European Review for Medical and Pharmacological Sciences 2015; 19: 98-112

Photoprotection: facts and controversies

K. SKOTARCZAK[1], A. OSMOLA-MAŃKOWSKA[2], M. LODYGA[2], A. POLAŃSKA[3], M. MAZUR[2], Z. ADAMSKI

[1]Faculty of Pharmacy, Specialisation Cosmetology, Poznan University of Medical Sciences, Poznan, Poland
[2]Department and Clinic of Dermatology, Poznan University of Medical Sciences, Poznan, Poland
[3]Department of Dermatology and Venereology, Faculty of Health Sciences, Poznan University of Medical Sciences, Poznan, Poland

Abstract. – Excessive exposure of the skin to sunlight can lead to many negative effects, such as sunburn, photoaging and skin cancer development. Pollution and stratospheric ozone layer depletion are factors that increase exposure to ultraviolet radiation.

This work is an accurate summary of the current state of knowledge on broad-spectrum photoprotection. Avoiding the sun, skin protection through the use of protective clothing and protective filters are currently the most effective methods of sunscreen provided that they are suitably used. In addition, discussed are controversial issues such as the toxicity of zinc used in sunscreen preparations and the potential for deficiency of vitamin D3 in relation with the application of strict photoprotection.

The study has also addressed issues concerning the most recent lines of research in the exploration of modern methods of photoprotection both local and systemic, such as with the use of photolyase or examination of various enzymes repairing damage after sun exposure, as well as the promising future in photoprotection technology.

Key Words:
Photoprotection, Ultraviolet radiation, Infrared radiation.

Introduction

The earth is constantly exposed to radiation from the sun, which is essential for life. Such emitted radiation includes visible, infrared (IR), and ultraviolet (UV) light. The strongest radiation reaches the earth in the summer months, between the hours of 10 am and 5 pm, when the rays fall perpendicularly. With greater elevation above sea level, the atmosphere becomes thinner and smaller amounts of UV rays are absorbed. Thusly, radiation intensity increases by 4% for every 300 m. Snow reflects approximately 90% of ultraviolet radiation, which is far more than any other granular material, such as sand (approximately 15-30%). The sun's rays can pass through water to a depth of approximately 1 m. Water also strongly reflects UV rays. Another physical factor that affects radiation intensity is pollution. The air contamination compromises the ozone layer and consequences in the formation of the Ozone Hole, resulting in greater incoming radiation to earth and exposed skin.

Ultraviolet radiation (UVR) is one of the most important environmental factors influencing the human body. Discovered in the early nineteenth century by Johann Wilhelm Ritter, ultraviolet electromagnetic radiation is invisible to the human eye, with a wavelength shorter than visible light (390-700 nm) and longer than x-rays (0.01-10 nm). Due to the different biological effects of UVR, there is a division into three main areas:

- UVA – wavelength range of 320 to 400 nm.
- UVB – wavelength range of 280 to 320 nm.
- UVC – wavelength range of 100 and 280 nm[1].

The most dangerous ultraviolet radiation is UVC, as it is nearly entirely absorbed by the ozone layer. UVC has the shortest wavelength and the highest energy of the three UVRs and posses strong mutagenic properties and erythema causation. Characterized by a bacteriostatic and bactericidal action (particularly radiation having a wavelength of 254 nm), UVC was applied in medicine as germicidal lamps.

UVB radiation, comprising approximately 5 to 10% of the entire spectrum of UV radiation reaching the earth's surface, is characterized by a relatively high energy and is a potent erythema

Corresponding Author: Agnieszka Osmola-Mańkowska, MD, Ph.D; e-mail: agnieszka.osmola@wp.pl

inducer. Responsible for the most important biological effects (e.g. sunburn, pigmentation, vitamin D3 synthesis, immunosuppression and carcinogenesis), UVB is absorbed in the stratum corneum of the skin by chromophores. Effected elements in the skin are melanin, cellular DNA, urocanic acid, proteins, lipids and amino acids[2]. UVB directly damages the DNA strand, resulting in the formation of pyrimidine dimers and distortion of repair mechanisms, which lead to mutations[3]. The reactions induced by UVB radiation are immediate, resulting in the release of inflammatory mediators (e.g. histamine, serotonin, and prostaglandins), which lead to dilation of capillaries and the development of erythema and edema[4]. This range of rays easily penetrates through water and quartz glass. However, these rays are filtered through clouds and windowpanes. Greatest ray intensity is reached during the summer, between the hours of 10 am and 5 pm.

UVA radiation is divided into two ranges: UVA2 (wavelength range of 340-380 nm) and UVA1 (wavelength range of 315-400 nm). UVA1 is in the category of UV radiation with the lowest energy. However, it represents up to 95% of total UVR emitted and is minimally attenuated by the ozone layer. Rays reach the earth year-round and despite weak energy, UVA1 penetrates through clouds and windowpanes. Intensity is independent of time of day or year. Despite lesser induction of erythema, UVA1 stimulates production of pigment to a much greater extent than other UVRs. It penetrates into the deeper layers of the dermis, impairing the normal functioning of cells, affecting blood vessels and collagen fibers. UVA rays have indirect effects on cellular DNA through generation of reactive oxygen species. These are so-called “delayed reactions”, which are related to the destructive action of free radicals on the structure of proteins and nucleic acids. Such changes in structure of collagen and elastin lead to premature aging of the skin. UVA irradiation plays a significant role in phototoxic and photoallergic reactions, leading to immunosuppression and photocarcinogenesis. UVA2 is a transitional range of UV radiation, which can be used to detect the biological effects of both UVA and UVB radiation[1].

Biological Effects of UV Radiation on Human Skin

Positive Effects of UV Radiation

In moderate amounts, ultraviolet rays promote wellbeing by reducing stress, increasing mental activity and activating the synthesis of vitamin D3, whilst, also demonstrating beneficial effects on the course of various dermatological disorders, such as atopic dermatitis or psoriasis[2]. Thus, providing the basis for the use of phototherapy as a method of therapy.

Negative Effects of UV Radiation

Acute Adverse Reactions of UV Radiation

Negative effects of UV radiation on the body may be acute (immediate) in character and manifest in the form of erythema. The sun can also provoke immediate reactions in people suffering from photodermatoses. Photodermatoses are a group of diseases, which aggravate hypersensitivity reactions to ultraviolet radiation. Increased frequencies of dermatoses induced by UV occur in the spring when intensity of natural sunlight increases. Polymorphic light eruption is the most common idiopathic acquired photodermatosis[4].

Phototoxic and photoallergic reactions are dependent on external factors. Reactions of phototoxicity predominately occur under the influence of substances that increase the impact of UV rays on the skin, mainly UVA rays[5]. Such factors are usually substances of vegetable origin, drugs, or chemicals administered either externally or orally, i.e. psolarens, sulfonamides, tetracyclines, furanocoumarins or colorants[6]. In contrast to phototoxic reactions, photoallergies are initiated by specific immunological reactions caused by the combination of ultraviolet rays and exogenous photosensitizing substances[7]. Reactions are not dose-dependent on either the photosensitizing substance or radiation. Manifestation occurs, on an average, 24-48 hours following exposure to UVA. Presentation may occur in the form of eczema, itching or burning and can develop into a permanent hypersensitivity to sunlight [8]. Photoallergic substances may be derivatives of salicylates, non-steroidal anti-inflammatory drugs (NSAIDs), fragrances, and even constituents of sunscreens.

