic filters are active ingredients that absorb UV radiation energy to various extents within a specific range of wavelengths depending on their chemical structure (4). Absorbed energy is conveniently converted into unnoticeable infrared energy (4). Pigment grade powders of metal oxides such as titanium dioxide or zinc oxide have been used for many years in combination with organic filters to enhance protection in

the longer UVA range (> 370 nm) (4). Unlike organic filters, they work by reflecting and diffusing UV radiation, instead of involving an absorption process (4). As far as UVB protection is concerned, a large choice of suitable filters has been available for a number of years (4). The choice is far more limited and questionable when efficient UVA filters have to be found (4). Recently more focus has been placed on finding effective UVA filters.

Two widely used representatives of classes of chemical UV filters are the cinnamates (UVB) and dibenzoylmethanes (UVA) (5). Cinnamates have received much attention, as they are the most widely used UVB blocking compounds amongst the various cosmetic sunscreen agents (7). Cinnamates achieve UVB blocking from a $\pi \rightarrow \pi^*$ absorption (using the energy gap between the π and π^* orbitals to transition the molecule from the more stable trans configuration to the less stable cis configuration) followed by a cis-trans isomerization (the release of energy to transform the molecule back to the more stable trans configuration) at the propenyl double bond in the S1 state and a relaxation to the ground state involving nonradioactive decay (7). Parasol 1789 or Avobenzene (4-tert-butyl-4'-methoxydibenzoylmethane) is one of the most common UVA filters present on the market because of its high absorptive capacity over almost the entire UVA range (8). Although Parasol 1789 has a high absorptive capacity it can become photoactive. This photo-decomposition of the UV filter results in the formation of free radicals and other reactive/toxic intermediates which may directly or indirectly initiate skin damage (8). Parasol 1789 produces free radicals when activated by UVA that lead to a reduction in photo-protective power and to an increased potential to damage biologically relevant molecules, such as proteins, plasmid DNA and more recently cultured keratinocytes (8). Properties like this have led to governments setting 'safe' limits to the amount of a filter that can be used. The list of substances and the maximum allowed concentration are established by each country for example, European Union, USA, Japan, and Brazil (6). In European legislation, titanium dioxide is the only inorganic UV filter allowed at 25% maximum concentration (6). This has led to additional research to either find a filter with the same absorption rate/range or some combination of compounds to retain the absorption while minimizing the photoactivity.

In recent years there has been some concern about the absorption of chemical UV filters into the skin and the detrimental effects it can cause. The skin is the largest organ in the body and the main purpose of it is to prevent dehydration. Skin is composed of three main layers the topmost is the epidermis then the dermis and last the subcutaneous layer. The subcutaneous layer

is the deepest part of the skin and consists of lipocytes and loose connective tissue (14). It serves as an energy source, and protects us from trauma and acts as thermal insulation (14). The dermis is the middle layer and consists of different types of protein fibers, nerves, glands, muscles and blood vessels. The epidermis is the outer layer and the first point of contact with the outside world. The epidermis is broken into several layers with the stratum corneum being the outmost of these layers. The morphology and physical-chemical properties of the stratum corneum, which consists of layers of flattened, keratin-filled cells, embedded in a lipid matrix, don't allow most substances to penetrate rapidly. Lipophilic substances, with low molecular mass, are the exception to this general rule. The concern with sunscreens has been the ability of some organic UV filters to penetrate the stratum corneum, distribute to the rest of the body via the blood, and cause detrimental effects such as estrogenic effects, carcinogenesis, or developmental abnormalities. Additionally, there is concern as to whether sunscreen can act as a penetration enhancer for other substances such as herbicides and bug sprays, specifically DEET (19). This is especially a concern in children; their surface area to body weight ratio is much higher, and their skin is more pervious. There have been a multitude of studies into popular organic UV filters, such as benzophenone-3 also known as oxybenzone (BP-3), 4-methylbenzylidene camphor (MBC), octyl methoxycinnamate (OMC), and octyl salicylate, to see if there is any truth to these concerns (several examples of studies can be found in the reference section of Appendix A). Inorganic filters have not been found to have these concerns even when reduced to nanoparticle size.

Sunscreens are classified as chemical absorbers (organic) and inorganic UV blocking materials (3). Traditionally organic sunscreens have been popular and widely used. However, some of these organic absorbers have caused irritation on the skin of sensitive individuals and therefore may pose a safety problem when used at higher concentrations (3). The culture has shifted from one where people only wore sunscreen at the beach or going to a ball game to a culture in which people are now more inclined to wear sunscreen every day. Some individuals have found it difficult to find formulas that are gentle enough to be worn daily but still offer the protection desired. In addition, very small amounts (of the sunscreen) can sometimes penetrate the topmost layers of the skin and render the UV filter less effective (3). In contrast to the organic absorbers, greater emphasis is now being put on the use of inorganic UV blocking materials which are far less likely to penetrate the stratum corneum and thus do not reach and

