Review article

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Ultraviolet Filters as Endocrine Disruptors in Sunscreen Products

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Ultraviolet (UV) filters are classified as substances commonly found in sunscreen products and cosmetics, primarily designed to protect the skin from the harmful effects of ultraviolet (UV) radiation. Although they are very effective in preventing skin damage and the development of melanoma, a growing number of studies indicate the potential negative effects of certain organic UV filters that act as endocrine disruptors. Endocrine disruptors are substances that act on a living organism by interacting with hormone receptors, modulating the synthesis and activity of hormones, causing a number of harmful effects. UV filters such as octinoxate, homosalate, avobenzone and oxybenzone have been detected in human biological samples (blood, urine and breast milk), indicating that they are absorbed systemically. A growing body of *in vitro* and *in vivo* studies suggest their potential ability to bind to hormone receptors, modulate the expression of enzymes involved in steroidogenesis, and affect the hypothalamic-pituitary-gonadal (HPG) axis, which can lead to hormonal imbalance and long-term health consequences.

Keywords: UV Filters, Endocrine Disruptors, Octinoxate, Homosalate, Avobenzone, Oxybenzone

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Ultraljubičasti filteri kao endokrini drisruptori u proizvodima za zaštitu od Sunčevog zračenja

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Ultraljubičasti (engl. *ultraviolet* – UV) filteri se klasifikuju kao supstance koje su široko prisutne u proizvodima za zaštitu od Sunčevog zračenja, kozmetici, a njihova glavna uloga je da zaštite kožu od štetnog UV zračenja. Iako su veoma efikasni u prevenciji oštećenja kože i razvoja melanoma sve veći broj istraživanja ukazuje na potencijalne negativne efekte pojedinih organskih UV filtera koji deluju kao endokrini disruptori. Endokrini disruptori su supstance koje deluju na živi organizam tako što interaguju sa hormonskim receptorima, moduliraju sintezu i aktivnost hormona izazivajući niz štetnih efekata. UV filteri poput oktinoksata, homosalata, avobenzona i oksibenzona detektovani su u humanim biološkim uzorcima (krvi, urinu i majčinom mleku) što potvrđuje njihovu sistemsku apsorpciju. Sve veći broj *in vitro* i *in vivo* istraživanja ukazuju na njihovu potencijalnu sposobnost da se vezuju za hormonske receptore, moduliraju ekspresiju enzima uključenih u steroidogenezu, kao i da utiču na osovinu hipotalamus-hipofiza-gonade (HPG), čime mogu da dovedu do hormonskog disbalansa i dugoročnih zdrastvenih posledica.

Ključne reči: UV filteri, endokrini disruptori, oktinoksat, homosalat, avobenzon, oksibenzon