Extracts can also be dermatoses, in which sunlight is a factor in exacerbation or triggering, (e.g. Lupus erythematosus)[9].

Chronic Adverse Reactions of UV Radiation

Photoaging

Prolonged exposure to ultraviolet rays causes the formation of visible skin changes, through

the deterioration of the skin's structure and function. All these changes are defined as premature skin aging or photoaging[10]. Clinical presentation of photoaging of the skin includes lines and wrinkles, dryness and hyperkeratosis, hyperpigmentation, telangiectasia, and loss of elasticity of the epidermis[11]. Formation of these changes is contributed by both UVA, as well as the shorter in wavelength UVB rays. UVB radiation is responsible for damage to the lipid barrier and structural changes within Langerhans cells. UVA, although largely responsible for damage to connective tissue, enhances the effect of UVB on the epidermis. Weakening of the connective tissue and the changes in skin microcirculation can cause permanent dilation of blood vessels, which emerge in the form of telangiectasia. As in the case of physiological aging, where a decrease in collagen content in the skin is observed, UV radiation stimulates metalloproteinases to promote breakdown of collagen.

The most characteristic for the process of photoaging is the elastase phenomenon, namely the accumulation of abnormal elastin masses. At first, elastic fibers undergo hyperplasia and thickening. Subsequently, these fibers develop into a twisted and highly branching compact mass. Repeatedly exposing the skin to sunlight results in consistent darkening. A feature of photoaging is the uneven stimulation of melanocytes, which most commonly results in the manifestation of freckles and lentigines.

Photoaging is not solely influenced by UV radiation (e.g. UVA) but also infrared (IR), largely of the infrared A (IRA) spectral range. IRA has the ability to penetrate deeply into the subcutaneous tissue causing mutations in mitochondrial DNA (mtDNA) called common deletions and also has the ability to stimulate the formation of free radicals reactive oxygen species. Topical application of mixtures of antioxidants such as grape seed extract, ubiquinone, vitamin C and E, have an inhibitory effect on oxidative stress resulting from the impacts of infrared radiation[12].

Photoimmunosuppresion

The skin is an organ, equipped with its own immune system, which protects against pathogens and identifies and eliminates damaged cells. Langerhans cells, or primary dendritic epidermal cells, are macrophages of myeloid lineage that present antigens to T cells and begin immune reactions in the skin. Along with keratinocytes, T cells, vascular endothelial cells, macrophages, granulocytes, mast cells and melanocytes, Langerhans cells are part of lymphoid tissue associated with the skin (skin associated lymphoid tissue – SALT), where its primary function is to provide immune surveillance. Exposure to UV radiation can significantly reduce the amount of Langerhans cells, which can lead to impairment of immune surveillance mechanisms, and consequently contribute to the development of skin cancer[13]. As a result of UVR penetration, photon energy is absorbed by chromophores in the skin. DNA that is damaged by UVB radiation forms pyrimidine dimers and 4,6-photoproducts[11]. If the resulting photoproducts are numerous and cannot be repaired, the damaged DNA enters into the next replication cycle. Accumulation in the epidermis undergoes photoisomerization by changing the molecule's structure from trans to cis form. This photoelectrochemical process is responsible for the immunosuppression. Ultraviolet radiation, especially UVA, indirectly influences membrane lipids, such as cholesterol and phospholipids. As a result of these reactions, free radicals are produced and consequently, reaching the inhibition of lipid peroxidation and membrane enzymes and transport proteins.

Photocarcinogenesis

The most serious consequences of UV radiation are associated with the increased risk of neoplasia. Carcinogenesis by UV radiation is a long-term process. The first stage is initiation or the carcinogenic action (UV) on the cell DNA, causing mutations therein. After adoption of UV photons, DNA is excited, resulting in the formation of various types of photoproducts. The passage of at least one replication cycle results in the fixation of mutation. Promotion is the subsequent stage, during which the initiated cells acquire phenotypic characteristics of neoplastic cells. The following stage is that of progression, where tumor cell counts increase. There are DNA repair mechanisms, which are responsible for the removal of harmful photoproducts[14]. One of them is incorrect nucleotide excision, which is responsible for the NER system – nucleotide excision repair. Malfunctioning of this system leads to duplication of DNA mutation and the development of tumors. Mutations induced by UVB radiation consist of transitions of thymine instead of cytosine (CT or CC-TT) and are referred to as markers of UVB damage, which are found in all types of skin neoplasms.

The form of exposure to ultraviolet radiation plays a significant role. Actinic keratosis (AK) and squamous cell carcinoma (SCC) are consequences of chronic exposure to cumulative doses of ultraviolet radiation, while malignant melanoma and basal cell carcinoma are associated with excessive exposure or periodic high doses of radiation in childhood[15].

Natural Skin Protection Against UV Radiation

Human skin is constantly exposed to sunlight and consequently, has developed a number of various protective mechanisms against the immunosuppressive and mutagenic effects of ultraviolet light. Endogenous mechanisms include thickening of the epidermal layer, mechanisms of DNA repair, apoptosis, antioxidant enzymes and pigmentation.

Darkening of color of the skin, or tan, indicates increased melanin production in response to environmental factors such as ultraviolet light. There are three types of pigment reactions: immediate-type, permanent-type and delayed-type. Darkening immediately (IPD – immediate pigment darkening) caused by UVA, occurs after a few minutes of exposure to the sun. The skin becomes a grayish hue, which turns brown within minutes or even days, depending on the dose of UV radiation and the natural color of the skin. Immediate pigment darkening is the result of preexisting melanin photooxidation and redeployment of the nuclear part of melanosomes to dendritic[16]. A consequence of IPD is permanent darkening of pigmentation (PPD – permanent pigment darkening), which is also considered the effect of oxidation of melanin. Manifestation occurs after a few hours of exposure to UV rays and maintains approximately 3-5 days[17]. More strongly induced by UVA than UVB rays, this observation is the basis for examination of efficacy of different filters that protect against UVA radiation[18]. Delayed darkening reactions (DT- delayed tanning) are consequences of the action of UVB rays. Browning of the skin is visible approximately 2-3 days after exposure to sunlight. This is due to stimulation of melanocytes, an increase in melanin synthesis and increase in melanosome count. Darkening effects are maintained from 10 days up to 3 weeks depending on the amount of doses of UV radiation and the natural color of the skin.

Photoprotection

Modern photoprotection is based upon on three basic pillars of sunscreen. These include appropriate behavior during expose to sunlight, use of clothing and sunscreen preparations. The most effective method of sun protection is avoiding exposure to sunlight by seeking shade and reducing the time of exposure, especially during the hours of 10 am and 2 pm.

An important element of photoprotection is the correct choice of clothing, which provides adequate protection against both UVA and UVB radiation. In contrast to creams, clothing does not cause allergies and irritation. However, not all fabrics provide the same protection from the sun. To accurately determine efficacy levels of different sun protective fabrics, ultraviolet protection factor (UPF) is utilized. Similar to sun protective factor (SPF), which only measures the level of UVB radiation blocked, UPF measures levels of blocked radiation of both UVA and UVB. The higher the UPF, the more superior the protection against UV rays[19].