cannot damage viable skin tissue (3). Titanium dioxide, TiO₂, is one of the more popular choices for inorganic filters in sunscreens. As noted above inorganic filters block both UVA and UVB radiation. This is done mostly through scattering and diffraction but like organic filters there is also some absorption. As a result it gives the effect of being gentle while offering protection. The main cosmetic downside to inorganic filters is their tendency to leave a whitish residue or tint on the skin. It has previously been reported that the combination of organic filters and inorganic substances offers many advantages in sunscreen formulations; for example, the diminution of the organic filter content to avoid the intrinsic irritation provoked by some of these compounds; the achievement of higher sun protection factors with simpler formulations and the reduction of the whitening effect caused by the use of large quantities of inorganic sunscreens, i.e. TiO₂ (9). In combination with organic sunscreen agents, TiO₂ gives impressive SPF numbers as well as displaying broad absorption in the UVB and UVA regions (6). The combination of the organic and inorganic gives the best of both worlds while allowing for the broadest spectrum of protection.

Chapter 2 - Research Presented

As stated above inorganic filters have been gaining in popularity but there is still a great deal of research that can be done. A trend in sun protection is the increased use of inorganic UV filters, especially in sun care products for children and people with sensitive skin (6). The increasing use of inorganic UV filters is due partly to their low potential for producing irritant reactions and partly to their sunscreen efficacy (6). With the development of micro ionization techniques, it has become possible to incorporate titanium dioxide in sunscreen formulations without the previous whitening effect; hence its use in cosmetics has become an important research topic (6). While titania is the most popular inorganic it has been shown to have some drawbacks; as a result, ceria has started to be investigated as a possible alternative. As mentioned above the high refractive index of titania can make the skin appear white when applied. Additionally the high photocatalytic activity facilitates the generation of reactive oxygen species, which can oxidize and degrade other ingredients in the formulation (10). Conversely the lower refractive index of ceria allows it to appear transparent when applied to skin while maintaining excellent UV absorption properties and generally lower photocatalytic activity than titania. For the purposes of this report, several articles were studied with respect to titanium dioxide;

adsorption of microfine TiO₂ in skin (11), the photostability of TiO₂ with organic surface treatment (3), and the combination of TiO₂ and carnauba wax (9). Two topics for ceria are included: the shielding properties (10) and the photocatalytic activity and photocytotoxicity (12).

Titanium Dioxide

Microfine metallic oxides such as titanium dioxide or zinc oxide have been found to be highly protective against harmful UV rays because they mobilize electrons within their atomic structure while absorbing UV radiation (11). However, the long term use of these highly efficient UV attenuators could potentially lead to health effects, in particular if significant amounts of these microfine metallic oxides would be absorbed through the skin (11). Some initial research had been done showing that this was not the case but it only scratched the surface of proving that absorption through the skin is not a problem. For this experiment porcine skin was studied in vitro because the permeability properties of the stratum corneum are unchanged by removal from the body and the porcine skin structure is very similar to human skin.

Three formulations were made, one of zinc oxide and two of titanium dioxide (T-Lite SF-S and T-Lite SF). The zinc formulation was 10.3 wt % zinc oxide, 8.3 wt % zinc, with a particle size of 80 nm. The titanium dioxide formulations were both 10 % titanium dioxide corresponding to 6 wt % titanium (11). Both formulations had needle-like particles with dimensions of 30 - 60 X 10 nm; the T-Lite SF-S was coated with both silica (2-5 wt %) and methicone (4.5-6.5%) but the T-Lite SF was coated with only methicone (3.5-5.5 %). Full thickness skin samples (epidermis and dermis) of visually intact skin from the lateral abdominal region of 5 month old domestic pigs were used (11). Bovine serum albumin was used to represent physiological conditions and because it was expected to increase solubility by providing a sink for metal ions by protein binding (11). The test formulations were applied to 1 cm² exposed skin at doses of 4mg/cm² for 24 hours. Samples of receptor fluid (about 0.4 g/sample) were taken at various time intervals (3, 6, 12, and 24h) after application (11). After the last sample was taken the samples were put through a stripping procedure(washing and taping) to remove the titanium and zinc oxides.

The total zinc recoveries ranged between 102% and 107% (11). For the titanium recoveries the range was between 98-100% for the T-Lite SF-S and 86-93% for T-Lite SF. The receptor fluid for the zinc and both titanium formulations was in line with untreated skin. Thus it

was shown that irrespective of surface characteristics, particle size or shape of the micronized pigments there was no indication of penetration through the skin (11). Moreover, the absence of dermal penetration and the lack of material in the skin indicate that the three formulations did not absorb through the skin (11). Thus this research shows that microfine zinc oxide and titanium dioxide may not pose the health risks previously believed.

