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Sunscreen products: finding the allergen...

Like any cosmetic or any product repeatedly applied on the skin, sunscreen products may sensitize their users and cause an allergic reaction. Finding the responsible allergen implies good knowledge of what a sunscreen product is, what are the potential allergens it contains and the manifestations they may cause.

Key words: sunscreen, allergy

Definition

In the EEC Commission Recommendation of 22/09/06, the following definition for the term sunscreen product (SP) was applied: “*sunscreen product* means any preparation (such as creams, oils, gels, sprays) intended to be placed in contact with the human skin with a view exclusively or mainly to protecting it from UV radiation by absorbing, scattering or reflecting radiation.”

Legislation

The laws regarding SP vary from one country to another. In the USA, in Canada and in Australia, they are classed with medicines, whereas in Japan and in Europe, they are considered as cosmetic products, within the meaning in Europe of Article 1 of Council Directive 76/768/EEC of 27 July 1976 on the approximation of the laws of the Member States relating to cosmetic products, but with specific recommendations on their protective effect, especially on UVA. Thus in Europe, to be recognized as an SP, a product has to meet 3 criteria: 1) have a sun protection factor (SPF) over 6, 2) have a UVA protection factor of at least a third of the SPF, and 3) have a minimal critical wavelength of 370 nm, that is to say a broad enough spectrum [1]. In order to meet these criteria, it is necessary to associate several photo-protective agents in an SP. The list of these authorized agents also varies from one country to another. The list of photo-protective agents authorized in Europe and their various properties were detailed by J.P. Marty and C. Lafforgue at the GERDA conference in Angers [2]. In outline, a distinction is made between mineral screens, which mainly reflect UV mechanically and organic filters, which are chemically reactive substances that mainly absorb UV. Recently, a new category has emerged with *methylene-bis-benzotriazolyl-tetramethylbutylphenol* or Tinosorb M[®], which is an organic screen forming a meshing on the skin surface that stops UV.

Epidemiology

Sensitization to SP may concern the active principle, in this case the photo-protective agent, but also, less frequently, one of the vehicle components. It is therefore highly important, if contact dermatitis to an SP is

suspected, to test all its ingredients in order to determine which component(s) is or are responsible, as combined allergies are frequent.

The sun protection campaigns aimed at preventing skin ageing and photo-induced skin cancer have had a beneficial impact on the use of SP. Indeed, their use has increased a lot. However, the prevalence of allergic reactions to SP remains unknown. It is probably low – even if there are many publications – in view of the widespread use of these products. Few studies clearly specify the characteristics of the population concerned. In 1997, Schauder [3], in a 15-year review of 402 German patients suspected of photosensitisation, found 80 (20%) allergic or photoallergic patients to SP or cosmetics containing photo-protective agents. This population was clearly female (72%) and adult. No case of a child in the 0-10-year-old age group was reported and only 1 in the 11-20-year-old age group. Nearly 60% of the patients had polymorphic light eruption or chronical actinic dermatitis. Thus, in this study, idiopathic light eruption appears as a major risk factor for intolerance to an SP, in all likelihood this is due to the fact that SP are widely used in these patients. Female predominance is found in reviews and isolated cases and this is probably due to a more frequent use of SP by women. Other risk factors have also been suggested, such as atopy and outdoor work.

Clinical manifestations [4, 5]

The most frequent clinical manifestation of allergy to an SP is eczema. Its intensity varies according to the responsible allergen, it can be either subacute or chronic but it is frequently acute and vesiculous. It is located in the parts of the body where the cream was applied, *i.e.* the sun-exposed parts that need protection. This eczema is often, particularly with sun filters, a photoallergic eczema affecting the treated and sun-exposed areas and sparing the treated but non-sun-exposed areas, for instance the upper eyelids and the under chin [6]. In practice, the distinction is often difficult to make. A unilateral or limited localization can be seen if the SP was applied on only one part of the body, if one side of the body was more sun-exposed or in case of contact with another person who had applied the photo-protective agent: it is eczema by passive transfer, *i.e.* connubial dermatitis, which means the allergen is strong. Immediate manifestations such as contact urticaria,

sometimes even with anaphylactic shock, have been reported with benzophenone 3; so has erythema multiform, exceptionally.

The problem is rather to recognise that the dermatitis is related to the SP. It is something one has to consider when confronted with face dermatitis occurring in the summer – and which is not necessarily due to the usual cosmetic products – the worsening of a pre-existing dermatosis or photodermatosis, dermatitis of exposed parts, “peculiar” sunburn...