Taking into account types of fabric composition and their levels of protection, synthetic materials should be chosen over natural fibers, as they reflect and block radiation more effectively. Densely woven fabrics block more UV rays than those with looser weaves. Thick fabrics, such as denim, are more effective at blocking UV rays than cotton. Dark hues absorb more radiation than lighter tints, which reflect sunrays. The darker the pigment, there is a greater absorption of radiation. While, the lighter the pigment, there is greater reflection of radiation. Moisture content also plays a significant role in photoprotection. Dry textiles provide better protection over moist counterparts. After washing, some types of fabric undergo structural changes. The weaves morph and fuses together, allowing the shortening of gaps between fibers and, thereby, reducing the area of penetration and increasing protection. UV absorbers may be added to laundry detergents. Studies have shown an increase in UPF by 400% after impregnating fabrics with such preparations. Stain-resistant fabrics have similar effects[20].

An important element of dress is headgear. Recommended are wide-brimmed hats, not only for the protection of the head, but also the skin of the forehead, eyes, cheeks and nose. In addition to a hat that protects the face, sunglasses are recommended to protect the skin around the eyes, eyelids and eyes, as to protect from the onset of

ocular complications. Exposure to UV light can lead to changes in organs of vision; cornea, conjunctiva, lens and retina. Photoprotective properties of glasses depend on the following factors:

- Shape and fit – glasses should lie close to the face without touching the eyes.
- Colors of lens – darker lenses unnecessarily filter more visible rays, causing mydriasis and allowing increased penetration of unfiltered light from the UV spectrum and blue light (400-440 nm) to access the retina.
- UV filtering properties[21].

Frequent exposure of the retina to blue light radiation is a potential risk factor for macular degeneration[22]. In addition to appropriate lenses and high-degree of UV protection, glasses should have a suitable shape to prevent UV light from passing through the sides. Orange and yellow lenses provide the best protection against both UV and visible blue light. Sunglasses should also be worn in the morning and evening, when the sun shines more parallel to our eyes.

Sun Protection Factor (SPF)

The measure of effectiveness of a sunscreen is SPF (sun protection factor), which is the ratio of the amount of UV radiation causing erythematous reactions (MED – minimal erythema dose) using a filter to the amount of radiation resulting in the same burn without filter protection[23]. Determining the minimum erythematous dose of sun protection factor can be expressed by the formula:

$$SPF = \frac{\text{MED protected skin}}{\text{MED unprotected skin}}$$

Frequently, SPF is misinterpreted[24]. For instance, a preparation's label advertising "SPF 4", does not signify that the time of skin exposure to sunlight can increase 4-fold, but that the UV dose required for inducing erythema after preparation use must be four times stronger than that of unprotected skin. A preparation with a degree of protection of SPF 2 that is applied at a rate of 2 mg/cm^2 absorbs 50% of UVB rays. SPF 15 provides 93% protection against UVB rays. SPF 30 is effective in 97% for UVB, while SPF 50 provides 98% protection[25]. No preparation containing UV filters can provide 100% protection against UV radiation. Many people believe that the percentage difference between a sun protection of SPF 30 and SPF 50 is negligible and that higher filters do not provide greater protection. However, it is not a preparation's filtered radiation dose that determines the degree of protection, but rather the dose of radiation that penetrates deep into skin and is responsible for sunburn. As exemplified by comparing SPF 15 and SPF 30 preparations, doses that are able to penetrate the skin are reduced by one-half. The same goes for preparations with SPF 30 and SPF 50. This signifies the fact that SPF 30 provides protection two times greater than SPF 15, as does SPF 50 compared to SPF 30[26].

Substances Used As Physical Filters

Physical filters are substances of mineral origin, which operate on the principle of knocking and scattering radiation from the entire wavelength range. Molecules of these filters are large enough to not penetrate the skin, but form a barrier to UV radiation on its surface. Physical filters include color pigments and micronized pigments. This group of compounds includes titanium dioxide (TiO2) and zinc oxide (ZnO). Both compounds are snowy white in color and are insoluble in water. Currently, the only acceptable material is titanium dioxide[6]. Less commonly used compounds are iron oxides, talc, kaolin and mica. Titanium dioxide is the purest and most durable pigment. Macromolecules of sizes greater than 200nm guarantee complete protection from radiation from the entire UV spectrum. Despite these properties and given size of molecules, chromatic pigments are matt and inconvenient to use as they leave a white coating on the skin. Moreover, to provide sufficient protection, a thick occlusive application layer is required, which can be comedogenic. Micronized titanium dioxide particles have a size of 20-80 nm. They are able to diffuse radiation with a wavelength 400 nm and greater, but do not leave a visible white coating on the skin. However, less protection against UV is provided, as the particles can accumulate and create a single break in the first coating layer. Maximum concentrations in cosmetic formulations may be 25%. Micronized particles can, however, enter into photochemical reactions produced by reactive oxygen species (ROS) and contribute to efficacy reduction of sun protection. To avoid such reactions, particles are

coated with silicone. Newer methods have allowed for the development of higher quality natural filters. One method is to combine inorganic carnauba wax, which acts synergistically with titanium dioxide, providing a solid dispersion of microparticles. Combination provides for an ideal viscosity and increase in protective effect[27].

Physical filters do not cause allergies or react with skin; thus, are recommended for children and adults with allergies.

Substances Used As Chemical Filters

Chemical filters are molecules of aromatic structure, having a carboxyl group that undergoes isomerization under the influence of absorbed energy from radiation. Rays short, less than 380 nm, are absorbed and converted into thermal energy, while the remaining portion of radiation with a wavelength longer than 380 nm, i.e. visible and IR, is reflected[28].

Synthetic substances are most active. They are regulated and authorized for use by ministries and departments of health around the world. Such authorization lists include permitted concentrations at which substances can be used as ingredients in UV protectant preparations[29].

Efficacy of chemical substances as filters is mainly due to physicochemical properties, e.g. absorption coefficient and absorption spectra, and properties of remaining particles on the skin surface, which depend on chemical structure.

Substances that Protect Against UVB Radiation

Compounds that provide protection against UVB radiation can be structurally divided into several groups. These are: derivatives of para-aminobenzoic acid, salicylic acid derivatives, p-methoxycinnamic acid derivatives, camphor and mixtures.

Para-aminobenzoic Acid (PABA) and Derivatives

The main substance of this group, para-aminobenzoic acid (PABA), has been introduced as one of the first chemical filters in the 1920s. Use is limited, due to its staining properties and photoallergic contact dermatitis (PCD). Additional limitations include poor solubility in water, which can lead to precipitation of PABA from preparations and crystallization on skin surfaces. Maximum authorized concentration is 5% in cosmetic products.

The most commonly used derivative is an ester called octyldimethyl-p-aminobenzoate, which is characterized by increased rates of absorption and stability at elevated temperatures and in presence of light. Furthermore, activation on skin is quite good. Tendencies to degrade into acid, levels of absorption depend on the environmental pH.

Maximum authorized concentration is 5% in cosmetic products. Common synonym names used in creams are Escalol 507, Eusolex 6007 and Padimate O.

Salicyclic Acid Dervivatives

These compounds are rarely used due to a low absorption coefficient, and the need of high concentrations (at least 8%) to maintain a reasonable level of protection. Benefits include: low irritant properties and inability to penetrate into the epidermis.

Examples of compounds belonging to this group are homomenthyl salicylate and octyl salicylate. Both compounds are insoluble in water, which makes them more stable under conditions of increased perspiration and bathing. Homomenthyl salicylate (Homosalate) goes under the following names: Homosalate or Helipan. At a maximum authorized concentration of 10%, homomenthyl salicylate is rarely used in Europe, but still remains the product of choice for reference for calculations of sun protection in the United States.

