Chapter 5

About Suncare Products

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Additional information is available at the end of the chapter

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1. Introduction

The prevalence of skin cancer varies greatly according to the geographic location and is developing rapidly in Western countries. This type of cancer is most frequent in fair-skinned people. In Australia, the rate of melanomas increased annually by 6.3% in men and 2.9% in women between 1959 and 1985. This type of cancer is the most frequent one in fair-skinned people. Since 1985, the rate has levelled off, which is reassuring even though the incidence of skin cancer in Australia is the highest in the world [1] (table 1) [2], followed by New Zealand and Norway [3]. As a comparison, we can look at the rate of non-melanoma skin cancer (NMSC) in Japan, which is between 1.2 and 5.4 per 100,000, that is to say a factor of 50 compared to Australia [4]. Skin cancer in children is rare. In teenagers (from 15 to 19 years old) the prevalence in England is 10 cases per million per year for melanomas and 24 cases per million per year for NMSC. The risk factors are: a family history of melanomas, *Xeroderma pigmentosum* [5] and pathologies responsible for states of immunosuppression. Cases of congenital melanomas are extremely rare [6]. Excessive sun exposure has long been recognised as the most important environmental factor to be taken into account; indeed, ultra-violet radiation (UV) is the cause of 90% of NMSC and 67% of melanomas [7]. The high incidence of skin cancer in certain countries of the world is therefore not just down to chance but has a direct link to the population's skin type (fair-skinned, blue-eyed people who burn easily, who never tan and who often have freckles) [8] and to the level of sunshine [9]. Although UV rays only represent 3% of the total radiation which reaches Earth, from a point of view of energy, it is thought that they account for 10% of light energy [10]. Mountainous regions bring a greater risk of developing sunburn, as the quantity of UVB increases by 4% every 300 metres [11], and in a similar way, the position with relation to the equator is of utmost importance, (the risk is greatest around the Tropics). UV radiation (UVA and B) causes alterations in DNA by either direct or indirect actions (by means of an oxidizing stress). The types which react to oxygen can cause either an increase in cell proliferation or their apoptosis, accordingly [12]. The notion of

phototypes, put forward by Fitzpatrick as early as 1975 within the framework of the care of patients treated with PUVA therapy, is linked to the concept of sun-reactive skin. This scale enables Caucasian subjects to be classed according to their sensitivity to UV rays. At first, 4 phototypes were established, called I, II, III and IV (Table 2), then this scale was later extended to include phototypes V (brown skin or Asian skin) and VI (black) [13]. A classification concerning Japanese people was also drawn up by Kawada [14]. The three corresponding groups are JI (always burn and rarely tan), JII (burn and tan moderately), JIII (never burn and always tan). These three groups should be linked to the Caucasian phototypes II, III and IV [15]. In the 1990s, JP Césarini introduced the notion of melano-compromised subjects (Phototypes I and II), melanocompetent subjects (Phototypes III and IV) and melanoprotected subjects according to their varying capabilities to protect themselves against skin cancer [16]. The best level of photoprotection is reached by black subjects, who are shown to have a low incidence of skin cancer (1 to 2% of cancers affecting black people are skin cancers compared to 20 to 30% for Caucasians). The phototypes are linked to melanin, which is a biopolymer functioning as a filter and which enables black people to produce an SPF (Sun Protection Factor) of around 13. The dispersion of melanosomes and their lack of degradation throughout the keratinization process forms an effective barrier. A black person's melanin filters twice as much UVB radiation as a Caucasian's melanin. The black epidermis is much more protected than a Caucasian one, as it transmits 7.4% of UVB radiation and 17.5% of UVA radiation compared to 24 and 55% for a Caucasian epidermis. In terms of Minimal Erythemal Dose (MED), it can be observed that this dose is between 6 and 33 times higher in black subjects [17]. It is important to create new classifications on a regular basis because of the interbreeding of races in the population. For example, in 1990, the US Census Bureau registered 6 races and 23 sub-types in the United States; 10 years later, the Census Bureau still counted 6 categories, but the number of sub-types had increased to 67, creating a multiplicity of sensitivities to the sun [18]. It seems that precautions taken by people who work outside to protect themselves from the sun are related to their phototype, as an American study shows that fair-skinned people are more aware in this respect [19]. The current way of life in industrialized countries goes hand in hand with an increase in the frequency of the length of exposure to the sun during leisure time. Contrary to previous centuries where pale skin tones were all the rage, the fashion of having a sun-tan, which began in the Thirties, is still current. The SUVIMAX study which was conducted in France in 1994 showed that in the cohort of 7,822 subjects questioned, 196 (110 women and 86 men) had travelled to a country with high levels of sunshine (high UV index) within the previous year and for a period of at least one month. Women, in particular, appear to be most concerned with daily exposure to sunshine (more than 2 hours per day) and admit that "getting a tan" is very important for them [20]. Sunbathing is still popular. Professor Dubertret is pessimistic and considers that if nothing is done in the way of prevention campaigns, the rate of skin cancer will double every ten years and a child born in 2000, if he behaves in the same way as his parents regarding his exposure to the sun, will have a 1 in 75 risk of developing a melanoma and a 1 in 7 risk of developing basocellular cancer [21]. The behavior of young Europeans tends towards improvement. Indeed, an increase in the use of sun products throughout exposure can be observed. In 10 years (between 1990 and 2000), the use of sun products increased from 52 to 63% in boys and from 80 to 87% in girls. It is a pity

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that a minority is still so resistant to using sun products [22]. On the other hand, young Australians (from 12 – 17 years old) largely ignore prevention campaigns and the use of sun products decreased between 1993 and 2000 (going from 54 to 36% for teenagers in general and from 73 to 50% for girls in particular) [23]. A second more optimistic study praises the SunSmart television advertising campaign, which seems to be bearing fruit [24]. Indeed, the slogans are well-chosen and are likely to bring about a change of attitude; as proof: « Leave your hat on » (1991 – 1992), « How to remove a skin cancer » (1996 – 1998) and « No tan is worth dying for: Clare Oliver » (2008). In short, depending on the panels and on the authors, opinions differ [25]. The fact remains that young people in general, and more particularly young Americans (from the south of the USA) are stubborn and are still fond of exposing themselves to the sun. Sunburn at the end of the weekend is not uncommon [26]. A lot of efforts still have to be made, as only 1/3 of parents questioned say that they prefer activities for their children which avoid exposure to the sun and confirm that they apply sun products whilst doing beach-based activities [27]. Public awareness campaigns are necessary, as childhood is a key stage and it is important to understand that people who do not want to use sun products whilst continuing to expose themselves to the sun, do so for aesthetic reasons, in order to have a tan [28]. We set out, therefore, to present a method for topical skin protection: the use of sun products.