Having greater confidence that titanium dioxide does not penetrate the skin, the photostability can now be examined. In contrast to the organic absorbers, greater emphasis is now being put on the use of inorganic UV blocking materials which are far less likely to penetrate the stratum corneum and thus do not reach, and cannot damage, viable skin tissues (3). As mentioned, titanium dioxide tends to impart a white color on the skin when used; this is minimized as the particle size is decreased. In order to avoid this problem (whitening), manufacturers reduce the particle size to the range of 20 - 50 nm, because in this size range the interaction with light obeys Rayleigh's laws of light scattering, whereby the intensity of scattered light is inversely proportional to the fourth power of the wavelength (3). This means they scatter the short UV wavelengths far more efficiently than the visible ones (3). The protection afforded by titanium dioxide is not just because of scattering but also due to absorption. As a result of titanium dioxide being a semiconductor the UV light can cause electrons to jump to higher energy bands and release energy as they drop back to the original state. Any wavelength shorter than approximately 385nm will achieve this, thus both UVA and UVB take part. When the electrons don't return to their original bands, the strong oxidizing and reducing ability of the electrons can degrade the organic components present within the sunscreen as well as damage the tissue constituent (3). For this reason the use of an organic surface treatment on the titanium dioxide has been studied to see if the damage can be minimized.

For these experiments the rutile type of TiO₂ was used and methacryloxypropyltrimethoxysilane (MCPTMS) was used as the organic surface treatment. Slides were prepared with the non-modified and surface modified samples; both were treated with 1,3-butanediol to allow for a color difference when the slides were exposed to UV radiation. The color difference before and after the slides were exposed for 1 hour was measured, the greater the difference the greater the photocatalytic activity. The measurements were taken using a digital spectrophotometer and from this the photocatalytic activity was calculated. The results demonstrate that the MCPTMS-modified TiO₂ particles have a much higher photostability to

UV light compared to non-modified TiO₂ (3). The low photocatalytic activity is attributed to covering the active catalytic sites by chemical blocking through the reaction between surface hydroxyl group of TiO₂ and MCPTMS (3). There was a decrease of approximately 31% from the non-modified to the modified TiO₂. The MCPTMS composition with 40 wt % silane was found to have the best results and as the reaction time (between TiO₂ and MCPTMS) was increased (from 1 hour to 24) the photocatalytic activity was found to decrease. Additionally, when the reaction temperature was increased, the inhibition of photocatalytic activity also increased. There was a slight drop in the UV shielding ability of the modified TiO₂ due to the surface layer hindering the scattering by TiO₂ but the transparency in the visible region was still excellent. The hinderance was mostly due to the fact that there was less TiO₂ in the solution overall but also could be accounted to the grafting of the MCPTMS to the TiO₂.

Similar to the advantages that the surface modifications can give to TiO₂ the addition of carnauba wax to TiO₂ has also been studied. The rational combination of cinnamates (in carnauba wax) and titanium dioxide has shown a synergistic effect to improve the sun protection factor (SPF) of cosmetic preparations (9). Several cinnamic acids and cinnamates can be found in carnauba wax. Cinnamates are widely used as organic filters in sunscreens. As discussed above, the UV absorption of organic filters works through the electron delocalization while inorganic filters work through jumps in the energy bands. Thus, considering the intrinsic properties of both materials, it could be expected that an increased UV absorption would take place if both substances were intentionally combined (9). Additionally carnauba wax through its properties as a nanostructured lipid carrier (NLC) is thought to reduce the potential skin irritation risks while optimizing the organic/inorganic filter ratio by avoiding the use of unnecessary quantities of inorganic pigments. An NLC is a modification of solid lipid nanoparticles (SLN), in which the solid lipid phase of these nanoparticles has been loaded with liquid lipid, i.e. oils (9). They have attracted attention as a novel delivery system for organic and inorganic sunscreens due to their intrinsic UV blocking properties attributed to their size (200 - 400nm), and the possibility to integrate organic and inorganic filters inside a single particulated structure combining the UV absorption properties of both (9).

An ethanolic extract of carnauba wax (CW-EE) and an ethanolic solution of ethylcinnamate (EC-E) were added to diluted samples of high pressure homogenized titanium dioxide crystals to observe their qualitative UV absorption spectra (9). Furthermore, the *in vitro*

sun protection factors (SPFs) of both substances combined with titanium dioxide crystals either inside a liquid suspension or within a hard fat matrix were measured (9). The crystal lattices were also studied for possible modifications. Four different formulations were made: nanosuspension containing carnauba wax matrices (A), nanosuspensions containing titanium dioxide without lipid phase (B), nanosuspensions containing carnauba wax matrices with titanium dioxide distributed in the aqueous phase (C), and nanosuspensions containing carnauba wax matrices with titanium dioxide distributed in the lipid phase (D). UV absorption studies were done using a spectrophotometer in a wavelength range between 200 and 400nm (9). Thermal behavior studies were carried out by means of a calorimeter (9). The sun protection factors of the preparations were measured by means of a SPF-290 computer operated analyzer (9).