1. INTRODUCTION

In the modern era, humans are exposed to various environmental factors on a daily basis that can have harmful effects on health. One of the most important natural factors that, besides its benefits, can have serious negative effects on the human body is natural UV radiation (1). In order to prevent skin damage caused by UV radiation, cosmetic products containing UV filters are increasingly used. The first UV filters were introduced in the mid-20th century. The original formulations were based on fatty components (petrolatum, lanolin) with minimal photoprotective effect. Later, with the development of the first substances capable of selectively absorbing UV-B radiation, as well as filters capable of absorbing UV-A radiation, significant progress was made and UV protection became a commercial segment of cosmetics (2, 3). Organic UV filters can be classified according to their chemical structure into several key groups, wchich include: benzophenone derivatives (e.g. oxybenzone), salicylic acid derivatives (e.g. homosalate), cinnamic acid derivatives (e.g. octinoxate), para-aminobenzoic acid (PABA) and its derivatives, benzylidenecamphor derivatives (4-MBC), phenyl benzimidazole derivatives (e.g. ensulizole), and triazines (e.g. Tinosorb S and M). Based on the radiation absorption spectrum, these filters are divided into those that protect against UVB radiation (octinoxate, homosalate, octocrylene, and ensulizole), filters that primarity cover the UVA range (avobenzone), and broad-spectrum filters with absorb radiation in both ranges (oxybenzone, Tinosorb S and M). Although the primary function of UV filters is photoprotective, a growing body of scientific studies indicate their potential dual nature, since some UV filters can be absorbed, enter the systemic circulation, and produce biological effects, particularly concerning the endocrine system (4, 5). For this very reason, this paper focuses on organic filters with confirmed systemic absorption and the potential for endocrine disruption, with a special emphasis on octinoxate, homosalate, avobenzone, oxybenzone and octocrylene. The mechanisms of potential endocrine-disrupting action of these compounds include interaction with hormone receptors (6), modulation of the expression of enzymes involved in steroidogenesis (7), and influence on the hypothalamic-pituitary-gonadal (HPG) axis. These changes can lead to disruption of hormonal homeostasis, disorders of reproductive functions and other systemic consequences (8). Of particular concern is the fact that UV filters, in addition to sunscreens, are also found in a wide range of everyday cosmetics, which may increase the risk of chronic and cumulative exposure. An additional problem is the photochemical instability of some UV filters, which, under the influence of UV radiation, form biologically active degradation products with increased endocrine-disrupting potential (9-11). In light of these findings, it is necessary to examine in detail not only the photoprotective efficacy and mechanisms of action at the molecular level, but also the effects of degradation products in order to adequately assess the overall safety of UV filters for human health.

2. UV FILTERS

The skin, as the largest organ of the human body, represents the primary barrier and effectively protects the body from the harmful effects of UV radiation. In human skin, UV-B radiation stimulates the synthesis of vitamin D_3, which is an important physiological process with a significant role in maintaining general health. However, UV-B radiation causes several harmful effects, including erythema, burns, hyperpigmentation, and the initiation of carcinogenesis. UV-A rays penetrate deeper into the skin compared to UV-B rays, but the effects are weaker, cumulative, and manifest only after a longer period of exposure (1). This type of radiation negatively affects DNA, functional proteins, and cell membranes, and can additionally enhance the harmful effects of UV-B radiation (1, 12, 13).

UV filters are substances that absorb light in the UV-B and UV-A wavelength ranges. For a molecule to have absorbance in the appropriate UV range, it must have at least three conjugated π-bonds and allow structural modifications. Benzene meets these requirements, which is why most organic (chemical) UV filters in cosmetics contain a benzene ring. However, benzene itself does not absorb in the desired wavelength range, and it is necessary to shift the absorption to higher wavelengths (14). This is achieved by introducing substituents with activating and deactivating effects or by choosing an appropriate solvent for a given UV filter.
UV filters used in cosmetic products must satisfy several requirements, with physical and chemical stability being the most important. However, they do not have to be photochemically stable. Many UV filters undergo photodegradation under the influence of light, which reduces their protective efficacy. The resulting degradation products may or may not be UV active, may be absorbed through the skin, or may show toxic effects (4, 14). A significant advantage of organic filters is their solubility in either aqueous or oily phases, allowing for good spreadability on the skin and the ability to combine with other filters. However, the biggest disadvantage is

the potential toxicity of organic filters as well as photochemical and metabolic degradation products (15, 16).

In addition to organic UV filters, inorganic (physical) UV filters are also used in cosmetic products. Inorganic UV filters have a different mechanism of action. In addition to absorption, they have the ability to reflect or scatter UV radiation (17). Currently, only two inorganic UV filters are in use: titanium dioxide (TiO_2) and zinc oxide (ZnO). They reflect light in the visible range, and when used, they leave white marks on the skin, which is considered an aesthetic drawback. In order to reduce the degree of reflection of visible light and avoid visual discomfort, newer product formulations contain oxides with particle sizes in the nanometre range (17, 18). Inorganic filters in nano-form tend to form agglomerates and precipitate in cosmetic preparations, which makes them difficult to disperse and maintain in the form of individual particles. The greatest disadvantage of inorganic UV filters is their ability to generate free radicals. Some scientists believe that inhalation of TiO_2 nanoparticles can lead to lung cancer, which is why its use in aerosol form is avoided (19).