Countries	Prevalence
France	7/100000
Sweden	11/100000
US	14/100000
Australia	50/100 000

Table 1. Prevalence of skin cancers - 1995 [2]

Phototypes	Sensitivity to sunlight
I	Always burns, never tans
II	Burns easily, tans minimally
III	Burns moderately, tans gradually to light brown
IV	Burns minimally, always tans well to moderately brown
V	Rarely burns, tans profusely to dark
VI	Never burns, deeply pigmented

Table 2. Phototypes according to the Fitzpatrick classification

2. Topical photoprotection

2.1. Definition

There are many methods of sun protection, such as photoprotection by clothing, systemic photoprotection (medicine and dietary supplements) and topical photoprotection, using sun products with a variety of dosage forms.

Sun products are used to avoid skin damage due to the sun. These products contain molecules which can work through absorption or by reflecting UV rays [29].

The classification of sun products as either cosmetics, or as over-the-counter medicines, differs according to the health authority governing bodies concerned.

The Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSaPS) [The French Agency for Health Safety and Health Products – equivalent to the FDA – Food and Drugs Administration (USA) and the MHRA (UK) remains cautious, saying that "Sun products are effective in the prevention of actinic erythema" It insists, by saying that their preventive effects concerning photo-ageing and skin cancer is yet to be proved [30]. In France, although the Code de la Santé Publique (Public Health Code), defines cosmetics in a general way, it does not, however, give a specific definition for sun products [31].

In the USA, an over-the-counter sunscreen drug product in a form suitable for topical administration is generally recognized as safe and effective and is not misbranded if it meets each condition. Here, we are talking of harmlessness and of efficacy (but without being specific about possible prevention regarding effects of UV radiation) [32]. This notion of harmlessness can be found in the Public Health Code [33], in European directives [34] and more recently in regulation N°1223/2009 [35] which has just been written and whose aim is to suggest a more legible type of legislation bringing together successive directive demands.

2.2. Which regulatory status for sun products?

2.2.1. Different categories of sun products

As we mentioned earlier, the status of sun product is not unique and differs from country to country. We will mention more specifically the two main legislations on suncare products, namely the European and American ones. It should be noted that the indices which may appear on the packaging of sun products are not the same for European products as they are for American ones (Table 3). In Europe, all of the products which have an SPF (Sun Protection Factor) lower than 6 are not considered as sun products (compared to 2 according to American legislation). The number of categories is bigger in Europe than in the USA (4 large categories and 8 indices in Europe compared to 3 large categories and an infinite number of indices which could be seen on the packaging in the USA. In Europe, in order to make the consumer's life easier and to avoid swamping them with too many indices, a standard index system on packaging was established. Therefore, on the market, products with indices of 17, 24, 36, 54 etc. cannot be found. The index value is always rounded down. In Europe, the tendency is to

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reduce the number of indices, and the aim of the creation of an index of 50+ concerning all products which have a determined SPF equal to or higher than 60 was to avoid having indices higher than 100 on packaging, as this could have led the consumer to believe that the product provided total protection.

	European regulation	American regulation
Different categories of sunscreens	- Low protection SPF labelled: 6, 10 - Moderate protection SPF labelled: 15, 20, 25 - High protection SPF labelled: 30, 50 - Very high protection SPF labelled: 50+	- Minimal sun protection product (2 < SPF < 12) - Moderate sun protection product (12 ≤ SPF < 30) - High sun protection product (SPF ≥ 30)

Table 3. Different categories of sunscreens

2.2.2. Authorized filters

Whichever legislation is considered, a limited number of filters are authorized in the formulation of sun products. In Europe, Appendix VI of the Regulation lists the 26 authorized filters, that is to say 25 organic filters and one screen, titanium dioxide, each one having a maximum concentration of use (% m/m) and perhaps a list of comments which should feature on the packaging. In the USA, the original list was made up of 16 filters (15 filters and 1 screen). In the period from 1997 to 2008, 8 filters recognized safe and effective were gradually added to this list. The FDA gradually authorized a certain number of products which were synthetized and patented in Europe in order to beef up the original list. It should be noted that zinc oxide is not mentioned in Appendix VI of the Regulation (Table 4). The concentration of zinc oxide is therefore not limited. This, however, remains theoretical, as the limit is imposed by its dosage form, as in high percentages of concentration, a paste is obtained, which would be difficult to market. Seventeen filters are currently in common between the European and American legislation.

2.2.3. The combination of different filters or the combination of filters with active ingredients

European formulators have a great deal of freedom. They can combine as many filters as they want, as long as the combinations are not already patented, of course. They can also combine filters with active ingredients which have a softening, antioxidizing or soothing effect, etc. They have to check that the raw material they want to incorporate is not banned and they must check to see if the material is on a list if regulated ingredients (Appendix III: substances with restricted use in particular). In the USA, combinations with **protectants** are authorized within the limits of the maximum authorized concentrations (Table 5). **A skin protectant drug product is defined as «a drug product that temporarily protects injured or exposed skin or mucous membrane surfaces from harmful or annoying stimuli, and may help provide relief to such surfaces».**