The sun protection factor of each of the four formulations was studied. Formulation A was found to have an SPF of only 2.2. Formulation B was found to have increasing SPF (from 1.51 - 2.10) with the increase in weight percentage of TiO₂ (from 2-6 wt %). Considering the SPF values of Formulations A and B, it could be expected a simple additive effect would give a SPF of about 4 (9). However, when the titanium dioxide was distributed in the aqueous phase (formulation C), increases between 2.33 and 10.9 times were observed and when the titanium dioxide crystals were added to the lipid phase of nanosuspensions (formulation D) the SPFs presented increases varying from 7.25 to 16.5 times in comparison to those exhibited by Formulation B. Thus it was shown that the addition of carnauba wax to titanium dioxide could enhance the UV absorption of the TiO₂. The surface contact between organic molecules possessing double conjugated systems such as the cinnamates and hydrophobic titanium dioxide increased the UV absorption capacity of both species (9). There is great promise to this research but a good deal more has yet to be studied especially the photoactivity of the solutions.

To incorporate inorganic filters into sunscreen products, it is a common practice to mix them with liquid lipid before being distributed in oil-water emulsions (13). But, in those cases, the formulations generally require high concentrations of pigments or the combination with many other substances to obtain an acceptable sun protection factor (13). In order to increase efficiency and efficacy of sunscreens, suitable carrier systems have to be developed (13). Solid lipid nanoparticles have been discussed as a suitable carrier system but they are known to have a lack of drug load capacity and drug expulsion during storage which decreases

their attractiveness. These organics could enhance the scattering and UV absorption of the inorganic; furthermore, the new formed vehicles could provide the inorganic crystals with a support structure for a better fixation when applied to skin (9).

Cerium Dioxide

Cerium dioxide (ceria or CeO₂) is one of today's most promising nanobiomaterials (12). Where there has been some doubt as to the safety of titanium dioxide ceria has stepped in to fill the void. A number of reports exist indicating the possibility of brain cells, blood lymphocytes, and lymphoblastic cell damage by titania nanoparticles (12). Moreover, nanoparticles of zinc and titanium oxides possess enormous photocatalytic activity (12). By contrast ceria is thought to be much more stable. Ceria becomes strongly non-stoichiometric in nanocrystalline state and due to this reason is able to participate in various redox processes, in particular to inactivate some of the most toxic ROS (reactive oxygen species), such as superoxide radical, hydrogen peroxide, and nitroxyl radical (12). In addition vacancy engineered ceria nanostructures can protect from radiation-induced cellular damage, radiation-induced pneumonitis and can prevent retinal degeneration by photons of light (12). When looking at the MSDS for CeO₂ there is a concern of skin irritation but this is in quantities much larger than those used in sunscreens. All of these reasons make ceria a popular choice for expansion into the sunscreen arena.

For these experiments a colloid solution of ultra small ceria nanoparticles were stabilized with sodium citrate. Particle size was determined through the use of powder X-ray diffraction (XRD) analysis and calculated using the Scherrer formula (14). Line profiles for (111) and (200) reflections were fitted to pseudo-Voigt functions (12). To determine the values of unit cell parameter the Rietveld refinement was performed and peak profiles were fitted to pseudo-Voigt functions in the range of 15 - 90 degrees (12). Ceria samples were out gased at 40 degrees C in a vacuum for 5 hours to determine the surface area via low-temperature nitrogen absorption. The photodegradation of methyl orange was used to measure the photocatalytic activity of ceria and titania. This was done using colloid solutions that were irradiated by a xenon lamp for 60 min while monitoring the dye concentration; recording spectra every 30 seconds. Toxicity of nanocrystalline ceria sols under UV-irradiation and in the dark was studied using reference cell lines including mouse fibroblasts (L929) and fibroblast-like cells of African Green monkey (VERO) (12). Different concentrations of ceria sols were added either 30 minutes before, 5

minutes before, or 30 minutes after, UV -irradiation. An optical absorption superavital dye was added, and the difference between the samples calculated. An additional method for cell viability and integrity visualization consisted in staining cell monolayers by mixture of luminescent dyes Hoechst 33342 (HOE) and propidium iodide (PI) (12).

UV shielding properties of ceria nanoparticles were studied in comparison with the corresponding properties of TiO₂ and ZnO containing systems by measuring the light absorption in the middle (UVB) and near (UVA) ultraviolet regions (12). The SPF was used to estimate the efficiency of skin protection in the UVB range. The efficiency of protection in the UVA region is usually evaluated using so called critical absorption wavelength (λ_c) (12). According to the data obtained SPF value for ceria sol is nearly equivalent to corresponding values for TiO₂ and ZnO preparations of the same concentration (12). In the UVA range 1% ceria sol was found to have a λ_c of 355 nm or in the 'good' range for the FDA. TiO₂ has a similar value of 364 nm while ZnO is in the 'excellent' range with 379 nm. As an alternative, FDA recommends to estimate the efficiency of shielding in near UV region by the UVA/UVB ratio (12). For ceria sol the ratio was 0.28; again similarly TiO₂ was 0.36 but ZnO was much higher at 0.86. While ceria is in line with titanium oxide the increase for zinc oxide can probably be attributed to particle size. It is well known that the UV shielding properties of oxide particles strongly depend on their size (12). Additionally the increase in ceria particle size leads to noticeable increase in the UVA/UVB ratio, up to 0.41, and critical wavelength, up to 362 nm (12).