Derivatives of P-methoxycinnamic Acid

Compounds belonging to this group are often used in Europe. Two most common are octyl methoxycinnamate (Parsol MCX) and isopentyl p-methoxycinnamate. Both compounds are used in products at a maximum authorized concentration of 10%. Characterized by a high absorption rate, absorbing radiation within a narrow range, including the most intense wavelength of 308 nm. Despite the good tolerability of these compounds in cosmetic products, data from various literature finds that chronic results in an increase rate of hypersensitivity to cinnamates.

Camphor Derivatives

Compounds from the group of camphor derivatives are common in Europe. They are characterized by high photostability and rare reported causes of allergic. Five compounds are clinically approved for use which include the following:

- 4-methylbenzylindene camphor (4-MBC, enzacamene), in Europe known under the name of Eusolex 6300. Maximum authorized concentration is 4%.
- Benzylidene camphor (Mexoryl SD). Maximum authorized concentration is 2%,
- Benzylidene camphor sulfonic acid (Mexoryl SL). Maximum authorized concentration is 6%.
- Polyacrylamidomethyl benzylidene camphor (Mexoryl SW). Maximum authorized concentration is 6%.
- Camphor benzalkonium methosulfate. Maximum authorized concentration is 6%.

Other Chemical UVB Filters

Other approved chemical compounds that are listed for use in cosmetic products are the following:

- Phenylbenzimidazole sulfonic acid
- Octocrylene
- Ethylhexyl triazone (Not approved by the United States FDA).

Phenylbenzimidazole sulfonic acid, known under the name of Eusolex® 232, is often used in salt form. The chemical compound absorbs radiation having wavelengths of 310 nm. Due to its water-soluble properties, actions of fat-soluble filters are enhanced. Maximum authorized concentration is 8%.

Octocrylene was just recently approved for use in Europe. Absorbing UVB radiation with the greatest absorption of larger wavelength lengths, 303 nm. The maximum authorized concentration is 10%.

Ethylhexyl triazone (Uvinul T150) is a water-insoluble compound and frequently used in cosmetic products labeled as "waterproof". Maximum authorized concentration is 5%.

Substances that Protect Against UVA Radiation

Awareness of the negative effects of UV radiation is increasing. Also known, are adverse effects of UV radiation, such as skin photoaging, which is mainly responsible by UVA. Only a small number chemical compounds, absorbing UV rays of the UVA range, are registered on the FDA and European list for authorized active substances in sunscreens. This small group includes:

- Dibenzoylmethane derivatives
- Benzylidene camphor derivatives
- Phenylobenzimidazole sulfonic acid

The most effective at UVA protection are dibenzoylmethane derivatives, such as avobenzone with trade names of Parsol 1789, Eusolex 9020 and Escalol 517. Avoenzone is a derivative of butyl methoxydibenzoylmethane and has been long used in Europe with a maximum authorized concentration of 5%. Despite benefits such as nonirritating to skin, disadvantages are its low stability of isomerization resulting in shorting between the keto and enol forms, thereby changing the absorption maximum[30]. This property can, however, be changed by photostabilizing substances. Combinations of physical filters, TiO_2 and ZnO, are not recommended.

In contrast to the previous compounds, Mexoryl SX, a benzylidene camphor derivative, has a very high stability against UVA rays. The maximum authorized concentration in cosmetic products is 10%. Phenylobenzimidazole sulfonic acid exhibits maximum absorption at a wavelength of 335 nm, and authorized concentrations do not exceed 10%.

Filters of Broad Spectrum (UVA + UVB)

Chemical filters of broad spectrum include benzophenones and phenylobenzotriazole sulfonic acid. Two absorption peaks are observed due to the properties of dual absorption of UVA and UVB radiation.

Benzophenones

There are 12 types of benzophenones, but only three are authorized for marketed use and include the following:

- Benzophenone-3 (Oxybenzone)
- Benzophenone-4 (Sulisobenzone-sulfonic acid)
- Benzophenone-5 (Sulisobenzone sodium-sodium salt)

Benzophenone-3, a fat-soluble substance, provides the photoprotective basis in cosmetic products as oxybenzone. Concentrations may not exceed 10%. Due to the frequent cases of hypersensitivity, product descriptions should list the presence of this compound as an active ingredient.

Benzophenone-4 and benzophenone-5 are both water-soluble substances with less cases of hypersensitivity. Concentrations may not exceed 5% in cosmetic products.

Phenylbenzotriazole Sulfonic Acid

Compounds of phenylbenzotriazole sulfonic acid origin are just recently introduced for cos-

metic purposes. Their action covers a wide spectrum ranging from UVB to visible light, while simultaneously being a very good absorbent of UVA radiation. Registered substances of this group include the following:

- Drometrizole trisiloxane (Mexoryl® XL)
- Bisoctrizole (Tinosorb® M)
- Bemotrizinol (Tinosorb® S)

Drometrizole trisiloxane is a compound that is well persisting on the skin suface, due to the siloxane portion of the molecule. Concentrations may not exceed 15% in cosmpetic products.

Bisoctrizole, or Tinosorb® M, is a pigment that is water-soluble. Its fine particles remain on the skin surface, but physicochemical properties do not allow for penetration of the compound through the skin. In cosmetics, presence may not exceed a concentration more than 10%.

Tinosorb® S is a compound very similar to Tinosorb® M, but is fat-soluble. The maximum authorized concentration in cosmetic products is also 10%.

The Safety of Sunscreens

All substances permitted for use in marketed products are registered under regulated lists. Before approval, these substances must first pass many tests, including toxicology, in order to ensure the greatest possible safety. These compounds cannot penetrate the skin barrier and enter systemic circulation nor penetrate into cells where they could cause mutations in the cellular DNA. Ideal UV protectants are non-toxic and do not cause allergic reactions. Modern cosmetic formulations are based on completely insoluble compounds, which minimize the risk of a compound's penetration. Additionally, these preparations contain more than one UV protectant compound to ensure a wider-range of protection. Most combine several compounds of different chemical groups with different absorption maximums in order to reduce the concentration of each individual substance, hence, obtaining the widest possible range of protection and improving durability and stability by combining filters fat-soluble and water-soluble filters. Increased use of these compounds is the cause for allergic reactions, mainly photoallergic contact dermatitis. A study conducted in 2010 confirmed that the compounds used as chemical filters were the main allergens causing photoallergetic contact dermatitis[31]. Chemical filters with unstable molecules can be inactivated by UV light, thereby, losing protective ability. Accordingly, mixtures of different UV-filters cannot be produced without proper scrutiny, because there is the possibility of negative interactions.

Unfortunately, older substances (e.g. PABA and its derivatives, salicylic acid esters and benzophenones) relied on molecules of low molecular weight, which could penetrate the skin, and further be absorbed into the dermis. PABA and its derivatives are responsible for many causes of allergic reactions. Any chemical compound providing UV protection can cause such allergic reactions, but in addition to PABA, the most common allergenic compounds are avobenzone, octocrylene, and benzophenone-3. Despite strong allergenic properties, benzophenone-3 is widely used in cosmetics. Studies in human volunteers have shown the presence of benzophenone-3 in urine and plasma even four days after the initial topical application of substances on the skin. Finding the substance in the urine suggests its capacity to pass into the circulatory system and its potential effects on other organs or accumulate sites. The tested concentration was 10%, which is the permitted maximum concentration of benzophenone-3 in the European Union. However, concentrations of benzophenone-3 cannot exceed 6% in the United States as approved by the FDA. After four days of initial topical application, octyl methoxycinnamate was also observed in human plasma. The European Union approved concentration, 10%, was used during the study; however, concentrations cannot exceed 7.5% in the United States[32]. Concerningly, studies show PABA being able to induce the formation of free radicals in phosphate buffered saline (PBS) without sunlight. Similar effects are alleged in octocrylene and octyl methoxycinnamate[23].