Allergy to photoprotective agents (table 1)

The photo-protective agents responsible for allergy are chemical filters; no case has been reported with mineral sunscreens. The first “sun creams” appeared in the 1930s, when sea-bathing became fashionable. The first filter used

in the USA was benzylsalicylate, followed by para-aminobenzoic acid and the first cases of intolerance to this filter appeared at that time. Other filters were subsequently marketed and each time “epidemics” of allergy or photoallergy to these agents ensued, leading to their withdrawal or restriction of their use. Thus was the case for benzophenone 3 in the 1980s, for isopropylidibenzoylmethane in the 1990s and the 2000 decade is witnessing an emergence of cases of allergy to octocrylene.

Para aminobenzoic acid (PABA) and its esters [7]

PABA was one of the first chemical filters used. It absorbs UVB but does not block UVA nor visible light. It penetrates the corneal layer where it remains active, which makes it highly water resistant. It was responsible for contact dermatitis, as were its esters: glyceryl PABA, amyl dimethyl PABA with cross-allergy with other para-amines such as paraphenylene diamine and benzocain. Octyl dimethyle PABA, which does not contain that amine group, is thought to be lower-risk. For those reasons, PABA and its esters have almost disappeared from SP. Yet, it is still authorized in SP, with a maximum concentration of 5% in Europe and 10% in the USA. However, very recently, a case of serious generalized rash leading to the hospitalization of a young English woman was reported [8], she had applied an SP – P20[®] – containing PABA when she was known to be allergic to benzocaine. It was a case of contact photoallergy, as only the PABA exposed to UVA testing was positive.

Benzophenones

Benzophenones have been used since the 1950s, particularly in “PABA-free” products. They are organic compounds derived from benzophenone, a bicyclic ketone. They are very widely used as photoprotective agents in cosmetics but also in the textile and plastic industries. The most famous and most used benzophenone is oxybenzone, 2-hydroxy-4-methoxy-5-sulfonic acid benzophenone, INCI name: *benzophenone 3*. The other benzophenones most commonly used in cosmetics are sulisobenzene, 2-hydroxy-methoxy-5-sulfonic acid benzophenone, INCI name: *benzophenone 4*, and mexenone, 2-hydroxy-4-methoxy-4-methyl benzophenone, INCI name: *benzophenone 10*. The action spectrum is broad and covers UVB and UVA. For this reason, benzophenones are widely used in cosmetics with two different purposes, either as “preservatives” to protect the cosmetic formulation from deterioration, or directly as a photoprotective active principle in day creams or in sunscreen products, in this case often in association with other chemical UV filters.

The first cases of contact dermatitis from benzophenone 3 were reported in the 1970s [9, 10] and many publications ensued, particularly in the 1990s [11, 12]. Benzophenone 3 remained the sun filter usually responsible for allergic reactions until recently, when the results of an Italian multicentric study [13] were published and showed that it has been replaced by octocrylene. It is responsible for contact dermatitis, but mostly for contact photoallergy [14, 15]. Immediate reactions, such as photo-worsened [16] or sun-induced contact urticaria [17, 18] have also been reported and might be severe if the product is applied on a large surface area [19, 20]. Japanese authors

Table 1. Marketed chemical filters for patch tests

INCI name (on packing)	Trade names	% pet	Supplier
UVB sun filters			
PABA	PABA	10%	C, T
Octyl dimethyl PABA	Escalol 577, Eusolex 6007	10%	C, T
Octyl methoxycinnamate	Parsol MCX, Eusolex 2292, Escalol 557, Neoheliopan AV	10%	C, T
Isoamyl p-methoxycinnamate	Neoheliopan E	10%	C, T
4-methylbenzilidene camphre	Eusolex 6300, Parsol 5000	10%	C, T
Octylsalicylate	Escalol 587	5%	C
Homosalate	Filtrisol A, Eusolex HMS	5%	C
Octyltriazone	Uvinul T50	10%	C
UVA sun filters			
Butylmethoxy- dibenzoylmethane	Parsol 1789, Eusolex 9020	10%	C, T
Broad spectrum sun filters			
Benzophenone-3 (oxybenzone)	Escalol 567, Eusolex 4360, Neoheliopan BB, Uvinul M-40	10%	C, T
Benzophenone-4 (sulisobenzene)	Uvinul MS-40	2%	C
Benzophenone 10 (mexenone)	Uvistat	10%	C, T
Phenyl benzimidazole sulfonic acid	Eusolex 232, Parsol HS	10%	C, T
Octocrylene	Uvinul N539	10%	C
Drometrizole trisiloxilane	Meroxyl XL	10%	C
Methylene- bis-benzotriazolyl tetramethylbutylphenol	Tinosorb M	10%	C
Bis-ethylhexyloxyphenol methoxyphenyl triazine	Tinosorb S	10%	C

C: Chemotechnique[®] T: Trolab[®].

have also described an erythema multiform-like eruption following photoallergic dermatitis to an SP containing benzophenone 3 [21].