Further investigations showed that the ceria photocatalytic activity is also determined by the ceria particle size (12). According to the data, 1-2 nm ceria nanoparticles did not exhibit any photocatalytic activity (12). Moreover, addition of citrate-stabilized ceria sols to the solution of methyl orange lead to a considerable decrease in the rate of methyl orange photodegradation due to partial blocking of UV-irradiation by nanoceria (12). It can be clearly seen that 4.5nm ceria particles also prevent methyl orange photodegradation but the degree of shielding is substantially lower (12). Depending on the concentration of ceria it should be pointed out that the photocatalytic activity of even the coarsest ceria samples was lower than that of titania (12). The normal trend is for photocatalytic activity to increase with an increase in surface area but for ceria the opposite trend is shown. This is most likely due to the considerable amount of oxygen in the ceria nanocrystalline structure. While looking at the biological activity of ceria the results were found to be promising. Depending on the amount of concentration of ceria and the time

between ceria addition and UV-irradiation (before or after) there is a significant effect. Preliminary (30 min before UV-irradiation) treatment of L929 cells by 0.32 - 0.5 mM ceria sols provides their complete protection (12). Treatment of L929 cells by ceria sols 30 min after irradiation was accompanied by dose-dependent decrease in protection; thus providing efficient protection of L929 cells (12). Similarly 0.32 - 0.5 mM ceria sols provided efficient UV-protection of VERO cells both before and after UV-irradiation (12).

The focus now moves to the UV shielding properties of a ceria when modified, specifically zinc-oxide doped ceria. It can be shown that Ce^{4+} is not large enough to stabilize a fluorite structure. To take on more stable eight coordinations of fluorite structure, some of Ce^{4+} would have a tendency to be reduced to Ce^{3+} which has a larger ionic radius than Ce^{4+} (10). Therefore, it is expected that the evolution of oxygen (when oxygen molecules are released to form oxygen vacancies by the accompanying reaction) may be depressed by doping with metal ion possessing both larger ionic size and lower valence than Ce^{4+} to stabilize fluorite structure and shift the equilibrium (10). It has been reported that the oxidation catalytic activity of ceria was greatly decreased by doping with calcium ion possessing larger ionic size and lower valence (10). Ceria's large solubility in water leads to difficulties in its use leading to the investigation of zinc oxide as a candidate. Zinc oxide offers the large size and lower valence while not having the solubility problems of ceria.

Undoped and zinc oxide doped cerias were synthesized via soft solution chemical routes at 40 degrees C (10). The ceria solutions (1 M) were mixed with deionized water and a 2M hydrogen peroxide solution that was brought to a pH of 6. The solutions were dried at 85 degrees C overnight and the crystalline phase collected. After the crystalline phase was identified by XRD, the thermal analysis was done, the size distribution was found via TEM, the specific surface area was found using nitrogen sorption analysis, and the catalytic activity was determined by the conductometric determination method (Rancimat method). The UV shielding property was evaluated by measuring the transmittance of a thin film, of 0.0125 mm thickness, containing the sample powder with an UV visible spectrophotometer (10). The inductively coupled plasma atomic emission spectrometer (ICP-AES) was employed to determine the contents of Zn and Ce elements in the end supernatant solution and powder sample, where the powder sample was dissolved in a hot HNO_3 -HCl mixed solution (10).

Zinc oxide and calcia doped ceria powders were prepared with a $Zn/(Zn + Ce)$ and $Ca/(Ca + Ce)$ molar ratios of 0.2 at various final pHs (10). It was found that calcium ion will precipitate out at pHs above 12, zinc ion will precipitate out at pHs above 7, and cerium ion precipitates out at pHs above 6. According to the results found in this experiment the maximum value of zinc ion content, solubility limit, was found to be 0.561. For calcia the solubility limit was around 0.3 showing that the zinc ions have better solubility in ceria than the calcium ions. The lattice parameter is extremely sensitive to the chemical composition; therefore, it is widely used to determine the solubility limit of solid solutions (10). When the crystalline lattice was investigated it was found that the calcia doped ceria lattice constant increased linearly with the increasing calcia content up to the solubility limit. For zinc oxide doped ceria there was an initial decrease, at 0.078, which then increased with the increasing zinc content up to 0.454 and then dropped suddenly again to the solubility limit, 0.561. This is most likely the result of the crystal lattice compensating for the charge imbalance. The net variation in the lattice parameter of CeO_2 by doping with a smaller metal ion can be a combination of the lattice contraction due to the substitution of a smaller ion for Ce^{4+} and the lattice expansion due to the formation of an interstitial cation (10).