Another danger cosmetics with chemical filters pose, is the inhibition of erythema, which is an alarming sign of skin irritation. Without the physiologic sign of erythema, individuals are allowing for longer periods of exposure to radiation. Hence, preparations should not contain both sunscreens and anti-inflammatory agents, as erythema formation reduction encourages longer stays in sunlight. This exposes a much longer exposure to radiation. Anti-inflammatory agents are used in mitigation formulations labeled "after sun".

A recent major topic of discussion is sunscreens and potential inhibition of vitamin D3 synthesis, which could lead to vitamin D shortages. Theoretically, the correct application of sunblock could cause a significant reduction in the level of vitamin D3, but this is not clinically proven. In most cases, filters are not properly applied or in the correct amount. Moreover, extending the duration of exposure to sun's synthesis of vitamin D3 occurs despite application of skin preparations. A proper diet also minimizes the risk of deficiency. A recent study by Lindqvist et al[33], conducted in Sweden, suggested that avoiding exposure to the sun increases the risk of mortality. In people deliberately sunbathing, there was no proven increased risk of melanoma or mortality associated with the activity. There are also reports that lower levels of vitamin D may be associated with an increased risk of cardiovascular disease and the presence of a thicker and more invasive melanoma. It is additionally hypothesized that UVA increases the activity of nitric oxide (NO) lowering blood pressure and risks of cardiovascular complications[10].

Many controversies surround the use of nanotechnology, mainly concerning physical filters. Particles of a small size avoid an unpleasant white film remaining on the skin after application of a formulation containing the titanium dioxide macromolecule. Particle size is significant. The smaller the molecular size, the greater the risk of penetration of substances into the skin and further, into the bloodstream. Many studies alert the ability of very small titanium dioxide particles to penetrate into the skin, and then, under the influence of UVA, to induce DNA mutations that can be the starting point for the development of cancer[34]. These mutations are induced by excessively generated reactive oxygen species, resulting in damage to proteins and lipids. There is also suspicion of accumulation of nanoparticles in hair follicles and sweat glands[35]. In order to avoid the above mentioned adverse effects, TiO_2 particles are coated with organic or inorganic compounds. This procedure ensures greater stability and lower toxicity of the substance. A study[23] conducted in 2009 showed the absence of titanium dioxide particles in the deeper layers of the skin, even after application under an occlusion. A year later, the reciprocal influence of physical and chemical filters was also examined. Studies have shown that nanoparticles of TiO_2 coated with PABA did not activate Langerhans cells, which indicates absence of immune response and inflammation[36].

Policy on the Use of Sunscreen Creams

In order to provide comprehensive protection, crutial is adequate knowledge about the application of sunblock sunscreen. The main reasons for the use of UV-creams are: protection against sunburn, photoaging, cancer prevention, and increasing planned exposure time in the sun[31,34]. Despite the frequent use photoprotectants, sunburn is a very common phenomenon. This is due to improper use of cosmetics, which reduces its effectiveness. The amount and frequency of preparation application are determinants of effective protection. International standards recommend that application of 2 mg/cm^2 to achieve the degree of protection provided by the manufacturer. However, studies in human volunteers have shown that only 0.5 mg/cm^2 is needed to considerably reduce the effects of ultraviolet radiation[37]. To achieve the desired protection, the teaspoon rule should be applied. In order to attain a density of 2 mg/cm^2, one teaspoon of preparation should be applied on the face, neck and nape. For each upper limb, one teaspoon is required and two teaspoons for the stomach, back and each lower limb. Mouth and ears should not be omitted. A total of 12 teaspoons (approximately 60 ml) of the solution should be applied on one occasion[38].

Physical filters containing mineral pigments may leave a white film on the skin, hence are applied in lower doses[39]. Often overlooked is the need for additional applications. Sunscreen should be re-applied after each swim, persping, toweling and every 2-3 hours during a stay at the beach. Even the use of creams labeled, "waterproof", requires re-applying. Wind causes cooling of the skin and can give a false sense that the next application of the product is unnecessary[40]. Using creams with a lower filter, so called "city blockers", is recommended throughout the year, even during the winter months, especially when the sun's rays work harder, eg. in the mountains in the presence of ice and snow. Reasons for why people resign completely from the use of photoprotective filters are: not easily burnt skin phototypes, having a tan, high length of application process, high costs, desire for a deeper tan and spending too little time outdoors to consider the need of filter application[41].

An important aspect of proper protection is the right choice for the sunscreen preparation for skin phototype. Individuals with phototype I skin, taking photosensitive or phototoxic medications or phototoxic procedures, e.g. aesthetic

surgery, laser and chemical peels, should choose creams with the highest degree of SPF protection (SPF 50+)[42]. Individuals with phototype II skin should use preparations with at least SPF 30, while those with darker skin phototypes can use SPF 15 preparations. Ideally, all phototypes and ages should use prepartions with SPF 50+ daily regardless of the time of the year[43].

Extreme caution should be used in exposing young children to the sun. In babies under 6 months of age, the use of hats, protective clothing, and staying in the shade is recommended over the use of sunscreen preparations. In older children, in addition to protective clothing, you can sunscreen can be added, preferably with a natural filter, designed for children[44].

Oral and Systemic Photoprotection

Protection against harmful UV rays with oral formulations has several advantages. The main ones include the convenience and ease of use[45]. Their performance is not affected by external conditions, such as swimming, types of garment or sweating. In contrast to agents used externally, oral and systemic agents are not dependent on the degree of absorption through the skin[46]. Substances used orally have antioxidant capacity, neutralizing free radicals formed under the influence of ionizing radiation, ultraviolet radiation, inflammation or metabolism of xenobiotics[47]. The increase of fixed concentrations of free radical species is referred to as oxidative stress. Free radicals first attack the fatty acids of cell membranes of the skin and structural proteins, in particular collagen and enzymatic proteins.

Antioxidants are substances that inhibit the oxidation of other molecules. Due to their properties and mode of action, antioxidants are divided into hydrophilic and hydrophobic. Hydrophilic antioxidants protect the aquatic environment of cells, while hydrophobic protect cell membranes. They can be delivered to the body locally or systemically with a proper diet[48]. Substances, which are used as antioxidants, must meet a number of requirements. The first condition is to have a strong capacity to neutralize reactive oxygen species. The end products of a reaction cannot be free radicals and demonstrate a high degree of stability.

Unfortunately, to date, there are no reported substances that can provide sufficient protection when used alone. However, antioxidants are proven to complement photoprotection[49].

Carotenoids

Carotenoids are organic substances responsible for the yellow, orange and red pigments in plants and animals. A requirement for such observed colors is the presence of at least 7 double bonds in the chain. Compounds with fewer bonds are colorless. The main feature of carotenoids is a high activity against reactive oxygen species[50]. Antiradical activity of carotenoids is achieved by two mechanisms: the first one relies on the transfer of electrons and the other from the formation of radical adducts. The most well known carotenoids are β-carotene and lycopene, which are compounds present in carrots, tomatoes and peppers. β-carotene prevents skin burns, which is associated with its ability to scavenge free radicals caused by UVA[51]. This compound is also provitamin A. Conversely, lycopene is more effective in neutralizing nitric oxide radicals[11]. When dissolved in vegetable oils, carotenoids are the complementary ingredient in synthetic sunblocks[52].

