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Review

Photoprotection of ultraviolet-B filters: Updated review of endocrine disrupting properties

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ABSTRACT

The Ultraviolet (UV) radiation is emitted by the sun and is part of the electromagnetic spectrum. There are three types of UV rays (UV-A, UV-B and UV-C), however only UV-A and UV-B have biologic effects in humans, with UV-B radiation being primarily responsible for these effects. Among the measures of photoprotection advised by the health authorities, the topical application of sunscreens (containing UV-B filters) is the preferred worldwide. Currently, octylmethoxycinnamate (OMC) is the most commonly used UV-B filter in sunscreens. Their application has proven to be effective in preventing burns, but its efficiency against melanoma continues under intense controversy. Studies have shown that OMC behaves like an endocrine disruptor, altering the normal functioning of organisms. However, few studies have evaluated their multiple hormonal activities. Some studies suggest that the OMC exerts an estrogenic, anti-androgenic, anti-progestenic and anti-thyroid activity. But, through what mechanisms? In humans, few studies were performed, and some questions remain unclear. Thus, the purpose of this review is to present the multiple hormonal activities established for the OMC, making a critical analysis and relationship between the effects in cells, animals and humans.

1. Introduction

Ultraviolet (UV) radiation is divided into three regions defined as UV-C (200–290 nm), UV-B (290–320 nm) and UV-A (320–400 nm), from lowest to highest energy levels, respectively [48,50]. Humans are exposed to UV-C radiation only by artificial sources [54], since this radiation cannot cross the Earth's atmosphere [48,49]. Thus, UV-C radiation is not considered a significant source of human adverse effects. On the other hand, UV-B radiation represents about 5–10% of all UV radiation reaching the Earth's surface [89]. UV-B radiation can penetrate the epidermis, and is primarily responsible for the most important biologic effects in humans. These effects include: sunburn, problems in pigmentation, induction of vitamin D_3 synthesis, immunosuppression and carcinogenesis [48,89,95]. The other 90–95% of radiation reaching the Earth's surface is UV-A radiation. This radiation can penetrate deep into the skin and reach the dermis, where melanocytes that reside in the basal layer are responsible for photoaging [48,49,95,100]. Both UV-A and UV-B radiations cause direct and indirect damage to DNA and other cellular structures [12,49,95]. Nevertheless, it is demonstrated that the human skin is more sensitive to UV-B radiation [44].

During the last decade, there has been an increase in the use of UV-B filters in sunscreens as a result of the increasing public concerns about the effects of UV radiation on human skin [30,82]. Nowadays, the solar UV filters constitute the active ingredients of sunscreens, being responsible for the temporary protection conferred by these cosmetics [49]. Its application is currently the preferred protection worldwide against the harmful effects of UV radiation [38].

Despite being documented that the protection conferred by sunscreens is capable of decreasing photoaging and reducing the risks of developing age-related skin diseases, [12,95] a series of in vivo and in vitro experimental studies have indicated UV filters as endocrine disruptors [36,39,75,76,78,80,84,85]. Endocrine disruptors (EDs) are chemical substances capable of mimicking, blocking or altering the activity of endogenous substances that are synthesized by the endocrine system [94]. There are several mechanisms by which EDs play their endocrine disruption [14,18], being able to directly alter the production, release, metabolism, elimination and/or action mechanism of the hormones [14]. Since many of the EDs are small lipophilic compounds (steroids), a privileged way for them to act is through direct interaction with a determined nuclear receptor, such as oestrogen (ER), androgen (AR), progesterone (PR) and thyroid (TR) receptors [14].

Octylmethoxycinnamate (OMC) is one of the most world widely used UV-B filter in personal care products, namely sunscreens [37,87]. Currently, in some countries, the OMC constitutes one of the most used and discussed substances in personal care products [51,52]. Marketed under the name of Uvinul® MC 80 [81], the OMC is one of the 27 UV

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filters approved to be used in cosmetic formulations, in the European Union (EU) and in the United States of America (USA) [99], where the maximum authorized concentration is established to 10% and 7.5%, respectively [38]. Moreover, OMC is an integral part of a priority list of ED active compounds in the European Commission database of 2014, and the SIN database of 2014, http://sinlist.chemsec.org/, in EDC DataBank [57].

The OMC is now considered by the European Union's database as an endocrine disruptor, but whose knowledge of its effects on human health is largely unknown or unclear [87]. In fact, some studies have shown that the OMC can act as an endocrine disruptor [75,78], but to date, few studies were developed to evaluate their multiple hormonal activities. It was already demonstrated that the OMC has an estrogenic, anti-androgenic, anti-progestenic and anti-thyroid activity. Most of the studies were performed in animals, and only a few studies evaluated the endocrine disruption effects of OMC in humans. Thus, the purpose of this work is to review the chemical properties and exposure pathways and to evidence the multiple hormonal activities of the OMC, reviewing the current literature of this compound in several organisms, including humans.