INCI name/American name (trade name)	C_{max} authorized (Europe)	C_{max} authorized (US)
Aminobenzoic acid	/	15%
Cinoxate	/	3%
Dioxybenzone	/	3%
Meradimate	/	5%
Trolamine salicylate	/	12%
Zinc oxide	/	25%
Camphor benzalkonium methosulfate (Mexoryl SO®)	6%	/
Homosalate (Eusolex HMS, Néohélipan HMS, Parsol HMS)	10%	15%
Oxybenzone (Eusolex 4360, Uvinul M40)	10%	6%
Phenylbenzimidazole sulfonic acid, Ensulizole (Eusolex 232, Parsol HS, Néohéliopan Hydro USP)	8% (in acid form)	4%
Terephtalydene dicamphor sulfonic acid, Ecamsule (Mexoryl SX)	10% (in acid form)	10%
Butylmethoxydibenzoylmethane (Eusolex 9020, Parsol 178)	5%	3%
Benzylidene camphor sulfonic acid (Mexoryl SL)	6% (in acid form)	/
Octocrylene (Uvinul N539T, Eusolex OCR, Parsol 340, Néohéliopan 303 USP)	10% (in acid form)	10%
Polyacrylamidomethylbenzylidene camphor (Mexoryl SW)	6%	/
Ethyl hexyl methoxycinnamate, Octinoxate (Uvinul MC 80, Eusolex 2292, Parsol MCX, Néohéliopan AV)	10%	7.5%
PEG-25 PABA (Uvinul P25)	10%	/
Isoamyl p-methoxycinnamate, Amiloxate (Néohéliopan E1000)	10%	10%
Octyl triazone (Uvinul T150)	5%	5%
Drometrizole trisiloxane (Mexoryl XL)	15%	
Diethylhexylbutamidotriazone (Uvasorb HEB)	10%	3%
4 -methylbenzylidene camphor, Enzacamene (Eusolex 6300, Néohéliopan MBC, Parsol 5000)	4%	4%
3-benzylidene camphor (Unisol S22)	2%	/
Ethylhexylsalicylate, Octisalate (Eusolex OS, Néohéliopan OS, Dermoblock OS)	5%	5%
Octyl dimethyl PABA, Padimate O (Eusolex 6007)	8%	8%
Benzophenone-4 et 5 , Sulisobenzone (Uvinul MS40)	5% (in acid form)	10%
Methylene bis-benzotriazolyl tetramethylbutylphenol, Bisoctrizole (Tinosorb M)	10%	10%
Disodium phenyl dibenzimidazole tetrasulfonate (Néohéliopan AP)	10% (in acid form)	/
Bis-Ethylhexyloxyphenol Methoxyphenyl Triazine, Bemotrizinal (Tinosorb S)	10%	10%
Polysilicone 15 (Parsol SLX)	10%	/
Titanium dioxide	25%	25%
Diethylamino hydroxybenzoyl hexyl benzoate (Uvinul A+)	10%	/

Table 4. Authorized UV-filters in Europe and in US

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	US	Europe
1 - Allantoin	0.5 – 2%	/
2 - Cocoa butter	50 – 100%	/
3 - Cod liver oil	5 – 13.56%	/
4 - Dimethicone	1 à 30%	/
5 - Glycerin	20 – 45%	/
6 - Hard fat	50 – 100%	/
7 - Lanolin	12.5 – 50%	/
8 - Mineral oil	50% 30 – 35% in combination with colloidal oatmeal	/
9 - Petrolatum	30%	/
10 - White petrolatum	30%	/
11 - Aluminium hydroxyde gel	0.15 – 5%	Annex III
12 - Calamine	1 - 25%	/
13 - Kaolin	4 – 20%	/
14 - Zinc acetate	0.1 – 2%	Annex Colorant (CI 77950)
15 - Zinc carbonate	0.2 – 2%	Annex III (1% expressed in Zinc)
16 - Zinc oxide	1 – 25%	Annex Colorant (CI 77947)
17 - Colloidal oatmeal	0.007% minimum 0.003% minimum in combination with mineral oil	/
18 - Topical starch	10 – 98%	/
19 - Sodium bicarbonate	/	/

Three ingredient groups in US : group 1 [1 to 10] – group 2 [11 to 16] and group 3 [17]

The active ingredients in each of these groups can be combined only with the other active ingredients in the same group. Active ingredients in different groups cannot be used in the same drug product. For example, cocoa butter can be combined with glycerine, but not with aluminium hydroxide gel.

Table 5. Comparative regulation of ingredients called « protectants » in US

2.2.4. Labelling rules

The comments which must be included on the packaging are presented in Table 6. The same concern for public health governs the labelling rules, no matter which legislation is concerned. It is a pity that at present, on the packaging of European sun products, there is no clear reference to the size of the recommended dose of the product which should be applied on the skin. This lack is currently being studied, and it has to be said that having directions on the packaging

as to how much of the product should be used would be very useful, as it is known that consumers do not use as much of the product as they should, on average 4 times less [36]. It is known that the effect is linked to the dose. A good initiative of the Colipa should be noted concerning sun protection cosmetics: this committee has in fact created a logo (Figure 1) which reminds us that the product in question provides protection against UVA rays. A ratio of UVA efficacy/UVB efficacy equal to or lower than 3 was imposed in order to avoid products which only protect against UVB rays.

	EU	**Europe**
Categories of sunscreens	2 ‹ SPF ≤ 12 : « provides minimal » or « provides minimum » « minimal » or « minimum » « protection against » « sunburn » or « sunburn and tanning » or "for skin that sunburns minimally" 12 ≤ SPF ‹ 30 : « provides moderate » or "moderate" « protection against » « sunburn » or « sunburn and tanning » or "for skin that sunburns easily" SPF ≥ 30 : « provides high » or "high » « protection against » « sunburn » or « sunburn and tanning » or "for skin highly sensitive sunburn"	SPF : 6 – 10 Low protection SPF : 15 – 20 – 15 Moderate protection SPF : 30 – 50 High protection SPF : 50+ Very high protection
Warnings	"When using this product keep out of eyes. Rinse with water to remove" "Sto use and ask a doctor if rash or irritation developps and lasts"	/
Particular allegations	« retains SPF after 40 minutes of activity in the water or sweating or perspiring » « retains SPF after 40 minutes of activity in the water or sweating or perspiring"	Water resistant Very water resistant
Quantity to apply	« apply » « liberally » or « generously » or « smoothly » or « evenly » ""reapply as needed or after towel drying, swimming, or sweating or perspiring"	
Cas of childrens	« children under 6 months of age : ask a doctor »	No sun exposure before 36 months

Table 6. Labelling of sunscreens

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Figure 1. UVA logo

2.2.5. Procedures to be followed

In Europe, it is just necessary to draw up a file on cosmetics which should remain relatively short. This is only consulted by authorized personnel from the authorities which are concerned (AFSSaPS or the Répression des Fraudes [Fraud Prevention]) in case of inspection. The status of an over-the-counter medicine is very restricting as solid clinical studies must back up the request for such a status. As an example, we can look at the Anthélios SX® product by the Laboratoires La Roche Posay whose sale is now authorized in the USA following FDA approval. The file was backed up by 28 clinical studies including 2500 patients from 6 months to 65 years of age. It can be said, therefore, that sun products destined for the American market are ones which have sufficient hindsight in Europe (enough time has lapsed to enable clinical studies to be compiled). What is more, very few active ingredients are present in the formula: ecamsule, avobenzone and octocrylene.