Vitamins

Vitamins C and E are the strongest duo of antioxidants used both orally and topically. The term “vitamin E” includes fat-soluble compounds from the group of tocopherols and tocotrienols. There are eight forms of vitamin E, which is the most active α-tocopherol. Due to its chemical structure, they are excellent inhibitors of free radicals. The main source of vitamin E are vegetable oils. The most important function of tocopherols is to protect lipid substances in the intercellular cement. Demonstrating a high affinity for cell membrane lipids, vitamin E is a great inhibitory agent for oxidation of these substances. It works by breaking the chain of radical reactions in the skin. Has the ability to easily enter into reactions of radicals, but does not itself converted into another reactive radical. Products, vitamin E radicals and tocopherol radicals, resulting from this reaction are harmless for cellular structures. This form may be dispersed as chemically inactive compounds or converted back into active antioxidant molecule of vitamin E. This process, however, requires the presence of vitamin C, therefore, combinations of these two vitamins are frequently used in preparatations. The demand for tocopherols is very high especially under conditions of oxidative stress. Lipophilic structures allow for good penetration by vitamin E through the skin. External application has a great number of

positive actions, such as reduction in erythema and delay of photoaging.

Vitamin C, or ascorbic acid, belongs to the group of water-soluble vitamins. As a powerful antioxidant, it is capable of disposing of free radicals. As a result of these reactions, it is converted to dehydroascorbic acid, which under the influence of enzymes is converted back to vitamin C. The natural source of this vitamin is rosehips, black and red currant, red and green pepper, and citrus fruits[53]. In preparations for the skin, ascorbic acid, due to high instability, is replaced by other formulas, where antioxidant activity is considerably lower.

Plant Extracts

Medicinal plants and their extracts are rich in compounds of different chemical structure and varying degrees of photoprotective and antioxidant activity. Plant extracts have a relatively low absorption coefficient, therefore, cannot form the basis of UV-preparations. Due to the absorption properties of only part of a radiation spectrum, they are the perfect complement of synthetic filters.

A group of compounds naturally-occurring in plants and presenting the strongest antioxidant activity are polyphenols, which are organic compounds from the phenol group containing at least two hydroxyl groups attached to an aromatic ring. Green tea is a rich source of polyphenols. The strongest active substance comprised in it is epigallocatechin gallate (EGCG). It prevents damage caused by UVA radiation, reduces free radicals damaging cellular lipids, and inhibits the expression of enzymes responsible for the degradation of collagen fibers.

A compound classified as a part of the plant polyphenol group is resveratrol, which was isolated for the first time in 1940 from the roots of a white hellebore. It is found in the skin and seeds of grapes, nuts, fruit and red wine. Resveratrol has potent antioxidant activity, neutralizing free radicals and being neuroprotective. It also has anti-inflammatory properties, as was demonstrated by tests in mice, when this compound inhibited the formation of edema, and infiltration of lymphocytes after exposure to UV radiation[54]. Additionally, contributing to the reconstruction of damaged cells in the deeper layers of the skin by stimulating regeneration processes of collagen and elastin. Subsequently, preventing the sagging of skin by strengthening skin structure and accelerating regeneration.

The best-known group of polyphenolic compounds is flavonoids, belonging to secondary plant metabolites. Rich sources are flowers and leaves, where they can be found in the superficial layers of tissues give them intense color, while protecting against UV radiation. Other common sources are fruits, especially grapes and citrus, vegetables, seeds, legumes, and green tea[55]. Almost all flavonoids have biological activity. Antioxidant capacities are possible through different mechanisms of action. Direct mechanisms are based on the capture of free radicals and limiting their arrangement in cells by inhibiting the activity of enzymes that participate in the formation of reactive oxygen species. Indirect antioxidant action involves interupting the cascade of reactions of free radicals and the chelation of metal ions, which prevents reactive hydroxyl radicals in cells. Compounds from the group of flavonoids having significance in photoprotection are genistein, silymarin, equol and quercetin.

A new material of plant origin used in photoprotection is ferulic acid, which belongs to the group of hydroxycinnamic acids. Rich sources are cell walls of plants, such as citrus fruits, wheat, spinach and beets. Ferulic acid is a compound of low toxicity, absorbed easily and safely when applied to the skin surface. Reduction in oxidative stress is achieved by increasing the activity of enzymes responsible for neutralizing reactive oxygen species and prevents them from occurring. It also possesses the ability to absorb radiation from the entire UVB spectrum and a selected portion from the UVA, thereby providing adequate protection against the formation of erythema, photoaging and development of tumors.

Pycnogenol® is an interesting substance, which is extracted from pine bark. Its photoprotective effects complement synthetic substance, as its activity is exhibited after exposure of UV radiation to skin. Active compounds are mainly flavonoids, which act as antioxidants. Pycnogenol® also has anti-inflammatory and anticarcinogenic[56].

Gaining popularity is the *Polypodium leucotomos* or *Polypodium aureum*, an epiphytic fern native to tropical and subtropical regions of the Americas. Extracts contain photoprotective properties and are a blend of hydroxycinnamic acids, such as ferulic and caffeic acid. Offering strong antioxidant properties by both external application and oral ingestion, it has the ability to reduce free radical counts and limit the extent of lipid peroxidation of cell membranes, resulting in de-

lays of pathology changes associated with photoaging and tumor development[57]. This compound also helps in the prevention of sunburn after phototherapy in conjunction with psolarens. Use of oral formulations of the *P. leucotomos* extract decreases phototoxicity experienced during PUVA therapy[17]. This extract is the first oral formulation that effectivitly lowers acute phototoxicity and hyperpigmentation associated with phototherapy. Its application leads to a significant protection of Langerhans cells, a decrease of "sunburn cells" formation and the prevention of inflammatory cell infiltration.

The Future of Photoprotection

Use of UV filters in cosmetic products function on the prinicple of UV wave absorption or reflection or neutralization of reactive oxygen species. These constituents have protective properties against cell damage. The future of sun protection agents will include a new generation of compounds with the ability of absorbing harmful radiation in combination with substances having the ability to repair damage caused within DNA. Modern cosmetic products, found on the market, have enzymes capable of regenerating genetic material. Current research identifies certain enzymes, which are responsible for the identification and removal of damaged cell DNA fragments. Two major enzymes are photolyase and endonuclease. There is much promise with the introduction of these natural occuring enzymes into cosmetic products[58].