In the modern environment, a wide range of substances have been identified that are classified as endocrine disruptors. These molecules interfere with hormone receptors, affect hormone synthesis and activity, and thus disrupt endocrine function, leading to hormonal imbalance (6). Although it has been proven that certain parabens, phthalates, and UV filters have endocrine-disrupting potential and can cause reproductive and other metabolic disorders, they are still widely used (8, 20). The skin, as the primary organ exposed to the effects of photoprotective preparations, represents an important route of entry of UV filters into the body, either by direct contact or indirect systemic absorption (21).

3. UV FILTERS AS ENDOCRINE DISRUPTORS

Sunscreen products are intended for daily use throughout life, and therefore require detailed testing for short-term and long-term health effects. Companies developing and marketing such products should conduct comprehensive toxicological studies, including assessment of skin irritation and allergic reactions, the degree of dermal absorption, and potential carcinogenic, reproductive toxic, and endocrine-disrupting effects (22). A study by *Matt et al.*, which included the active ingredients of sunscreens, showed that octinoxate, homosalate, avobenzone, and oxybenzone, after topical application, are absorbed into the body and detected in the blood and on the skin surface for weeks after the last application (23).

Octinoxate - (ethylhexyl methoxycinnamate or octyl methoxycinnamate, OMC, Figure 1) is an organic UV filter that absorbs UV-B radiation and thus prevents damage to cellular DNA and collagen degradation. Octinoxate is extremely lipophilic, easily passes through the epidermis and enters the systemic circulation, which represents the potential for exerting an endocrine effect (5).

In vitro studies have shown that octinoxate exhibits estrogenic activity by activating estrogen receptors (ERα and ERβ) and inducing transcription of estrogen-dependent genes (24). Under the influence of UV radiation, it can be degraded into photoproducts (e.g., methoxycinnamic aldehydes and phenols) that potentially possess stronger estrogenic activity (9, 25). Some studies also indicate antiandrogenic effects and interaction with progesterone receptors (PR), which implies the possibility of disrupting the balance of sex hormones (26).

In H295R adrenocortical cells, octinoxate can modulate the expression of steroidogenic enzymes, including CYP11B2 (aldosterone synthase and 3β-HSD2 (3β-hydroxysteroid dehydrogenase type 2), which may lead to potential effects on steroid hormones (27, 28). However, a recent study by the US National Toxicology Program did not show statistically significant changes in testosterone or estradiol levels in H295R cells (29).

In vivo studies indicate that octinoxate may also affect the hypothalamic-pituitary-gonadal (HPG) axis, reducing GnRH (gonadotropin- releasing hormone) release in the hypothalamus of young rats (30), while prenatal or postnatal exposure can lead to reduced testicular mass and testosterone levels in males, as well as increased uterotrophic activity and increased ERα expression in females (24). These results suggest potential transgenerational endocrine effects. Also, some studies on experimental animals indicate that exposure to octinoxate reduces the concentration of thyroid hormones (T_4/T_3) and disrupts the expression of genes related to thyroid function and hormone metabolism (31, 32, 33). As previously mentioned, octinoxate is not completely photostable. Its degradation under the influence of UV radiation can lead to the formation of various photoproducts and reactive organic radicals that potentially increase the level of reactive oxygen species (ROS) and thus contribute to oxidative stress at the cellular level (34, 35).

Homosalate - (homomenthyl salicylate, Figure 2) is an organic UV filter that primarily absorbs UV-B radiation (24). In addition to its undoubted efficacy, a growing number of studies point to its endocrine disrupting potential (36). Under the influence of UV radiation, homosalate can photodegrade, forming various transformation products, including salicylate or phenolic derivatives that are chemically more stable and potentially more biologically active than the parent substance. These photoproducts may contribute to the increased endocrine potential of homosalate, which highlights the need to assess its photostability and toxicological properties (10, 11).

