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Neurotoxic effect of active ingredients in sunscreen products, a contemporary review

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ABSTRACT

Sunscreen application is the main strategy used to prevent the maladies inflicted by ultraviolet (UV) radiation. Despite the continuously increasing frequency of sunscreen use worldwide, the prevalence of certain sun exposure-related pathologies, mainly malignant melanoma, is also on the rise. In the past century, a variety of protective agents against UV exposure have been developed. Physical filters scatter and reflect UV rays and chemical filters absorb those rays. Alongside the evidence for increasing levels of these agents in the environment, which leads to indirect exposure of wildlife and humans, recent studies suggest a toxicological nature for some of these agents. Reviews on the role of these agents in developmental and endocrine impairments (both pathology and related mechanisms) are based on both animal and human studies, yet information regarding the potential neurotoxicity of these agents is scant. In this review, data regarding the neurotoxicity of several organic filters: octyl methoxycinnamate, benzophenone-3 and −4, 4-methylbenzylidene camphor, 3-benzylidene camphor and octocrylene, and two allowed inorganic filters: zinc oxide and titanium dioxide, is presented and discussed. Taken together, this review advocates revisiting the current safety and regulation of specific sunscreens and investing in alternative UV protection technologies.

1. Introduction

Sunscreen application is the main strategy used to prevent the maladies inflicted by the sun since the 1930s. Unfortunately, although global use of sunscreen is continuously on the rise, so is the prevalence of malignant melanoma − a cancer type which is mainly caused by sun exposure [1–4]. There are several types of electromagnetic radiation emitted by the sun. One type − ultraviolet (UV) radiation − is composed of three wavelengths: UVA rays, which range at 320–400 nm and are not absorbed by the ozone layer, UVB rays, which range 290–320 nm and are partially absorbed by the ozone layer, and UVC rays, which are stopped by the ozone layer. The detrimental effects of exposure to UVA and UVB rays, which can cross the epidermis, have been reviewed and it was concluded that such exposure leads to reactive oxygen species (ROS) generation, DNA/protein/lipid damage, activation of various signal transduction pathways, compromised skin defense systems, altered growth, differentiation, senescence and tissue degradation, to name a few [5–7]. Two kinds of UV filters are currently being used in sunscreens for minimization of these adverse effects: organic (chemical) filters, e.g. octyl methoxycinnamate (OMC), benzophenone-3 (BP-3) or octocrylene (Table 1), which absorb light in the UV range, and inorganic (physical) filters, zinc oxide (ZnO) and titanium dioxide (TiO_2), which scatter and reflect UV rays. Sunscreens are usually comprised of more than one of these UV filters: organic, inorganic or a mixture of both types, which gives broad-spectrum of protection. Beyond its debatable efficiency, questions regarding the main ingredients of different sunscreens are being raised in recent years, mainly about the prevalence of these ingredients in the environment and about their potential toxicity.

1.1. Human exposure and detrimental effects

Many factors might influence human exposure to UV filters: geographic location, season, lifestyle, gender or occupation, which means it can be highly individualized. For instance, a study in Australia showed 56% of people apply sunscreens at least 5 days per week, and 27% of

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Table 1
Organic UV filters.

International nomenclature of cosmetic ingredients (INCI)	*United States adopted name (USAN)*	*Other names*
UVB filters		
4-methylbenzylidene camphor*	Enzacamene	
Homosalate	Homosalate	
Isoamyl-*p*-methoxycinnamate	Amiloxate	
Octyl dimethyl PABA	Padimate O	OD-PABA
Octyl methoxycinnamate	Octinoxate	2-ethylhexyl 4-methoxy cinnamate
Octyl salicylate	Octisalate	2-ethylhexyl salicylate
p-aminobenzoic acid	p-aminobenzoic acid	4-aminobenzoic acid, PABA
Triethanolamine	Trolamine salicylate	
UVA filters		
Disodium phenyl dibenzimidazole tetrasulfonate	Bisdisulizole disodium	
Butyl methoxydibenzoylmethane	Avobenzone	
Menthyl anthranilate	Meradimate	
Terephthalylidene dicamphor sulfonic acid	Ecamsule	Mexoryl SX
UVB-UVA filters		
Benzophenone-3	Oxybenzone	2-hydroxy-4-methoxybenzophenone
Benzophenone-4	Sulisobenzone	
Benzophenone-8	Dioxybenzone	
3-Benzylidene camphor[a]		Mexoryl SD
Bis-ethylhexyloxyphenol methoxyphenyl triazine[a]	Bemotrizinol	Tinosorb S
Cinoxate	Cinoxate	
Drometrizole trisiloxane[a]		Mexoryl XL
Methylene bis-benzotriazolyl Tetramethylbutylphenol[a]	Bisoctrizole	Tinosorb M
Octocrylene	Octocrylene	2-ethylhexyl 2-cyano-3,3-diphenylacrylate
Phenylbenzimidazole sulfonic acid	Ensulizole	

[a] Not approved by the Food and Drug Administration, used in other parts of the world.

people use it less frequently − 2 or fewer days per week [8] and a study in Denmark showed 65% of the sunbathers used one or more sunscreens [9].