Sulisobenzone (*benzophenone 4*) is increasingly used in cosmetics, particularly shower gels and hair care products, shampoos and texturizing gels. English authors have recently drawn attention to this possible emerging allergen [22] which is admittedly listed among the ingredients, but of which users can be unaware. In 1,693 patients patch tested with a “cosmetic” series, it was found positive in 2.3% of cases and came third after Amerchol L 101 and sodium metabisulfite.

Dibenzoylmethane derivatives

Dibenzoylmethane derivatives are UVA-absorbing filters. Isopropylidibenzoylmethane or Eusolex 8020 and *butylmethoxydibenzoylmethane* or Parsol 1789 appeared on the market in SP and cosmetics in 1979-1980. The association of isopropylidibenzoylmethane with methylbenzylidene camphor or Eusolex 8021 was also much used at that time. The first case of contact dermatitis from Eusolex 8021 found in a day cream was reported in 1981 [23], yet without being able to tell which of the two filters was responsible. The first authenticated cases of contact dermatitis from isopropylidibenzoylmethane were published in 1986 [24], others rapidly followed [25, 26]. In Schauder's study [3] isopropylidibenzoylmethane ranked first among sensitizing filters with 30 positive patch tests and 32 positive photopatch tests in 80 patients. This “epidemic” of allergic dermatitis cases led to manufacturing of isopropylidibenzoylmethane stopping in 1993. In all likelihood, cross-reactions between isopropylidibenzoylmethane and butylmethoxydibenzoylmethane probably exist; in the 1980s, the latter had positive patch tests or photopatch tests less often but was never positive in isolation. At the moment, it ranks 2nd among chemical filters after benzophenone 3 in the UK [27], 3rd in France [28], 5th in Italy [13] and 7th in the USA [29].

Cinnamates

Cinnamates are a group of substances derived from cinnamic acid. Some are used by the perfumery or food industries for their aromatic properties, others are used as sun filters with a UVB action spectrum. They are not very soluble in water and are often used to enhance the water-resistance of SP. The most commonly used is *octyl methoxycinnamate*, followed by *isoamyl p-methoxycinnamate*. They are responsible for photoallergic contact dermatitis, usually with variable frequency depending on the series: 9.7% of positive photopatch tests in an 82-patient series in Bogota [30], 7% in 1,155 patients in a recent English multicentric study [27], 5% in an Italian study [13]. Fisher [31] says that methoxycinnamates may cause cross-reactions with the other cinnamates that can be found in perfumes, topical remedies, cosmetics, food flavouring agents such as cinnamic acid, cinnamic aldehyde, cinnamon extract, balsam of Peru, coca leaves... and that sensitized patients should be advised to avoid such products. However, a recent study has not demonstrated this notion of cross-allergy [32].

Octocrylene

Octocrylene was introduced in SP some ten years ago in order to replace oxybenzone, due to the serious allergy problems that it had caused. Octocrylene is an ester formed by the condensation of a diphenylcyanoacrylate with 2-ethylhexanol. It is considered to belong to the family of cinnamates. Its diphenylcyanoacrylate component gives it a UV absorbing power with a broad spectrum action, ranging from UVB to short-wave UVA. The ethylhexanol part gives it moisturizing and water-resistance properties. Octocrylene is also used as a stabiliser of other filters, particularly cinnamates and butylmethoxydibenzoylmethane. All these qualities, together with its low cost, have made octocrylene a widely used filter in the high sun protection factor creams which are increasingly being used nowadays. It was found in over 200 SP in 2007.