Usually specific surface area is a very important factor to the catalytic activity (10). However, no clear relationship between the oxidation catalytic activity and specific surface area was observed (10). These results suggested that the decrease in oxidation catalytic activity might be mainly due to the formation of oxygen defect and stabilization of a fluorite structure by doping with zinc oxide (10). The photocatalytic activity of undoped and zinc oxide doped cerias where shown to be much less than that of titania; titania completely oxidized phenol in 3 hours where after 6 hours 90% phenol remained in the ceria solutions. Both the undoped and zinc oxide doped cerias showed high UV shielding property below 400nm showing no loss in shielding property when the ceria is doped with zinc oxide. In short doping ceria with zinc oxide gives a decrease in the catalytic activity, similar photocatalytic activity (less than titania), and similar UV shielding (excellent UV absorption and transparency in the visible region).

Chapter 3 - Conclusion

From the research reported to this point, inorganic filters have shown promising results. Although there is still some trepidation about the safety of metallic oxides from the initial research it appears as though this is not a concern. As more research is done a greater understanding of the health effects involved will be determined. While titanium dioxide, and to a lesser extent zinc oxide, are the most popular choices for inorganic filters, ceria is quickly becoming a viable alternative. While inorganic filters stand well on their own a combination of filters (both organic and inorganic) appears to give the best results. Additionally, modifications to the filters, such as doping, are the way of the future. Modifications to the surface or crystalline structure allows for equivalent or better protection while minimizing the risks of photoactivity. Future modifications could allow for higher SPFs, longer wear time, less chance of rubbing or washing off, or more user friendly application techniques. The purpose of sunscreen is to protect the skin from UV radiation but if people are not inclined to use the product the protection can't be provided. By determining/formulating modifications that will make the use of sunscreen easier for the consumer it will afford better protection in the long run.

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Appendix A - Sunscreen Handout

Below is a pamphlet with some facts on sunscreen. It is intended to be factual but not as in-depth as the studies reviewed. There is a lot of information out there about sunscreen between websites, academic studies, and news articles. The amount of information can be overwhelming and conflicting at times. This pamphlet goes into enough of the facts to let you know the opinions are based on research. Additionally several sunscreen topics are discussed to help from needing to find several different sources to get answers to multiple questions. This appendix is self-contained with respect to figure numbers and references.

Skin Protection with Sunscreen

This pamphlet has been created to gather facts and information about sunscreen in one location. It goes slightly more in-depth than most websites or magazine articles while still keeping a broad overview of the topic. This pamphlet will discuss the makeup of skin and how absorption occurs through skin. It will then go on to discuss sunscreen; how it works, what it's made of and its absorption properties. The last topic the pamphlet will touch on is other methods of protection from UV radiation.

Skin and its Layers

The skin is comprised of three main layers. The first, or outer, layer is the epidermis followed by the dermis and lastly the subcutaneous layer. The epidermis forms the protective barrier for the body and is made up of five sub layers; the stratum corneum, stratum lucidum, stratum granulosum, stratum spinosum, and stratum basale. The dermis is responsible for providing the skin its strength and elasticity.¹ It is broken into two regions the papillary and the reticular regions. The subcutaneous layer, also referred to as the hypodermis, is made up of fat and connective tissue.

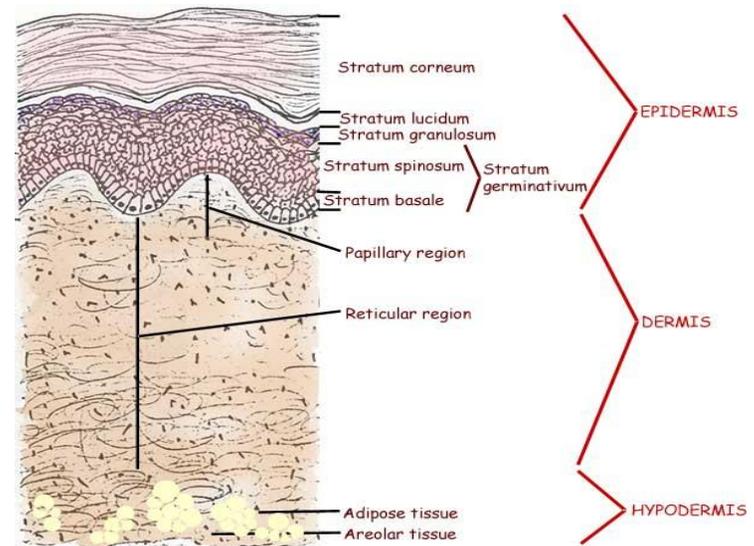


Figure 1. Layers of the Skin²

Absorption through Skin

The epidermis, specifically the stratum corneum, is skin's main barrier against absorption. The layers that follow are much more permeable than the stratum corneum. The thickness of the stratum corneum varies throughout the body from the thickest at the soles of the hands and feet to thinnest at the eyelids. The thinner areas of the epidermis are more susceptible to absorption. Additionally skin that has damages, abrasions, scratches or cuts, are also less protected from absorption. There are three methods of absorption through the skin; intercellular lipid pathway, transcellular

permeation, and through the appendages.³ With the intercellular lipid pathway, chemicals move through the areas between the cells of the stratum corneum that are filled with fats or oils known as lipids as seen in figure 2.