Homosalate binds to estrogen receptors (ERα and ERβ) and activates them *in vitro* (36). In some experimental models, it inhibits testosterone binding to androgen receptors (AR) and leads to a consequent disruption of hormonal balance and expression of hormone-dependent genes (7, 36, 37).

Studies on H295R adrenocortical cells indicate that homosalate can modify the activity of enzymes involved in steroidogenesis and, consequently, hormone levels. *Lee et al.* found that exposure to homosalate in the H295R model leads to a decrease in testosterone concentration and changes in the expression of steroidogenic genes (e.g. CYP7A1, HSD3B2, HSD17B1) [7]. Homosalate causes an increase or decrease in estrogen, progesterone, and testosterone levels depending on the concentration and duration of exposure, while the specific effects on the enzymes CYP11A1 and 3β-HSD2 are still poorly understood and require additional research (7, 38).

Homosalate has also shown the ability to affect aromatase (CYP19) by moderately inhibiting its activity and thus interfering with the process of converting androgens to estrogens. In addition, some *in vitro* studies suggest that homosalate may impair mitochondrial function, manifested by changes in membrane potential, disruption of oxidative phosphorylation and decreased ATP production, as well as increased generation of ROS in various human cell models (39-42).

Avobenzone - (butylmethoxydibenzoylmethane, Figure 3) is wide application organic UV-A filter that provides effective UV-A protection. In products with broad-spectrum protection, avobenzone is used in combination with other organic UV filters. It is highly photochemically unstable, and degrades in the presence of chlorinated water. The presence of appropriate components that act as stabilizers is necessary to prevent its photodegradation (14).

Scientific research indicates that avobenzone may act as a weak endocrine disruptor, especially when, under the influence of UV radiation or metabolic processes in the body, it is broken down into bioactive products (43).

In vitro studies suggest that avobenzone and its degradation products (e.g. aryl-benzophenones) may have weak interactions with estrogen receptors (ERα) and androgen receptors (AR). The effects are usually very mild and depend on the concentration, test conditions and the presence of endogenous hormones, with weak agonistic or antagonistic responses occurring (37, 44).

Oxybenzone - (benzophenone-3, BP-3, Figure 4) absorbs UV-A and UV-B radiation, thereby protecting skin cells from DNA damage. It provides high UV protection efficiency but is also known for its high dermal absorption and therefore its impact on the endocrine system. Oxybenzone is often detected in blood, urine and breast milk after topical application of sunscreen products (45-49).

Compared to the other UV filters mentioned, oxybenzone shows the most pronounced endocrine potential. Oxybenzone and its metabolites, especially benzophenone-1 and benzophenone-8, show the ability to bind to estrogen receptors (ERα, ERβ), acting as estrogen agonists, while they exhibit antiandrogenic activity towards androgen receptors (AR) by blocking the binding of endogenous androgens. In some cell models, action has also been observed on progesterone receptors (PR), where they show weak agonist activity. All this indicates that exposure to oxybenzone can lead to disruption of hormonal balance through simultaneous stimulation of estrogen pathways and inhibition of androgen pathways. The above effects have been confirmed in *in vitro* and *in vivo* studies (46, 50, 51).

The mechanism of action of oxybenzone is diverse and includes modulation of the HPG axis and inhibition of key enzymes of steroidogenesis. Experimental *in vitro* studies on H295R adrenocortical cells have shown that exposure to oxybenzone leads to an increase in the expression of CYP19 (aromatase), i.e. an increase in the conversion of testosterone to estradiol. At the same time, inhibition of the enzymes CYP17 and 3β-HSD was observed, which leads to a decrease in androgen synthesis (43, 51, 52).

In vivo studies have shown the impact of oxybenzone on central endocrine regulation mechanisms. A decrease in gonadotropin expression (LH- luteinizing hormone, FSH- follicle-stimulating hormone) and changes in gonadal morphology were observed in experimental animals, indicating a disruption of the aforementioned HPG axis. The above claims confirm that oxybenzone possesses a complex endocrine potential that manifests itself through peripheral and central effects (52, 53).