The first cases of allergic contact dermatitis from octocrylene were published in France [33] in 2003. They concerned two cases of photoallergic contact dermatitis confirmed by positive photopatch tests to octocrylene. Only a further 4 cases were published in the UK in 2005 [34] and in Belgium in 2006 [35]. But since 2007, cases have increased. In France, thanks to REVIDAL, 50 cases of (photo)allergic contact dermatitis from octocrylene or positive photopatch tests to octocrylene have been collected [36]. These data put together showed a difference in symptomatology depending on age. Children mostly have contact dermatitis, often beginning early before the age of 3. This particular frequency in children, especially in very young children, did not exist with other chemical filters. Adults more frequently have photoallergic contact dermatitis and, surprisingly, often have an associated history of photoallergic contact dermatitis from ketoprofen. Moreover, if octocrylene testing is added to the photopatch tests of ketoprofen-photoallergic patients, it is often positive but, in this case, not relevant. Indeed, some of these patients had never applied any SP... Similarly, when this filter was added to the baseline series of photopatch tests, photopatch tests were found positive to octocrylene in Belgium [37], in France [38] and in Italy [13], often also in association with ketoprofen photoallergy. It is known that patients with contact photoallergic dermatitis from ketoprofen very often have contact sensitization to fragrance mix and balsam of Peru [39] as well as to cinnamic alcohol, when it is tested. They frequently have positive PPT to benzophenone 3, fenofibrates and fentichlor [40-42]. Positive tests to benzophenone 3 are accounted for by the fact that it is chemically related to ketoprofen: it is a case of cross allergy. The same is true for fragrance mix, which contains cinnamic alcohol, and ketoprofen, as is shown by Foti [40] with a program enabling comparison of the spatial arrangement of molecules. But there is no chemical similarity between ketoprofen and octocrylene or fentichlor; as for octocrylene, the positive photopatch tests to fentichlor are not relevant as it has not been in use since the 1970s [43]. However the peculiar photosensitivity that exists in ketoprofen-photoallergic patients remains unexplained.

Be that as it may, octocrylene is a strong allergen and these observations lead to some recommendations. It seems reasonable to prefer clothes or at least mineral sunscreen products for photoprotection in children, especially very young children. The same obviously

applies to adults with ketoprofen-contact photoallergy who need to avoid fragrances, benzophenone 3 and octocrylene-containing SP.

Other chemical filters

Salicylates

Benzyl salicylate was the first chemical filter marketed in the USA. Salicylates are UV absorbing filters with an action spectrum between 280 and 320 nm. Only *octyl salicylate* (2-ethyl-hexyl-salicylate) and *homosalate* (homomentyl salicylate) are currently used in Europe in SP. Octylsalicylate is rarely responsible for contact allergy despite its frequent use. Two cases of contact dermatitis have been reported in two female patients after they had used an SP containing it. The first patient [44] had a history of allergy to perfumes and a positive test to her Cacharel® perfume and to the cis-3-hexenyl salicylate it contained and the author discussed the possibility of cross allergy between the two salicylates which have in fact very close chemical formulas. The other patient had only one positive test to her sun cream (Olay®) and to octyl salicylate [45].

Methylbenzilidene camphor

3-(4'-methylbenzilidene camphor) is a UVB filter that has been used for a long time and is probably a weak allergen. The first case of contact dermatitis from this sunscreen agent on its own was reported in Germany in 1983 [46]; most other reported cases were cases of allergy to Eusolex 8021, a mixture of methylbenzilidene camphor and isopropylidibenzoylmethane which was removed from the market at the same time as this highly sensitizing chemical filter. In these cases, the isopropylidibenzoylmethane test was always positive whereas the methylbenzilidene camphor test was far more occasionally positive [3, 25]. This might be accounted for by an occasional promotion phenomenon of the weak allergen by the strong allergen called "coupling allergy" [47].

Phenylbenzimidazole sulfonic acid

Phenylbenzimidazole sulfonic acid is a UV filter mainly absorbing UVB and has been on the market since 1933. It is mostly responsible for contact photoallergy but reported cases are few [3, 48].

Others

Other filters have very occasionally been held responsible for photoallergy and/or contact dermatitis. They were mostly found positive with other filters better-known as allergens.

– Such is the case for *octyltriazone*. The first and unique case was reported in the United Kingdom [49] in a 66-year-old woman who had developed bullous eruptions on sun-exposed areas during a holiday in Spain. She had positive PT to fragrance mix and balsam of Peru and positive PPT to butyldibenzoylmethane, octyltriazone and her sun cream, which contained both filters.

– Such is also the case for *drometrizole trisiloxane* or Mercoxyl XL, with one case reported in the United Kingdom [50] in a 59-year-old woman who, back from a short stay in the Canary Islands, was hospitalized for generalized eczema starting on her lower limbs. She had positive PPT to benzophenone 4 and positive PT to her two SP that did not contain benzophenone. Detailed analysis of photopatch

tests for one SP showed a slightly positive test to drometrizole trisiloxane whereas for the other it was negative.