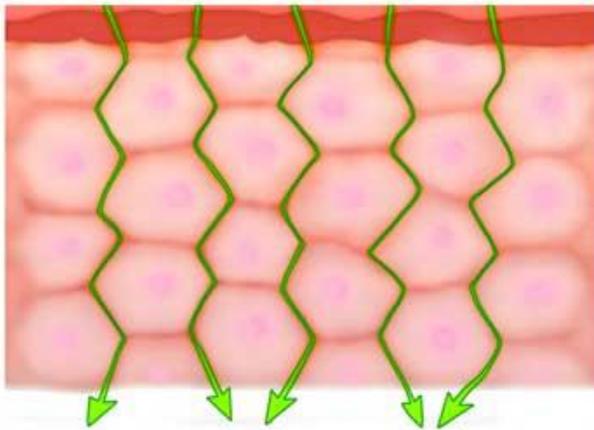


Figure 2. Intercellular lipid pathway method of absorption³

Transcellular permeation occurs when a substance diffuses from cell to cell through the epidermis, figure 3.

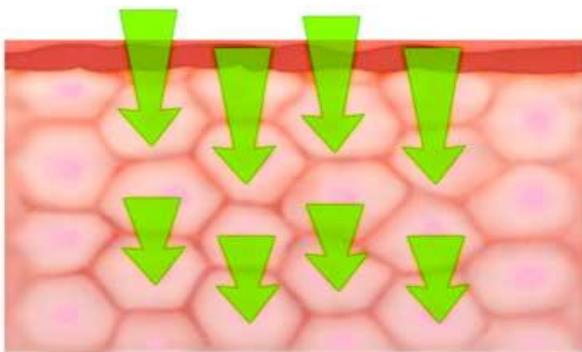


Figure 3. Transcellular permeation method of absorption³

The third method of absorption is through the appendages, hair follicles and sweat glands. This is the least significant method of absorption because these areas make up only a small portion of skin surface area as seen in figure 4.

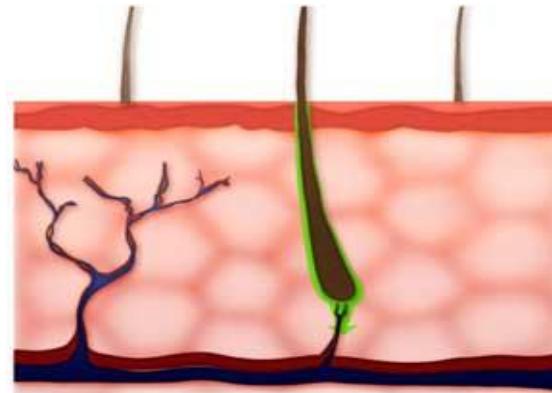


Figure 4. absorption through the appendages³

Sunscreen

Sunscreen was created to protect skin from ultraviolet radiation (UVR). Ultraviolet radiation comes in three wavelengths UVA (the longest wavelengths, between 320 and 400 nm), UVB (between 290 and 320 nm), and UVC (the shortest wavelengths, less than 290nm). Ultraviolet A (UVA) is the longer wave UV ray that causes lasting skin damage, skin aging, and can cause skin cancer⁴. Ultraviolet B (UVB) is the shorter wave UV ray that causes sunburns, skin damage, and can cause skin cancer⁴. UVC is made up

of the shortest wavelengths and normally doesn't make it through the atmosphere except for high elevations. Broad spectrum sunscreen protects against both UVA and UVB wavelengths. For this reason it's recommended to use broad spectrum sunscreen whenever possible.

Sunscreens use a sun protection factor or SPF rating as a measure of protectiveness/effectiveness; the higher the SPF the more protection the formula affords. Here's how it works: If it takes 20 minutes for your unprotected skin to start turning red, using an SPF 15 sunscreen theoretically prevents reddening 15 times longer - about five hours⁴. It is recommended to use an SPF of 30 or greater⁵. In order for sunscreen to have the SPF advertised it needs to be applied in an even layer of 2 mg/cm². This means the average adult in a swimsuit needs about one ounce, or enough to fill a shot glass, to cover their entire body.

Inorganic and Organic

There are two types of sunscreen, inorganic and organic. Organic filters or sunscreens are more commonly referred to as 'chemical filters' and inorganic filters are 'physical filters'. Sunscreens typically contain 'chemical filters', that is organic compounds that absorb strongly in the UV (most often UVB) and 'physical filters', such as TiO₂ and ZnO, that block UVB and UVA sunlight through reflection and scattering⁶.

Organic filters are used to block wavelengths in both the UVA and UVB ranges whereas inorganic filters are more effective blocking UVB. Organic filters are active ingredients that absorb UV radiation energy to various extents within a specific range of wavelengths depending on their chemical structure⁷. Absorbed energy is conveniently converted into unnoticeable infrared (heat) energy⁷. Unlike organic filters, inorganic filters work by reflecting and diffusing UV radiation, which reach skin level instead of involving an absorption process⁷. Increasingly sunscreens are being developed that use both organic and inorganic filters. This allows for compounding of their benefits while minimizing their unfavorable effects.