The photolyase enzyme is not present in genomes of all mammals, however, may be found in other animal species, plants and bacteria. Knowledge of this enzyme has been around for a long time, but the mechanisms behind function is still unclear. Photolyase was first isolated from the cyanobacteria, *Anacystis nidulans*, which are a component of plankton[59]. Activated by blue or violet light from the visible spectrum, photolyase is able to repair alterations and damage of DNA caused by exposure to UV radition. The most common alteration in DNA is the formation of pyrimidine dimers, which distort the double helix structure at the site of damage. These changes may cause errors in reading of the strands during phases of transcription and replication. The action of photolyasis is to destroy pyrimidine dimer. The enzyme is enclosed in a multi-layer phospholipid envelope that allows it to reach the deeper layers of the skin. During the time of penetration through the cell membrane, pH of the environment decreases, which causes opening of the envelope and enzymes released. In this manner, carriers are able to reach the living layers of skin and have the enzyme go into the cells. In addition to the ability to repair damaged DNA, photolyase aids in cell regeneration and reduces formation of skin inflammation caused by exposure to sun light. The mechanism involves inhibition of pro-inflammatory cytokine, interleukin 6 (IL-6). This involves the ability to reduce the secretion of mediator prior zapalnego-interleukin-6 (IL-6). Presence of this enzyme in cells inhibits UV-induced apoptosis[60]. Even after 30 minutes of exposure to light, photolyase starts to work with maximum efficiency. An *in vivo* study of 12 volunteers showed a reduction in number of cellular damages by approximately 45%, when applied skin nanosmomes of photolyasis followed by exposure to sunlight[61].

Another enzyme responsible for the repair of cells is endonuclease. Obtained from the bacteria *Micrococcus luteus*, which are one of the best known organisms protected from ultraviolet radiation. In cosmetic preparations, this enzyme is also encased in a multi-layer phospholipid coated envelope, which allows for the enzyme to easily enter cells. Endonuclease improves the efficiency and speed of DNA repair approximately four-fold[57]. It stimulates skin regeneration, reconstruction, as well as preventing the destruction of extracellular matrix components[32]. In addition, alleviates skin irritation by reducing pro-inflammatory mediators[8].

Recent studies emphasize the importance of the new photoprotective protein afamelanotide, which is a 13 amino acid analog of alpha-melanocyte stimulating hormone (α-MSH). This protein stimulates skin cells to produce melanin through activation of the melanogenesis process. The α-MSH analogue repairs damage induced by UV radiation by removing pyrimidine dimers. A recent investigation[32] observed a reduction of photohypersensitivity in subjects with erythropoietic porphyria and solar urticaria after the subcuntaneous administration of afamelanotide.

Negative effects of ultraviolet radiation is weakening of the immune system, however, naturally occuring repair enzymes are able to restore skin immune capacity. With advancements of science, researchers are able to examine

different severities of immunosuppression caused by radiation. The Immune protection factor (IPF), similar to SPF, quantifies the radiation dose necessary for immunosuppression. Studies have shown that the IPF for photolyase was 2.3 and 3.3 endonuclease. In comparison to control subjects, patients applying preparations with cell repair enzymes required three times as much of a dose to achieve one MED[56]. With continuing discoveries in mechanims of cellular photoprotection and repair, incorporation of molecules, such as photolyase and endonuclease, is the future in cosmetic protection against ultraviolet radiation.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Endres L, Breit R. Jordan W, Halbritter W. UV Radiation, Irradiation and Dosimetry. Dermatological Phototherapy and Photodiagnostic Methods 2009; pp. 3-59.
2) Narbutt J. Does the use of protective creams with UV filters inhibit the synthesis of vitamin D? – For and against. Przeglad Pediatryczny 2009; 41: 75-81.
3) Jabłonska S, Chorzelski T. Precancerous lesions and carcinomas in situ. Choroby skóry i choroby przenowszone drog płciow . PZWL, Warszawa, 2008; pp. 386-417.
4) Martini MC. Discoloration of the skin and protection products. Kosmetologia i farmakologia skóry 2007; pp. 157-192.
5) Wolnicka-Głubisz A, Smejda M. Mechanisms associated with immunosuppression induced by UV radiation. Alergia Astma Immunologia 2010; 15: 26-34.
6) Suber C, Urlich C, Hinrichs B, Stockfleth E. Photoprotection in immunocompetent and immunocompromised people. Br J Dermatol 2012; 167: 85-93.
7) Victor FC, Cohen DE, Soter NA. A 20 year analysis of previous and emerging allergens that elicit photoallergic contact dermatitis. J Am Acad Dermatol 2010; 62: 605-610.
8) Katiyar SK. Silymarin and skin cancer prevention: anti-inflammatory, antioxidant and immunomodulatory effects. Int J Oncol 2005; 26: 169-176.
9) Sime S, Reeve VE. Protection from inflammation, immunosuppression and cancerogenesis inducted by UV radiation in mice by topical Pycnogenol. Photochem Photobiol 2004; 79: 193-198.
10) Holick MF. Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. Am J Clin Nutr 2004; 80: 1678-1688.
11) Liu D, Fernandez BO, Hamilton A, Lang NN, Gallagher JM, Newby DE, Feelisch M, Weller RB. UVA irradiation of human skin vasodilates arterial vasculature and lowers blood pressure independently of nitric oxide synthase. J Invest Dermatol 2014; 134: 1839-1846.
12) Bowszyc-Dmochowska M. Action of ultraviolet radiation on the skin. Homines Hominibus 2010; 6: 29-42.
13) Georgiades J. A new method of control of free radicals (II). Medycyna Estetyczna i Przeciwstarzeniowa 2005; 4: 168-174.
14) Wei H, Saladi R, Lu Y, Wang Y, Palep SR, Moore J, Phelps R, Shyong E, Lebwohl MG. Isoflavone genistein: photoprotection and clinical implications in dermatology. J Clin Nutr 2003; 133: 3811-3819.
15) Burgaz A, kesson A, Öster A, Michaëlsson K, Wolk A. Associations of diet, supplement us and ultravolet B radiation exposure with vitamin D status in Swedish women during winter. Am J Clin Nutr 2007; 86: 1399-1404.
16) Webb AR, DeCosta BR, Holick MF. Sunlight regulates the cutaneous production of vitamin D3 by causing its photodegradation. J Clin Endocrinol Metab 1989; 68: 882-887.
17) Halski T. PUVA in modern medicine. Rehabilitacja w praktyce 2007; 2 : 32-35.
18) Routaboul C, Denis A, Vinche A. Immediate pigment darkening: description, kinetic and biological function. Eur J Dermatol 1999; 9: 95-99.
19) Diffey BL. Factors affecting the choice of a ceiling in the number of exposures with TL01 ultraviolet B phototherapy. Br J Dermatol 2003; 149: 428-430.
20) Dawe RS. Ultraviolet A1 phototherapy. Br J Dermatol 2003; 148: 626-637.
21) Jansen R, Wang SQ, Burnett M, Osterwalder U, Lim HW. Photoprotection: part I. Photoprotection by naturally occurring, physical, and systemic agents. J Am Acad Dermatol 2013; 69: 853.
22) Wang SQ, Kopf AW, Marx J, Bogdan A, Polsky D, Bart RS. Reduction of ultraviolet transmission through cotton T-shirt fabrics with low ultraviolet protection by various laundering methods and dyeing: clinical implications. J Am Acad Dermatol 2001; 44: 767-774.
23) Dolin PJ. Ultraviolet radiation and cataract: a review of the epidemiological evidence. Br J Ophthalmol 1994; 78: 478-482.
24) Sunscreens: an update. Medical Letter on Drugs and Therapeutics 2008; 50: 70-72.
25) Jabłonska S, Chorzelski T. Photodermatoses. Choroby skóry i choroby przenowszone drog płciow . PZWL, Warszawa, 2008: pp. 189-204.

26) Lecha M. Idiopathic photodermatoses: clinical, diagnostic and therapeutic aspects. J Eur Acad Dermatol Venereol 2001; 15: 499-504.