2.3. Dosage forms

Sun products come in different dosage forms: liquid forms (oils), thick pasty forms (emulsions which are referred to as milks or creams according to the texture) and solid forms (sticks). The most interesting forms are the systems which contain 2 phases enabling hydro- and liposoluble filters to be incorporated together. The role of the excipient is a minor one, and will have little influence on the SPF measured. However, it will have an important role to play in terms of how the product is spread [36], in terms of its substantivity (a sun product must stay on the surface and the phenomenon of transdermal penetration must be reduced to as little as possible) [37]. Pickering emulsions are interesting as their formula contains titanium dioxide which not only carries out the role of an active sun-protection ingredient but also that of an emulsion stabilizer [38].

2.3.1. Liquid forms: Sun oils and waters

Oils and waters are single-phase systems and are forms which provide minimal sun protection. Generally, they are composed of thermal water to which a hydrophilic filter is added. As for

sun oils, they are generally composed of a vegetal oil, such as monoi, for example, or coconut or sesame oil, to which one or more lipophilic filters is added.

2.3.2. Paste forms: Gels and emulsions

Gels, often called "sun jellies", are forms which are not very photoprotective. These are aqueous or hydroalcoholic phases (the latter being quite incompatible with exposure to the sun!) which are thickened using a derivative of cellulose (carboxymethyl cellulose, for example) or a derivative of carboxyvinylic acid and incorporating a hydrophilic filter.

As for emulsions, they are the most commonly used dosage forms in the field of topical photoprotection. According to their viscosity and therefore their use limited to small surface areas (the face for example), or adapted to large areas (the whole body), they are referred to either as milks or creams. Whichever they may be, these forms provide a wide range of SPF values, going up to 50+. As they are two phase systems, (containing a hydrophilic phase and a lipophilic phase), they offer the great advantage of enabling all sorts of combinations of filters (hydro- and lipophilic ones) to which screens (such as zinc oxide and titanium dioxide) can be added. Lipophilic aqueous emulsions (W/O) are to be preferred due to their water-resistant character.

2.3.3. Solid forms: Sticks

The stick is a highly photoprotective cosmetic form which is adapted for application on small surface areas, obviously for the lips, and also for the sides of the nose, for example. A stick is made up of a mixture of waxes (animal wax, such as bees' wax, or vegetable waxes such as carnauba wax) which act as a "spine" for the finished product and give it its hardness, fats (vaseline, shea butter, etc.) and oils (sweet almond, jojoba, etc.). Lipophilic filters and screens are then incorporated into this mixture.

2.4. Determining the efficacy

2.4.1. Efficacy indicators: SPF and UVA-PF

In France, article L 5131-6 of the Public Health Code states that " a cosmetic product can only be put onto the market free of charge or against payment if the manufacturer, or their representative, or the person for whom the cosmetic product is made […], effectively makes available to the controlling authorities […] proof of the effects that it is claimed to have, when it is warranted by the nature of the effect or of the product". As for over-the-counter products, clinical trials must have been carried out, of course, in order for the product to be able to be put onto the market, as in this case, it is a medicine.

2.4.1.1. A few words about sun protection factor

The Sun Protection Factor (SPF) is a factor which indicates the efficacy of a sun product regarding erythema, as UVB rays are 1000 times more erythemogenic than UVA rays [39]. If we briefly recount the history of sun products, everything started in the 1930's with the

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marketing of a certain number of products containing sun filters (such as benzyl salicylate) [40] and claiming to prevent sunburn, without being able to evaluate precisely the level of efficacy. At this time, the product Ambre solaire® by the chemist Eugène Schueller could be found on the market. At the time, no particular attention was paid to the molecules used and a certain number of ingredients used were likely to cause what Freund defined for the first time as Berloque Dermatitis [41]. From the end of the Second World War, the number of companies involved in the field of sun protection (Coppertone, Piz Buin, etc.) increased, and more and more knowledge was gained about efficacy. Some errors were committed, however, such as the Bergasol products (in the 1970's) which were formulated with bergapten, which is a molecule with photosensitizing properties which are nowadays well-known [42]. The efficacy indicators which were initially very low, defined by Blum et al in 1945 [43], gradually increased, eventually reaching the values of 50+ which we know today.

2.4.2. In vivo methods of determination

Currently, whatever the country, protocols can be found which have similar conditions (type of panel, mass of the product applied, type of lamp used, etc.).

2.4.2.1. Definition of the MED

The FDA defines the MED as the "the quantity of erythema-effective energy (expressed as joules per square meter) required to produce the first perceptible, redness reaction with clearly defined borders".

The Colipa [44] gives its own definition, a precision of time, as we know that sunburn is likely to develop over a 24-hour period: "The Minimal Erythema Dose in human skin is defined as the lowest UV dose that produces the first perceptible unambiguous erythema with defined borders appearing over most of the field of UV exposure, 16 to 24 hours".

2.4.2.2. Definition of SPF

An individual Sun Protection Factor (SPF_i) value for a product is defined as the ratio of the MED on product protected skin (MED_p) to the MED on unprotected skin (MED_u) of the same subject:

$SPF = MED_p$ (protected skin) / MED_u (unprotected skin)

The SPF for the product is the arithmetic mean of all valid individual obtained from all subjects in the test, expressed to one decimal place.

2.4.2.3. Information concerning the volunteers

The comparative elements between the Colipa and the FDA concerning the subjects selected are presented in Table 7. As we can notice, the selection conditions are very similar. In Europe, the selection of subjects is made following the visual determining of the phototype of the subjects and by questioning or by instrumental methods using a chromameter which converts the colours into a digital code comprising 3 coordinates (Lab system). Using these coordinates,

we can determine the ITA (Individual Typological Angle) which is proportional to the degree of pigmentation of the skin. The darker the skin, the smaller the angle [45, 46]. However, it is regrettable that the minimum number of subjects required by the Colipa in order to obtain valid results is only 10. The FDA demands double that number, which seems more reasonable. No notion of latent period between the tests is mentioned by the FDA. It is a pity that the presence of nevi is not totally unacceptable in the US, indeed, the link between multiple nevi and melanomas is a well-established fact. The risk of developing a melanoma for a person with multiple nevi, that is to say between 100 and 120, is 7 times higher than for someone who only has a few nevi (between 0 and 15) [47, 48, 49]. It would be interesting, therefore, to limit the tests to subjects with a low number of nevi. It also seems absurd to find references to people with phototype I skin, as these subjects are at risk of developing skin cancer [50]. It therefore appears useless to subject them to UV irradiation, whether it be natural or artificial.