In *in vivo* experiments on mice, it was observed that prenatal exposure of mice to oxybenzone affects reduced fertility in offspring, and leads to developmental malformations of the gonads, disorders in hormone and receptor expression, thus confirming its transgenerational effects (53-55).

Octocrylene - (2-ethylhexyl-2-cyano-3,3-diphenylacrylate, Figure 5) is a very effective UV-B filter, while UV-A radiation is absorbed in a small part of the spectrum. Its structure is lipophilic, which allows it to pass through the cell membrane. Scientific research has shown that it has a toxic effect on aquatic organisms (56), and that it acts as an endocrine disruptor (8, 37). It potentially acts on estrogen receptors (ERα and ERβ) as a weak estrogen agonist, while by binding to androgen receptors (AR) it blocks the binding of testosterone and has antiandrogenic activity (8, 57). Octocrylene is degraded by UV radiation into benzophenone, which exhibits a more intense effect on the endocrine system (46, 58), which is one of the main reasons for concern regarding the use of octocrylene.

Ensulizole (2-phenylbenzimidazole-5-sulfonic acid, Figure 6) is an organic UV-B filter. Compared to other UV filters, such as avobenzone or octinoxate, ensulizole is photostable and hydrophilic, and is significantly less absorbed through the skin. To provide complete UV protection, it is necessary to use it in combination with UV-A filters in cosmetic preparations. Although it is considered a very safe UV filter that does not have the potential to cause significant skin irritation or photoallergic reactions, there is a lack of research on the impact of ensulizole on endocrine system function (59, 60).

Tinosorb S - (bis-ethylhexyloxyphenol methoxyphenyl triazine or bemotrizinol, Figure 7) and **Tinosorb M** (methylene-bis (benzotriazolyl) tetramethylbutylphenol or bisoctrizole, Figure 8) are UV-B and UV-A filters that provide protection in a wide range of the spectrum. They are extremely photostable and do not easily undergo degradation reactions under the influence of UV radiation (61, 62). Skin irritations that can be caused by these UV filters are very rare (63). The key difference between Tinosorb S and Tinosorb M is in the chemical structure (64). Tinosorb S is lipophilic and more suitable for creams/lotions with oils, while Tinosorb M is more suitable for fluid textures due to its higher solubility in water (gels, fluid creams) (61). Modern studies have not proven their effects on the endocrine system, and they are currently considered safe for use (8).