Dermal exposure is the most relevant entry route of chemicals related to sunscreen use, however considering a common human behavior related to sunscreen application, e.g. eating and drinking with sunscreen applied on hands and lips, gastrointestinal or pulmonary exposure should also be considered [10–12]. The typically recommended mode of application (2 mg/cm^2) [13] implies a single dose of sunscreen product may be as large as 40 g, assuming application on the total body surface (2 m^2 for an average adult male), which for an average adult male weighting 78 kg and a typical concentration of about 10% of active ingredient in a commercial product, means maximum exposure around 50 mg/kg body weight (bw) [14]. Simple calculation suggests that with a maximum skin penetration up to 5% for some organic filters [15], the total amount of compound absorbed from a single application might be up to 200 mg, or 2.56 mg/kg bw, assuming an average bw of 78 kg for adult males. However, with application frequently thinner than recommended, partial body cover and different properties of compounds, these doses are usually much lower. For instance, a study on Australian population showed that the median daily amount of sunscreen applied was 1.5 g/day (range, 0–7.4 g/day) and the median quantity of sunscreen applied was 0.79 mg/cm^2 [8], whereas sunbather in Denmark applied on average 0.5 mg/cm^2 [9], in both cases it was less than half the amount needed to achieve the labeled sun protection factor.

Levels of UV filters found in human samples are usually low. In one epidemiological study, 2517 urine samples from United States (US) general population were analyzed for the presence of benzophenone-3 (BP-3), as part of the 2003–2004 National Health and Nutrition Examination Survey [16]; BP-3 was detected in 97% of the samples, with mean concentration of 22.9 ng/ml and 95th percentile concentration of 1040 ng/ml. In another study, investigating correlation between couples' presence of urinary benzophenone-type UV filters and sex ratio of their offspring, the mean concentrations of these compounds ranged from 0.05 ng/ml to 8.65 ng/ml, with BP-3 as the most predominant among the study population (samples collected between 2005 and 2009 in Michigan and Texas) [17]. Interestingly, about nine times higher than previously reported levels of BP-3 (up to 13000 ng/ml, average around 200 ng/ml) were found in urine samples collected in 2007–2009 from Californian females, which is probably a result of specific demographics [18].

The experimental studies confirm substantial absorption and distribution of organic filters, whereas inorganic filters seem to penetrate the human skin in a minimal degree. When adults applied a sunscreen formulation containing 10% of BP-3, 4-methylbenzylidene camphor (4-MBC) and octyl methoxycinnamate (OMC) on a daily basis (2 mg/cm^2) for a week, the mean urine concentrations for these ingredients were 60, 5, 5 ng/ml for females and 140, 7, 8 ng/ml for males, respectively [19]. At the same time, maximum plasma concentrations for these ingredients, reached 3–4 h after application, were 200, 20, 10 ng/ml for females and 300, 20, 20 ng/ml for males, respectively. Similar findings were reported following a 4-day exposure to these ingredients, which were detectable in the plasma of human males and females merely 2 h following application [20]. More data on human skin penetration and distribution of various UV filters, both organic and inorganic, can be found in recent reviews [21,22,15].

Of importance, some UV filters were also found in human milk samples. In a cohort study between 2004 and 2006, 54 human milk samples were analyzed; UV filters were detectable in 46 samples and levels were positively correlated with the reported usage of UV filter products [23]. Concentrations of ethylhexyl methoxy cinnamate (EHMC), octocrylene (OC), 4-MBC, homosalate (HMS) and BP-3 ranged 2.10–134.95 ng/g lipid, with EHMC and OC being most prevalent (42 and 36 positive samples, respectively) and an average of 7 positive samples for the other three [23]. In other study, levels of BP-3 in maternal urinary samples taken in gestational weeks 6–30 were positively correlated with the overall weight and head circumference of the baby [24]. These reports rise concerns about potential prenatal exposure and developmental toxicity of UV filters.

Besides intentional sunscreen application, additional routes might intensify human contact, namely occupational and environmental exposure. Workplace contact may be a source of substantial exposure to sunscreens, especially inorganic filters − nanoparticles (NPs) of ZnO