	Colipa	**FDA**
Phototype	- Phototype I, II or III according to Fitzpatrick - or ITA°value > 28° by colorimetric methods	- Only fair-skin subjects with skin types I, II, and III using the following guidelines : I – always burns easily; never tans (sensitive) II – Always burns easily; tans minimally (sensitive) III – Burns moderately; tans gradually (light brown) (normal) (Skin type and Sunburn and tanning history based on first 30 to 45 minutes sun exposure after a winter season of no sun exposure)
Medical characteristics	- Exclusion of sensitive subjects (previous history of abnormal response to the sun) - children - pregnant or lactating women - subjects taking medication with photosensitising potential - subjects with dermatological problems - subjects accustomed to using tanning beds - subjects having marks, blemishes or nevi or presenting with existing sun damage	- Exclusion of sensitive subjects (previous history of abnormal response to the sun) - the presence of nevi, blemishes, or moles wille be acceptable if the physician's judgement they will not interfere with the study results.
Written consent	- Informed, written (signature) consent	- Legally effective written informed consent
Number of volunteers	- minimum 10 (10 valid results) - maximum 20	- minimum 20 (20 subjects must produce valid data for analysis) - maximum 25
Frequency of participation in tests	- Latence time of 2 months	/

Table 7. Characteristics of the panel

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A test will be considered as valid if "confidence limits (95% Confidence Interval) for the mean SPF should fall within the range of ± 17% of the mean SPF". In the case of a high level of uncertainty, the subject(s) having generated over-large standard deviation are excluded from the study.

2.4.2.4. The conditions of the test

2.4.2.4.1. Test area

The irradiation sites are similar whether it be for the Colipa or the FDA: between the scapula line and the waist. The minimum surface area required according to the FDA is one of 50cm² for an area, and of 4 to 5 cm² for a subsite area. For the Colipa, the minimum area for a product application site shall be 30 cm^2 and the maximum shall be 60 cm^2.

The dose of the product applied on the skin is **2 mg/cm**^{2} (this dose is universally recognized). The Colipa specifies that the quantity of the product applied on the skin before spreading should be 2 mg/cm^2 ± 2.5% (the sensitivity of the scales should be at least 0.0001 g, ie. with at least 4 decimal places). The product should be applied with a finger-cot and can be deposited with a syringe for liquid products, or for products which can be made into liquids after being warmed slightly. The Colipa states a quantity of 15 drops of the product for 30 cm^2 in order to obtain a homogenous distribution of the product. The application time is also measured and should be between 20 and 50 seconds according to the surface area in question. The products are applied in a randomized way.

The Colipa makes a clarification regarding the proximity of the test sites: there must be a minimum distance of 1 cm between the borders of adjacent product application sites.

A variable latent period is respected between application and irradiation: 15 minutes (FDA) or 15 to 30 minutes (Colipa).

The lack of information concerning the quantity of the product present on the skin after spreading is also regrettable. No *in vivo* method states the quantity of the product which remains on the finger-cot, a quantity which varies according to the nature of the product which is applied (a product which is either fluid or pasty, with either sticky or, on the contrary, film-forming ingredients).

The conditions of temperature of the room in which the tests are carried out are drawn up by the Colipa. It is recommended to use rooms with air-conditioning. However, the temperature range is quite wide (18 to 26°C).

2.4.2.4.2. The characteristics of the lamp used

The characteristics in terms of quality of emitted UV rays, of total irradiance and the uniformity of the beam are similar in Europe to the United States. The characteristics are the following: a solar simulator used for determining the SPF of a sunscreen product should be filtered so that it provides a continuous emission spectrum from 290 to 400 nm similar to sunlight at sea level from the sun at a zenith. No emission fluctuations should be seen through time and the

intensity of irradiation should be as uniform as possible. The material should be subjected to frequent radiometric controls.

The source of illumination should be either a tungsten light bulb or a warm white fluorescent light bulb that provides a level of illumination at the test site within the range of 450 to 550 lux (FDA) or a xenon arc solar simulator with a filtering system.

2.4.2.4.3. Determining the MED in practice

A series of UV radiation exposures expressed as joules per square meter is administered to the each subject with an accurately-calibrated solar simulator.

A Colipa – FDA comparison is presented in Table 8. The FDA suggests some examples for SPF from 8 to 15.

	Colipa	**FDA**
Unprotected skin	- a minimum of **5** sub-sites centred on the estimated MEDu shall be exposed with incremental UV doses using a recommended geometric progression of either **1.12** or **1.25**.	- a series of **5** exposures should be administered to the untreated skin. The doses selected shall be a geometric series represented by (1.25^n), wherein each exposure time interval is **25%** greater than the previous time .
Protected skin	- The centre of the UV dose range is that of the unprotected MED multiplied by the expected SPF of the product. - a minimum of **5** sub-sites centred on the estimated MEDu shall be exposed with incremental UV doses using a recommended geometric progression of either **1.12** or **1.25**	- **7** exposures - the doses selected shall consist of a geometric series of five exposures where the middle exposure is placed to yield the expected SPF plus two other exposures placed symmetrically around the middle exposure.
Measure	- 24 h after exposure	- 24 h after exposure

Table 8. MED determination

For a product with an SPF of 8, given that the MED must correspond to the dose or to the median time, it will be surrounded with values obtained according to a geometric sequence at a rate of 1.25:

0.64 x MED – 0.80 x MED – 1 MED – 1.25 Med – 1.56 MED

Furthermore, 2 doses placed symmetrically in relation to the median dose are added, here:

0.9 x MED and 1.10 x MED

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Sometimes, we speak in terms of SED (Standard Erythema Dose) which corresponds to the efficient erythemogenic exposure. For human beings, an SED corresponds to an exposure of 100 j/m^2. Caucasian subjects have an MED of between 150 j/m^2 (or 1.5 SED) and 600 j/m^2 (or 6.0 SED) according to the phototypes (as the Caucasian type includes phototypes which differ as much as phototypes I and IV) [51]. We can speak indifferently either in terms of dose or time.

2.4.2.5. Determining the UVA protection factor (UVA-FP)

2.4.2.5.1. Introduction

Although the protocol of determining the SPF is very clearly defined, both in Europe and in America, this is not the case concerning the UVA protection factor [52]. The two most frequently used methods are the IPD (Immediate Pigment Darkening) and PPD (Persistent Pigment Darkening) methods. Since 2007, taking the UVA protection in a sunscreen into account has become a necessity in Europe, with the establishing of 5 categories corresponding to no, low, medium, high and highest UVA protection [53].

2.4.2.5.2.- IPD and PPD methods

These methods are based on the evaluation of the Meirowski phenomenon consecutive to the action of UVA rays. To do this, a halide lamp or a xenon arc lamp equipped with UVB filters is used. The subjects who are recruited have phototypes III and IV because they are likely to develop a tan in the evening. If the reading takes place at a maximum of 2 hours after irradiation, we refer to the IPD (immediate pigment darkening) method. If the reading is taken later, we can refer to it as the PPD (persistant pigment darkening) method [54, 55, 56].