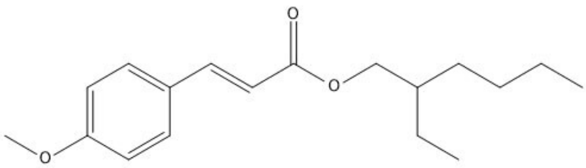

Figure 1. *Octinoxate - chemical structure*

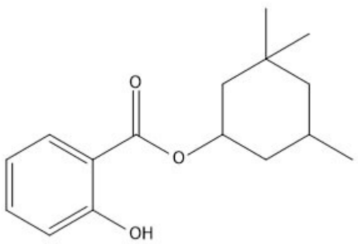

Figure 2. *Homosalate - chemical structure*

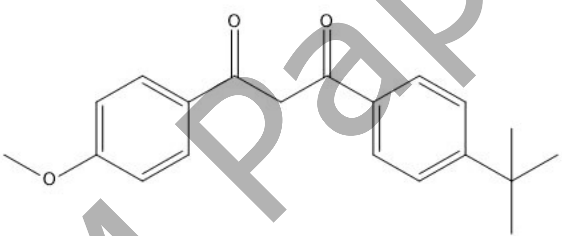

Figure 3. *Avobenzone - chemical structure*

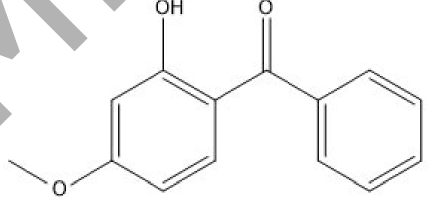

Figure 4. *Oxybenzone - chemical structure*

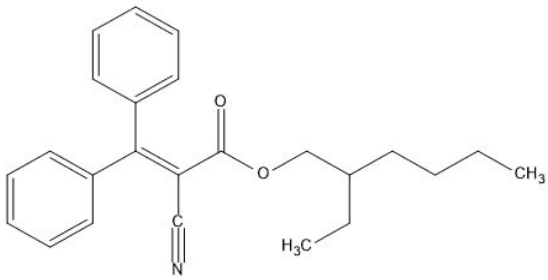

Figure 5. *Octocrylene - chemical structure*

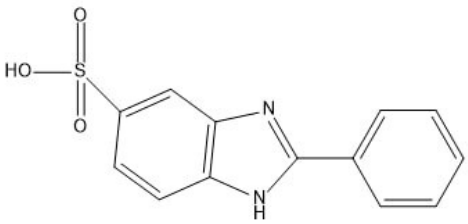

Figure 6. *Ensulizole - chemical structure*

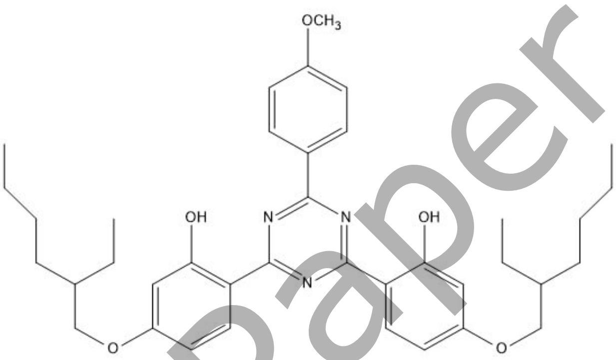

Figure 7. *Chemical structure of Tinosorb S*

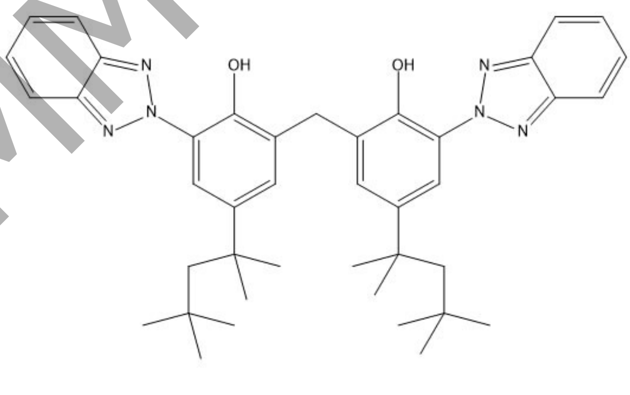

Figure 8. *Chemical structure of Tinosorb M*

4. LEGISLATION AND REGULATION

UV filters are regulated globally in Europe and Japan as cosmetics, in the USA and Canada as over-the-counter drugs, and in Australia as therapeutic agents (65). The maximum allowed concentrations of UV filters vary, as does the total number of UV filters present in cosmetic products. The concentration of UV filters in cosmetic products typically ranges from 2-10%, and the percentage depends on the desired zone of protection (UV-A, UV-B) and the protection factor (SPF) (14). The maximum permissible concentrations of UV filters are summarized in Tables 1 and 2.

Many UV filters exhibit potential toxic properties, making it a major challenge in recent years to find a balance between high efficiency in UV protection and minimizing possible adverse effects on human health. For these reasons, some UV filters have been banned for use in the EU and the USA (Tables 3 and 4).