27) Wolska H. External substances to protect from light. Dermatologia Estetyczna. 1999: 20-27.

28) Regulation of the Minister of Health on the lists of prohibited substances or permitted with restrictions for use in cosmetics and graphic signs placed on packaging. Appendix 5- List of UV-authorized substances for use in cosmetics 30.03.2005. http://www.nettax.pl/dzienniki/du/2005/72/poz.642.htm.

29) Schroeder P, Lademann J, Darvin M, Stege H, Marks C, Bruhnke S, Krutmann. Infrared Radiation-induced matrix metalloproteinase in human skin: implications for protection. J Invest Dermatol 2008; 128: 2491-2497.

30) Sarkany R. Photocarcinogenesis: introduction to photodermatology. An Educational Course Organized by the Photodermatology Unit, St. John's Insitute of Dermatology 2011, London, Great Britain.

31) Murphy G. Photocancerogenesis strategies for prevention. Proceedings of the second European Course of Photodermatology 2014, Dublin, Ireland.

32) Fitzpatrick T, Breathnach A. The epidermal melanin unit system. Dermatol Wochenschr 1963; 147: 481-489.

33) Lindqvist PG, Epstein E, Landin-Olsson M, Ingvar C, Nielsen K, Stenbeck M, Olsson H. Avoidance of sun exposure is a risk factor for all-cause mortality: results from the Melanoma in Southern Sweden cohort. J Intern Med 2014; 276: 77-86.

34) Moyal D, Wichrowski C, Tricaud C. *In vivo* persistent pigment darkening method: a demonstration of reproducibility of UVA protection factors results at several testing laboratories. Photodermatol Photoimmunol Photomed 2006; 22: 124-128.

35) Fitzpatrick T. The validity and practicality of sun-reactive skin types I through VI. Arch Dermatol 1988; 124: 869-871.

36) Wright MW, Wright ST, Wagner RF. Mechanisms of sunscreen failure. J Am Acad Dermatol 2001; 44: 781-784.

37) Osmola-Ma kowska A. Effects of ultraviolet radiaton on skin. In: Practical issues related to protection of laborworkers in agriculture. Ed: Solecki L. Institute of Rural Health, Lublin, 2013: 184-189.

38) McKinlay AF, Diffey BL. A references action spectrum for ultraviolet induced erythema in human skin. CIE J 1987; 6: 17-22.

39) Diffey B. Sunscreens: expectation and realization. Photodermatol Photoimmunol Photomed 2009; 25: 233-236.

40) Baron ED, Kirkland EB, Domingo DS. Advances in photoprotection. Dermatol Nurs 2008; 20: 265-272.

41) Pelizzo M, Zattra E, Nicolosi P, Peserico A, Garoli D, Alaibac M. *In vitro* evaluation of sunscreens: an update for the clinicians. ISRN Dermatol 2012; 2012: 352135.

42) Villalobos-Hernández JR Müller-Goymann CC. Novel nanoparticles carrier system based on carnauba wax and decyl oleate for the dispersion of inorganic sunscreens in aqueous media. Eur J Pharm Biopharm 2005; 60: 113-122.

43) Janjua N, Kongshoj B, Andresson A, Wulf, H. Sunscreens in human plasma and urine after repeated wholebody topical application. J Eur Acad Dermatol Venereol 2008; 22: 456-461.

44) Cantrell A, McGarvery D, Truscott T. Photochemical and photophysical properties of sunscreens. Comprehensive Series in Photosciences vol. 3: Sun Protection in Man 2001; pp. 495-519.

45) Rampaul A, Parkin IP, Cramer LP. Damaging and protective properties of inorganic components of sunscreens applied to cultured human skin cells. J Photoch Photobio A 2007; 191: 138-148.

46) Filipe P, Silva JN, Silva R, Cirne de Castro JL, Margues Gomes M, Alves LC, Santus R, Pinheiro T. Stratum corneum is an effective barrier to TiO2 and ZnO nanoparticle percutaneous absorption. Skin Pharmacol Physiol 2009; 22: 266-275.

47) Migdal C, Rahal R, Rubod A, Callejon S, Colomb E, Atrux-Tallau N, Haftek M, Vincent C, Serres M, Daniele S. Internalisation of hybrid titanium dioxide/para-amino benzoic acid nanoparticles in human dendritic cells did not induce toxicity and changes in their functions. Toxicol Lett 2010; 199: 34-42.

48) IARC handbook of cancer prevention: sunscreens. Lyon, France 2001; 5: 69-124.

49) Fesq H. Sunscreens for UV protection and repellents--who needs what? MMW Fortschr Med 2007; 149: 32-35.

50) Jansen R, Osterwalder U, Wang Q, Burnett M, Lim HW. Photoprotection. part II. Sunscreen: development, efficacy, and controversies. J Am Acad Dermatol 2013; 69: 867-880.

51) Meléndez-Martínez AJ, Escudero-Gilete ML, Vicario IM, Heredia FJ. Study of the influence of carotenoid structure and individual carotenoids in the qualitative and quantitative attributes of orange juice color. Food Res Int 2010; 43: 1289-1296.

52) Afaq F, Adhami VM, Ahmad N. Prevention of short-term ultraviolet B radiation-mediated damages by resveratrol in SKH-1 hairless mice. Toxicol Appl Pharmacol 2003; 186: 28-37.

53) Reeve VE, Widyarini S, Domanski D, Chew E, Barnes K. Protection against photoaging in the hairless mouse by the isoflavone equol. Photochem Photobiol 2005; 81: 1548-1553.

54) Casagrande R, Georgetti SR, Verri WA Jr, Dorta DJ, dos Santos AC, Fonseca MJ. Protective effect

of topical formulations containing quercetin against UVB-inducted oxidative stress in haireless mice. J Photochem Photobiol B 2006; 84: 21-27.

55) Williams S, Tamburic S, Lally C. Eating chocolate can significantly proctect the skin from UV light. J Cosmet Dermatol 2009; 8: 169-173.

56) Middelkamp-Hup MA, Bos JD, Rius-Diaz F, Gonzalez S, Westerhof W. Treatment of vitiligo vulgaris with narrow-band UVB and oral Polypodium leucotomos extract: a randomized double-blind placebo-controlled study. J Eur Acad Dermatol Venereol 2007; 21: 942-950.

57) Gonzales S. Polypodium leucotomos extract: a natural antioxidant and photoprotective tool fot the management of UV-inducted skin damage and phototherapy. Cosmet Dermatol 2009; 22: 604-609.

58) Stege H, Roza L, Vink AA, Grewe M, Ruzicka T, Grether-Beck S, Krutmann J. Enzyme plus light therapy to repair DNA damage in ultraviolet-B-irradiated human skin. Proc Natl Acad Sci U S A 2000; 97: 1790-1795.

59) Offredo H. Four enzymes to repair DNA after UV, oxidation or pollution damage. Cosmetic Ingredients and Biotechnology Congress Cosm'ing. Saint-Malo, France, 2004; pp. 67-77.

60) Kulms D, Zeise E, Pöppelmann B, Schwarz T. DNA damage, death receptor activation and reactive oxygen species contribute to ultraviolet radiation-induced apoptosis in an essential and independent way. Oncogene 2002; 21: 5844-5851.

61) Yarosh DB, Kibitel J, O'Connor A, Hejmadi V, Bennett P, Sutherland BM. DNA repair liposomes in antimutagenesis. J Environ Pathol Toxicol Oncol 1997; 8: 287-292.