The UVA-PF is defined according to:

$$\text{UVA-PF} = \text{MIPDD}_{\text{protected skin}} / \text{DMIPDD}_{\text{unprotected skin}}$$

with MIPDD, Minimum Immediate Pigment Darkening Dose

or :

$$\text{UVA-PF} = \text{MPPDD}_{\text{protected skin}} / \text{MPPDD}_{\text{unprotected skin}}$$

with MPPDD, the Minimal Persistent Pigment Darkening Dose.

2.4.3. In vitro methods of determining the efficacy of sun products

2.4.3.1. Determining the SPF in vitro

There is no official method in this field. All the methods which are proposed are spectrophotometric methods based on the Beer Lambert law which links the absorbance of a sample to its concentration of active molecules. The principal of determining the SPF *in vitro* is based on measuring the transmittance of a sun product applied on various kinds of support. In the 1980's, Sayre and Agin studied different spectral light sources enabling them to correlate the results obtained respectively by *in vitro* and *in vivo* methods [58]. The first trials were carried

out on supports such as certain animal skins (mice and pigs) or even on human skin. In 1989, Diffey and Robson tested a new substrate called Transpore® (3M, St Paul, US), a cheap adhesive system [59]. Its supple texture means that it must be placed on a rigid plate (such as quartz). The main disadvantage for its use is that it has varying sizes of pores depending on the part of the roll of the material which is used (which means that the first and last 60cm of the roll must be discarded and that the pores vary in size from one roll to the next. It is interesting for testing simple formulas, however, the results obtained are very different from those observed *in vivo* for formulas including complex mixtures of filters [60]. The quartz plates can also be used alone. They have 2 disadvantages: they are expensive and as they are not disposable, they must be rigorously cleaned between 2 series of measurements. Even though they are able to be used in research, they seem to be quite unsuitable for industrial use [61]. Skin substitutes (Vitroskin®) provide an interesting analogy with real skin, but they are expensive and they have a limited length of use once they have been rehydrated [62]. Different synthetic substrates are currently used, such as polyvinylchloride film (Saran Wrap®), Teflon [63] and polymethylmethacrylate (PMMA) [64, 65]. Whatever support is chosen, its efficacy in UVB light is determined by calculation, by effecting the convolution product of the spectrum of the source, of the spectrum transmitted through the sample and of the spectrum of the erythemogenic efficacy (figure 2) [66] and by integrating the area under the curve in the following formula:

$$SPF = \frac{\sum_{290}^{400} E_\lambda S_\lambda \Delta\lambda}{\sum_{290}^{400} E_\lambda S_\lambda T_\lambda \Delta\lambda}$$

with E_λ being the spectral erythemogenic efficacy (International Committee on Illumination), S_λ being solar spectral irradiance and T_λ being the spectral transmittance of the sample.

2.4.3.2. In vitro determination of the UVA-PF

The Colipa published guidelines in 2007 for determining the UVA index *in vitro*. The initial UVA-PF is calculated using the UV absorbance spectrum which was adjusted to the labelled SPF. Sunscreen samples were then exposed to a single UV dose of 1.2 times the initial UVA-PF (in joules/m²). The final UVA-PF values for the samples were calculated from the adjusted absorbance spectrum after irradiation [67]. Other calculations made are those of the SPF/UVA-PF ratio, which must be lower than 3, and the critical wavelength λ_c (the wavelength under which the product is 90% effective) which must be above or equal to 370 nm according to the recommendations of the AFSSaPS.

At the same time, the FDA suggested an *in vitro* method for determining the efficacy in UVA rays. The *in vitro* UVA proposed is based on measurement of UV transmission through a sunscreen film. The absorbance curve was obtained, in this case after pre-irradiation with a UV dose specified as two thirds of the SPF in Minimal Erythemal Doses (MEDs) (1 MED = 20 SED), and the mean absorbance in the UVA1 range from 340 to 400 nm and the entire UV range from 290 to 400 nm were determined. The ratio of mean UVA1 absorbance to mean absorbance

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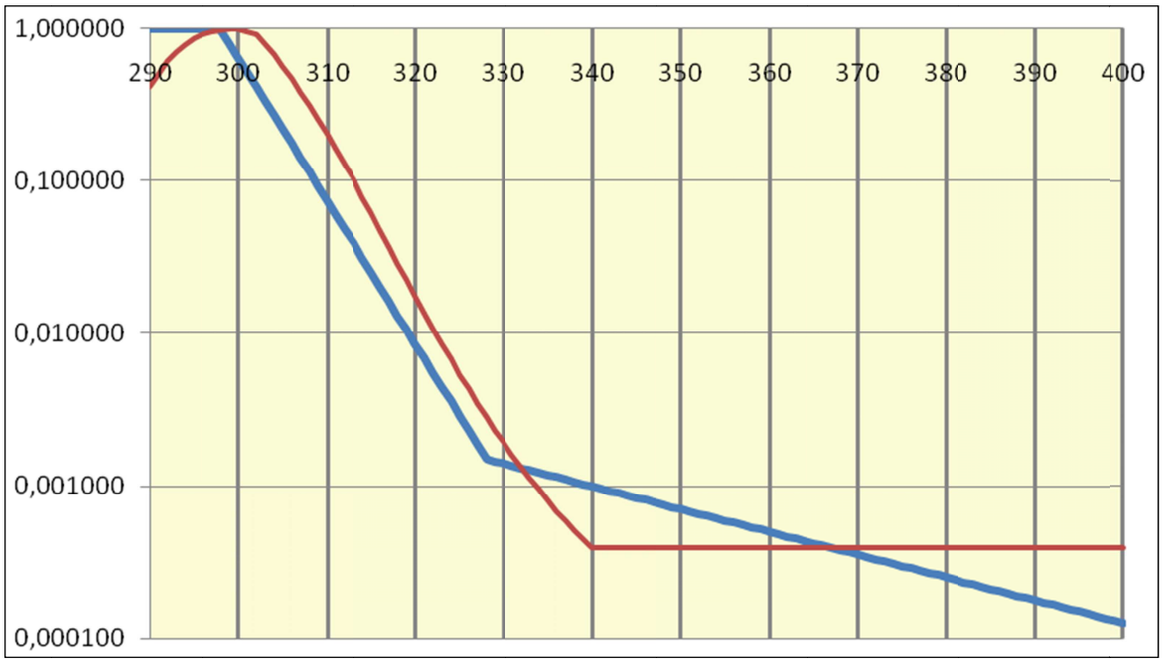

Figure 2. Variations of weighting coefficients for each wavelength concerning erythema and non-melanoma skin cancer (Norme CEI 60335-2-27, 2002)

determines the rating. There are 4 categories (ratio ≥ 0.2 "low – 1 star" ; ratio ≥ 0.4 "medium – 2 stars" ; ratio ≥ 0.7 "high – 4 stars" ; ratio > 0.95 "highest – 4 stars") [68].