2. Approach to systematic review

The latest studies of the octylmethoxycinnamate (OMC) effects on human and animal health will be presented in this review. For this purpose, a PubMed search was carried out for the chemical properties and exposure pathways of OMC, and for the studies performed in humans and animals. In general, the topics included the chemical properties and exposure pathways of OMC, animal studies and, finally, human studies. Regarding the animal studies, the subtopics were estrogenic, anti-androgenic, anti-progestenic, anti-thyroid activities, and an activity unrelated to the above. The search terms used were: sunscreens AND benefits OR photoprotection; endocrine disruptors AND sunscreens OR UV filters; skin AND 2-ethylhexyl 4-methoxycinnamate; UV filters AND EHMC AND chemical; octylmethoxycinnamate AND sunscreens; OMC AND endocrine disruptor; octylmethoxycinnamate AND humans OR human health; octylmethoxycinnamate AND reproduction; octylmethoxycinnamate AND oestrogens OR estrogenic activity; octylmethoxycinnamate AND androgens OR anti-androgenic activity; octylmethoxycinnamate AND progesterone OR anti-progestenic activity; octylmethoxycinnamate AND thyroid OR anti-thyroid activity; estrogenic AND UV filters AND water. Bibliographies of all the articles used in this review were searched for additional relevant citations. From all the articles retrieved, duplicate, unrelated and inaccessible papers were excluded. The review was made following a weight-of-evidence approach, and the results of the most important studies and those with greater relevance for this review are described below.

3. Chemical properties of octylmethoxycinnamate

The octylmethoxycinnamate (OMC), also known by its commercial name, octinoxate [91], and named ethylhexylmethoxycinnamate (EHMC) by the international nomenclature of cosmetic products [53] is a colourless or slightly yellow liquid at room temperature, very soluble in organic solvents and oils but insoluble in water. It is chemically represented by $C_{18}H_{26}O_3$ and has a molecular weight of 290 g/mol [81].

The OMC exerts its protective effects by absorbing high-energy photons of UVB radiation, thereby behaving like an organic ultraviolet filter [12,49]. The absorbed energy is transmitted to the electrons, which pass into an excited state, and when they return to the fundamental state, they release their energy in the form of heat or radiation, at a greater wavelength [49]. This UV filter, which belongs to the p-methoxycinnamic acid derivatives group, is an aromatic compound characterized by a molecular structure with an unsaturated bond between the aromatic ring and the carboxyl group [99] (Fig. 1). This

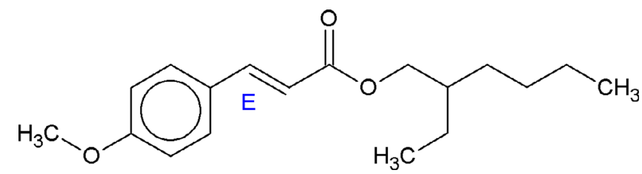

Fig. 1. Chemical structure of the 2-ethylhexyl (2E)-3-(4-methoxyphenyl) pro-2-enoate drawn in the ChemSketch.

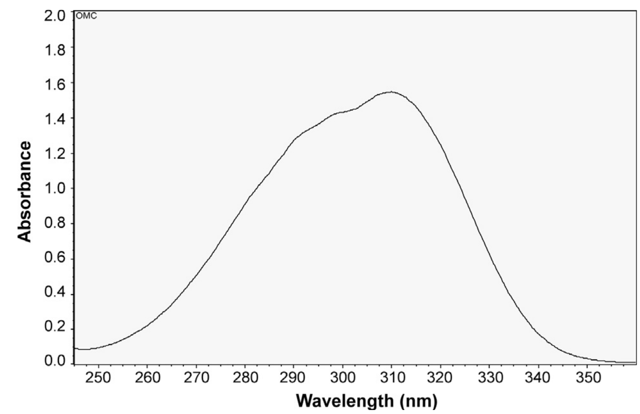

Fig. 2. Absorption spectrum of OMC in ethanol.

"special" bond allows the OMC to have its maximum absorption peak at a wavelength of 310 nm, as shown in its absorption spectrum (Fig. 2). The molar absorption coefficient (ε) of the OMC is quite high, approximately 22000–24000 $M^{-1} cm^{-1}$ [67].

The OMC presents two isomers (cis and trans), being that in sunscreens only the trans isomer is found, while in other sun protection products it is possible to find one or both isomers [69]. Some studies have shown that when exposed to sunlight, the OMC undergoes a photo-isomerization of the trans (E) isomer to the cis (Z) isomer [56,67,68]. Although the two isomers have similar maximum wavelengths, the cis isomer has a substantially lower molar absorption coefficient (12000 $M^{-1} cm^{-1}$) [56,67], which decreases the efficiency of the OMC as a UVB filter [56,68]. Both isomers also form degradation products (4-methoxybenzaldehyde (4-MBA) and 2-ethylhexanol (2-EH)) and can further dimerize to form various cyclodimers [47, p. 349]. Some of these photoproducts have already been isolated and characterized [47, p. 349]). For example, the photolysis mixture of OMC has been shown to be more toxic to mammalian cells than the OMC alone [20, p. 48]), but it turns out that this study was not able to assess the toxicity of the individual components of the OMC photolysate. Stein et al. succeeded for the first time, in 2017, in isolating, characterizing and evaluating the cytotoxicity of the OMC photoproducts, including cyclodimers. The results obtained suggest that different components of the OMC photolysate contribute differently to its cellular toxicity [91, p. 348]).

Taken together, these data raised the hypothesis that the toxicity of the OMC may increase due to its photo-isomerization after exposure to UV radiation [20,26] through, for example, an interference with cellular processes or an induction of oxidative damage on human skin [20]. Currently it is known that UV radiation can lead to reactive oxygen species (ROS) formation, by the epidermal chromophores, but the formation of ROS is further stimulated when there is a previous absorption of sunscreens/solar filters [26,27,95]. In this sense, it has been proposed the polymeric nano-encapsulation as a strategy for chemical stability. In the case of the OMC, a study already showed that the nano-encapsulation of poly (D, L-lactide) (PLA) can stabilize this UV filter, without losing its efficiency as an absorber. The aim is to reduce the contact between the UV filter and the skin surface. More specifically, with the aid of the nanoparticles, the release of the OMC is