More recently, researchers have started to focus on another equally important topic: the impact of UV filters on the environment. These filters enter aquatic ecosystems directly when they are washed off the skin during recreational activities in surface waters, and indirectly through wastewater. Although the overall use of UV filters is lower compared to other products of general use, such as soaps and detergents, their potential impact on the environment can be of great importance, bearing in mind their direct entry into surface waters and the ability to bioaccumulate in the tissues of aquatic organisms. Research has shown that certain UV filters in aqueous solutions, under the influence of UV radiation, can generate reactive oxygen species (ROS) and other free radicals, which can lead to increased toxicity towards certain aquatic organisms, as was reported in the case of oxybenzone (76-81). Due to the negative impact on the aquatic ecosystem, especially on corals, some UV filters are completely banned from use in the countries listed in Table 5.

Table 1. *UV filters and maximum allowed concentration in the European Union (66)*

UV filters	Maximum allowed concentration (%)
Avobenzone	5%
Octinoxate	10%

Octocrylene	10% (general format) 9% (spray form)
Homosalate	7,34%
Oxybenzone	6%
Ensulizole	8%
Tinosorb S and M	10%

Table 2. *UV filters and maximum allowed concentration in the USA (67-69)*

UV filters	**Maximum allowed concentration (%)**
Avobenzone	3%
Octinoxate	7,5%
Octocrylene	10%
Homosalate	15%
Oxybenzone	6%
Ensulizole	4%
Tinosorb S	Not approved, proposal - allow up to 6%
Tinosorb M	Not approved, currently no % allowed

Table 3. *UV filters banned in the EU to protect human health (14, 70-73)*

UV filters	**Reason for the ban**
4-methylbenzylidene camphor (4-MBC / enzacamene)	Proven endocrine disrupting effects, especially antiandrogenic and estrogenic
3-benzylidene camphor (3-BC)	Strong estrogenic effects, potential for systemic toxicity
OD-PABA (octyl dimethyl PABA / Padimate O)	Photochemical instability, ROS generation, potential genotoxicity
Amyl dimethyl PABA (amyl PABA)	Similar safety reasons as for PABA* derivatives
PABA* (para-aminobenzoic acid)	High rate of allergic reactions, cytotoxicity, photoallergic dermatitis

* PABA and its derivatives were banned and withdrawn from most markets 15 years ago (72).

Table 4. *UV filters banned in the US to protect human health (74)*

UV filters*	Reasons for the ban
PABA and PABA derivatives	Severe allergic reactions and phototoxicity
Trolamine salicylate	Insufficient safety data

Allowed only in special L'Oréal formulations: 4-MBC, 3-BC, enzacamene, Mexoryl SX / XL [14, 74, 75].

Table 5. *UV filters banned to protect aquatic ecosystems (65, 82-85)*

UV filters	Countries in which they are banned	Reasons for the ban
Oxybenzone	Hawaii, Palau, Aruba, U.S. Virgin Islands	Toxicity to corals, disruption of larval development of marine organisms
Octinoxate	Hawaii, Palau, Aruba, U.S. Virgin Islands	Ecotoxicity, disruption of the hormonal system of marine organisms
Octocrylene	Palau	Ecotoxicity, accumulation in corals and fish

5. CONCLUSION

UV filters play a crucial role in preventing skin damage caused by UV radiation, but modern research indicates that certain organic filters, such as octinoxate, homosalate, avobenzone, oxybenzone and octocrylene, can exhibit endocrine disrupting properties. Their systemic absorption and interaction with hormone receptors (ER, AR, PR), as well as the influence on steroidogenesis enzymes (CYP11A1, CYP17, 3β-HSD, CYP19), may lead to disturbances in hormonal balance. Also, the impact on the hypothalamus-pituitary-gonadal axis can result in reduced fertility and disruption of reproductive functions, including potential transgenerational effects. Compared to organic, inorganic UV filters (TiO_2 and ZnO), so far, have not been linked to significant endocrine effects, but their use, especially in nanoform, necessitates additional safety assessments. Further multidisciplinary research with special emphasis on degradation products caused by UV radiation is necessary. It is essential to develop safer and more photostable alternatives, along with continually enhancing regulatory measures to protect human health and the environment.

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