Sunscreen and Absorption

As discussed above the skin is made to be a barrier from the outside. One would assume then that sunscreen is not absorbed into the skin but simply sits on top of it, but this is not the case. For a long time scientists have been aware of the potential toxicity caused by the absorption of chemical filters topically applied to the skin into the viable cutaneous strata and transdermally.⁸ Inorganic filters show little to no absorption even when nanoparticles are used. Most studies do not support the idea that Titanium dioxide and Zinc oxide nanoparticles penetrate into viable skin.⁹ Titanium dioxide nanoparticles were found in furrows and opened infundibula, but not

in any viable skin layers.⁹ When Zinc oxide nanoparticles were studied using multiple techniques the particles were found to stay in the stratum corneum accumulating in skin folds or hair follicle roots but no penetration was seen past the stratum corneum. Inorganic filters are generally considered safe and recommended for small children in lieu of sunscreens with organic filters.

Organic filters on the other hand have shown some absorption. Specifically benzophenone-3 also known as oxybenzone (BP-3), 4-methylbenzylidene camphor (MBC), octyl methoxycinnamate (OMC), and octyl salicylate have been found to absorb through the skin and may be tied to detrimental effects. There is concern that absorbed organic filters can lead to estrogenic effects, causing cancer cells to grow more rapidly and triggering developmental abnormalities.⁸ The amounts of BP-3, OMC and octyl salicylate recovered from tape-stripped stratum corneum demonstrate that these UV filters penetrate into the epidermis.⁸ More research needs to be done but most of these studies caution against using organic UV filters on small children. Additionally work is being done to develop skin non penetrating sunscreens (NPSUNs). NPSUNs are new derivatives suitable for use in cosmetic and pharmaceutical products.⁸ The basic idea behind the design is to immobilize UV absorbing moieties in a chemical backbone that allows them to still function as UV filters but not be absorbed into the skin.

It has also been found that sunscreen can lead to better absorption of other solutions. UV-induced damage affects the barrier properties of the skin and has been shown to increase the dermal penetration of small hydrophilic chemicals such as caffeine, ethanol, nicotinic acid, and the moderately hydrophobic hydrocortisone but has less pronounced effects on the absorption of more hydrophobic molecules such as DEET.¹⁶ Additionally it has been shown that at least six of seven commercially available (and tested) sunscreens significantly enhance the transdermal penetration of the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D).¹⁶ Chemical penetration enhancers can act by altering the lipid domain of the stratum corneum by interacting with the proteins in the barrier, by increasing drug partitioning into the stratum corneum or by any combination of these mechanisms.¹⁶

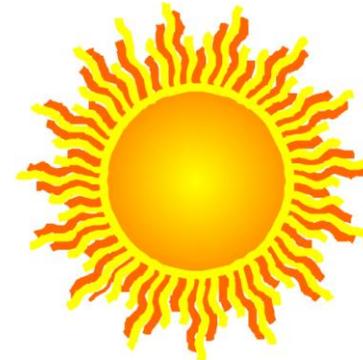
DEET (N,N-diethyl-m-toluamide) is a large concern when it comes to sunscreen and absorption. Commonly when one is outdoors you tend to use not only sunscreen but bug spray as well; most of which contain DEET. There has been one death linked to the use of sunscreen and DEET on an infant. Children are much more susceptible to issues concerning absorption due to their high surface area to body weight ratio and the lack of development of their body systems. As such there have been a multitude of studies done on the effects of DEET and sunscreen in combination.

The insect repellent DEET and sunscreen oxybenzone have been shown to produce synergistic permeation enhancement when applied concurrently in vitro and in vivo.¹⁸ The rate and extent of permeation varies, depending on application dose, formulation type and application method.¹⁸ Both DEET and oxybenzone have been shown to permeate the skin but when used together their penetration is enhanced. Several studies have found similar results with the permeation enhancement varying from 35% to 439% depending on the differences in formulations and application methods. All of the studies suggest further research into the permeation of DEET and sunscreen and the detrimental effects it may have. As with the sunscreen absorption alone the use of the combination on children is not recommended.

Other Sun Protection Ideas

Use of sunscreen on children younger than 6 months is not advised and as noted above due to the risk of absorption organic filters are not advised for young children⁵. This is due to the fact that young children have thinner skin that is not as impervious to absorption as adults. Additionally given that children are still developing any toxins that are absorbed would cause more damage than in an adult. With this in mind here are some guidelines from the American Academy of Dermatology for other ways to protect yourself (or your children) from harmful UV rays:

- **Wear protective clothing**, such as a long-sleeved shirt, pants, a wide-brimmed hat and sunglasses, where possible.
- **Seek shade** when appropriate, remembering that the sun's rays are strongest between 10 a.m. and 4 p.m. If your shadow is shorter than you are, seek shade.
- **Use extra caution near water, snow and sand** as they reflect the damaging rays of the sun, which can increase your chance of sunburn.



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