2.5. Determining water-resistance and photostability

2.5.1. Determining water-resistance

The technique and the quantity of the product applied on the skin play an important role in the obtained level of photoprotection. The same applies to the water-resistance of products [69] which is an important element to take into account when choosing a product which is going to be used on the beach.

2.5.1.1. In vivo methods of determining water-resistance

The FDA and the Colipa propose protocols for determining the water-resistance of sun products [70, 71].

The principal is the same in both cases. The subjects are immersed in a swimming pool or a jacuzzi, etc. On the other hand, the way of interpreting the results is not done in the same way in Europe and in the United States.

In the United States, a product can display the words "water resistant" on the packaging and the SPF mentioned is the SPF obtained after 2 successive baths of 20 minutes. For the product to qualify as being "very water resistant", it must have undergone a test of 4 successive baths of 20 minutes.

In Europe, a certain number of pre-requisites must be checked before the test is carried out to ensure that the incertitude is less than 17% of the average SPF. A percentage of water resistance is calculated by comparing the SPF obtained after 2 successive baths of 20 minutes and the initial SPF. If the percentage is higher than or equal to 50% of the initial SPF, then the product is declared as being "water resistant". In the same way, a product is declared as being "very water resistant" if after 80 minutes of immersion (4 periods of 20 minutes) the percentage of water resistance is higher than or equal to 50%. In both cases, the SPF displayed is the initial one (obtained before immersion).

2.5.1.2. In vitro method of determining water resistance

Very few studies exist concerning the development of *in vitro* techniques. Work by Choquenet et al can be quoted, which, by analogy with the Colipa method, provide the necessary conditions for distinguishing water resistant products from products which can be washed away with water [72]. The authors recommend immersing the PMMA plates, coated with the product which is to be tested, in a bath of distilled water, shaken gently (5 $L.min^{-1}$) and at a temperature of 29 ± 2°C. The creams are applied to the PMMA plates and their SPF is measured using an integrating sphere spectrophotometer (Labsphère UV1000S) before and after immersion. As in the *in vivo* method, the product is deemed "water resistant" if the SPF after the bath is at least 50% of the initial SPF.

2.5.2. Determining the photostability of sun products

The photostability of sun products is an important criterion for two reasons: if the product is not photostable, its efficacy will decrease rapidly over time and the subject will thus no longer be sufficiently protected. Furthermore, the production of photo-oxidation products can lead to problems of skin tolerance [73]. It is advisable therefore to study the photodegradation profile of the filters incorporated into the excipients and to determine efficacy kinetics over time. Certain filters such as PABA [74] or benzophenones [75] are reputed to be very photostable. Other filters which are not very photostable, such as avobenzone, have a varying degree of stability according to the composition of the medium [76]. The filters can be studied alone or in a mixture, they can be irradiated after being placed on a glass plate in the UVB/UVA field and their photostability can be assessed by the dose of HPLC [77] or they can be studied *in vivo*. L'Oréal carried out an *in vivo* study in 2008 on 5 subjects. This study consisted in applying a product (SPF 15 ; FP-UVA 15) onto the volunteers' skin, formulated with 3 organic filters, octocrylene, avobenzone and Mexoryl SX®, irradiating them at doses ranging from 64 to 200% of the SPF, in retrieving the product from the skin and then dosing the filters. There was no significant difference between the rate of filters before and after irradiation, even for the high doses (200% SPF ie. 30 MED) [78]. A systematic study of the 18 UVB filters which are authorized in Europe enabled the filters to be ranked in ascending order of photostability. The filters which

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retain more than 90% of their efficacy after irradiation in a solar simulator are deemed to be photostable. Eight filters (PABA, Oxybenzone, Phenilbenzimidazole sulfonic acid, Octocrylene, Diethylhexylbutamidotriazine, 4-methylbenzylidene camphor, Benzophenone-5 and Methylene bis-benzotriazolyl tetramethylbutylphenol) appear to be interesting and likely to stabilize the formulas they are incorporated into [79].

2.6. Active ingredients

There are two categories of active ingredients, inorganic filters, also known as screens, and organic filters.

2.6.1. Inorganic filters or screens

Two screens could be used: titanium dioxide and zinc oxide which act by reflecting the ultraviolet rays. Both take the form of an inert, particularly photostable white powder [80, 81]. They were used for a long time in pigmentation, but were considered not to be very effective and were not very aesthetic due to the fact that they leave a white film on the skin sometimes called the "Pierrot's mask". The micronization of powders brought a solution to these 2 disadvantages [82, 83]. The reduction of the size of the particles from 200 nm to 15 nm makes the products more acceptable and coating them makes them disperse more easily in the chosen excipient. However, the reduction of the size of the particles raises certain questions, namely as to whether they can cross the skin barrier. Studies on pig skin show that micro-thin zinc oxide and titanium dioxide powders do not penetrate into the skin [84]. Similar results were obtained *in vivo* by the stripping method and showed that zinc oxide (Z-Cote Max® BASF) was restricted to the superficial layers of the epidermis, namely the *Stratum corneum* [85]. As for harmlessness, the results contrast. Some people argue that a risk exists, zinc oxide could have potentially genotoxic effects on human epidermal cells [86] and titanium dioxide could be cytotoxic and genotoxic on cell cultures (hamster ovary cells) [87]. For others, these ingredients are totally safe [88, 89]. Concerning efficacy, titanium dioxide proves to be the most efficient, as it gives an SPF value of 10 (Eusolex TS®) as opposed to 5 for zinc oxide (Z-Cote Max®) for the same incorporation percentage of 10%. It can be noted, however, that zinc oxide has a wider spectrum as it proves to be as efficient in the UVA field as in the UVB field, contrary to titanium dioxide which is 2.5 times less efficient in UVA rays as in UVB rays [90].

2.6.2. Organic filters

2.6.2.1. Introduction

It is a question of molecules which have one or more aromatic cycles associated with a substituent electron donor and/or an unsaturated hydrocarbon chain. These molecules are characterized by a chromophoric group which absorbs the incident photons' energy at certain wavelengths. It is said that the filters are selective, as they only absorb energy in a well-defined range of the UV spectrum. Each filter is thus characterized by its wavelength of maximum absorption (λ_{max}).

2.6.2.2. The main families and their characteristics

PABA (λ_{max} = 309 nm) is now banned in Europe due to the fact that it is highly allergenic [91]. Its derivatives (PEG-25 PABA and Octyldimethyl PABA) are less allergenic and are still authorized in Europe. They are some examples of the few hydrosoluble filters available. According to the grafting which was carried out, the efficacy is variable. Octyldimethyl PABA (Padimate O) enables an SPF value of 9 to be attained for 8% of incorporation, and PEG-25 PABA gives an SPF of 4 for 10% [92].

Cinnamates are the most widely used UVB filters. As an example, we can give octylmethoxycinnamate (OMC) (λ_{max} = 310 nm). Indeed, it is found in a large number of products on the market. Cinnamates are well tolerated, even though they are linked with the notion of being endocrine disruptors. It should be remembered however, that OMC has 140,000 times less affinity for α receptors and 500,000 times less affinity for β oestrogen receptors than βestradiol, the standard oestrogen [93] and that its uterotrophic effects in animals is judged to be very low [94]. Cinnamic esters are quite efficient filters as they generate approximately 1 SPF unit per percentage of use [92].

Salicylates are poor photoprotectors. We can mention in particular homomenthyl salicylate or homosalate (λ_{max} = 306 nm) which, when incorporated into the recommended excipient at 8%, constitutes the FDA standard and which enables an average SPF of 4.47 (4.47 ± 1.279) to be reached. It is practically non-existent in European products. Certain publications report that octisalate (or octyl salicylate) has a proliferative effect on MCF-7 cells in breast cancer [95].

Benzophenones are wide spectrum filters which give 2 maxima of absorption in UV rays, one of 285 nm and the other close to 325 nm. As examples, we can mention benzophenone-3 (or oxybenzone) and benzophenone-4 and 5. Although they are not very efficient filters (SPF of 3 to 10% for oxybenzone and 4 to 5% for benzophenone-4), they are interesting, however, because they are very stable. Their low substantivity is a disadvantage, as is their poor tolerance (frequent allergic reactions for oxybezone) [96, 97]. Questions are being raised in other respects, as there could be a potentialization of the transdermic penetration of oxybenzone by a frequently associated repellent, DEET (NN diethyl-m-toluamide) but opinions are divided [98, 99]. What is certain is that oxybenzone is a filter which is found in the organism after topical application. It is known that 1 to 2% of the oxybenzone contained in a formula is absorbed after 10 hours. It is advised that these products should not be applied over large surfaces and that repeated applications should be avoided [100]. As for formulation, certain ingredients such as Transcutol® (diethylene glycol monoethyl ether) could be looked for, which increase substantivity without favouring crossing the skin barrier [101]. These are not therefore filters that should be rejected, but rather filters that should be used with care.

Triazines and derivatives (Bemotrizinal or Tinosorb S® -305 and 360 nm- and Bisoctrizole or Tinosorb M® -310 et 340 nm) are safe from a toxicological point of view [102]. They are marketed by a company called Ciba and are synergic. It is thus particularly interesting to combine them in the same formula. Bisoctrizole is both the best UVB and the best UVA filter on the market [92].

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Mexoryls® and more precisely Mexoryl SX® are derivatives of camphor. The latter is the only Mexoryl® of the series to be authorized in the United States. It is presented as an interesting filter regarding protection from skin damage caused by UVA rays both *in vitro* and *in vivo* [103, 104].

Concerning UVA filters, avobenzone is widely used and its lack of stability can be compensated for by combining it with other filters. Encapsulation, although fuelling many publications, has not enabled any industrial application so far [105, 106]. Neoheliopan AP® and Uvinul A+® are not authorized in the United States yet.

It is a pity that 3-benzylidene camphor (limited to 2%) is still authorized in Europe, as at this dose it is almost inefficient and it is also suspected of being an endocrine disruptor [107, 108].

2.6.3. Molecules of interest

Although a certain number of authors claim that the toxicity of organic filters is irrefutable, the same cannot be said for the others. The potential endocrine effect of certain filters is not conclusive and the controversy concerning parabens which has shaken the scientific community [109] lead us to believe that in the field, it is necessary to be prudent and indispensable ingredients for photoprotection should not be too hastily discredited. However, confronted with these threats, it would be advisable to find new filters, especially using plants as a source, as well as ingredients which could complete the action thanks to their original properties.

We could mention, for example, boldine, an alkaloid from the boldo tree, which has been known for a long time for its antioxidant properties [110] and more recently for a potential photoprotective effect [111]. Aromatic compounds contained in certain lichens [1 chloropannarine, epiphorelic acid I and II, calicine) prove *in vitro* to be of a level of efficacy comparable to that of OMC [112]. Flavonoids, natural colorants of many plants prove to be an interesting family too with chlorogenic acid in particular (SPF = 10), baicaline (SPF = 8), luteoline (SPF = 7), apigenine (SPF = 7), puerarine (SPF = 6) for a usage dose of 10% [113]. Coming from the sea, mycosporine-like aminoacids seem to be interesting in particular with a potential photoprotective effect in the UVA field [114, 115, 116].

3. Care products and make-up with SPF

Recently, there has been a wave of care products and make-up with SPF on the market, their SPF being mainly around 15. The justification for this is found in publications which state that there is a beneficial effect of using filters on a daily basis in order to prevent skin ageing and in particular using a mixture of avobenzone (1.5%) - ecamsule (1.5%) - octocrylene (4%) [117]. Even if we know very well that UV rays are responsible for actinic ageing, the daily use of products containing filters does not seem to be a good thing. It appears that filters, even though they are active, sometimes have adverse effects. They must be kept, therefore, for use in sun care products, all the more so as these other care products are not sun care products, so do not have to obey the same rules, namely those concerning the SPF / UVA-PF ratio and the critical wavelength [118].

4. Conclusion

Given the consequences for the skin of exposure to the sun, it seems necessary to ensure effective photoprotection. We have seen the various dosage forms, which offer a wide range of products adapted to the site of application. According to the quality-quantity of the product, the level of efficacy can vary greatly. The status of the products in itself is not unique, on one side of the Atlantic or the other, as cosmetics, medical devices and OTC medicines can be found. On the other hand, the methods for determining the efficacy of these products are almost universal.

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