– *methylene-bis-benzotriazolyl tetramethylbutylphenol* (Tinosorb M) is a sunscreen agent belonging to the new category of organic screens. Two cases of contact dermatitis to a SP containing it have been reported, with positive PT to this sunscreen [51-53]. In these cases, the authors managed to demonstrate that the allergen was in fact decylglucoside, a product that is added to ease spreading and enhance skin adherence of the tiny 200 nm particles dispersed in aqueous solution that form this screen.

– Combined photoallergies to several filters are not uncommon, by a mechanism of co-allergy. Two cases have been reported in children: the association of butylmethoxydibenzoyl methane with octylmethoxycinnamate in a 12-year-old girl [54] and of benzophenone 3 with methoxycinnamate in a 6-year-old boy [55]. However, allergy to sun filters is not frequent in children apart from cases due to octocrylene.

Allergy to excipients

The chemical composition of the excipient in an SP is important and plays a contributive role in its efficacy. We may find moisturizing agents, such as polyglycols, emulsifying agents such as wool alcohols, surfactants such as glucosides, preservatives such as Euxyl K 400, perfumes and more specifically film-forming agents that enhance the SP water and sweat resistance.

There are few studies mentioning contact dermatitis to SP excipients apart from Shauder's study in Germany in 1997 [3]. They found a high percentage of positive PT and/or PPT for perfumes, a lower percentage for preservatives.

A few isolated clinical cases have also been published but this small number probably does not reflect reality as many cases of contact dermatitis – for instance, only to perfumes – are not published.

Emollients

A case of combined allergy to *isohexadecane* and to *isopropyl myristate* in an SP was reported in 2004 [56] in a 64-year-old woman who had developed widespread contact dermatitis after applying this product. In 2007, two cases were published. The first one was a case of allergy to oil derived from castor oil – *polyethylene glycol-7 hydrogenated castor oil* – which was the only positive ingredient of a photoprotective lotion and caused face and neck dermatitis in a 73-year-old man [57]. The second case was a case of gradually worsening recurring dermatitis in a 64-year-old woman who had used Vichy® Capital Soleil cream. The responsible agent was *ethylhexylglycerine*, a moisturizing agent that also facilitates the action of preservatives [58].

Emulsifiers

A 67-year-old woman who, for three years, had had a history of a pruriginous eruption on her arms then legs in relation to sun exposure finally related it to the use of an SP with an SPF of 25. She had positive tests to her SP as well as to the *tetrahydroxypropyl ethylene diamine* it contained, with no cross-allergy to ethylene diamine [59]. An 8-year-old Taiwanese girl had acute eczema on

her cheeks after using a SP containing oxybenzone and octyl methoxycinnamate, but in fact the responsible agent was the *triethanolamine* contained in the SP [60]. Finally, Hausen reports a case of strongly positive tests to *pentylene glycol* in a 33-year-old woman who had had allergic reactions to several SP [61].

Preservatives

Only one case has been published. It was a case of allergy to *Euxyl K 400* contained in an Avène® 20B 7A cream and that was responsible for face dermatitis which lasted three months. The 45-year-old female patient was also sensitized to PPD and thiuram mix. The test to phenoxyethanol was negative and thus methylidibromoglutaronitrile was probably responsible [62].

Film-forming agents: copolymers

Copolymers are heteropolymers made of two different types of monomers arranged together in various ways to form a large molecule with high molecular weight. They are widely used in cosmetics for their antistatic, film-forming, skin-conditioning and emulsion-stabilizing properties. They increase viscosity and water resistance. They can be found in hair conditioners, skin moisturizers and sunscreen products. Among the 200 copolymers listed in An Goossens' article [63], 7 are reported to have caused contact allergy, but the nature of the hapten remains unknown: impurity, residual monomer, additive, degradation product? Three are frequently found in SP. 1) polyvinylpyrrolidone(PVP)/hexadecene copolymer – trade names: Antaron® V-216, Ganex® V-216, Unimer® U-151 – is found in 27 SP, sometimes used mixed with ethylhexylmethoxycinnamate; 2) PVP/eicosene copolymer – trade names: Antaron® V-220, Ganex® V-220, or Unimer® U-15 – is present in 90 SP, where it is sometimes encapsulated and mixed with sun filters (Suncaps®); 3) PVP/1-triacontene copolymer (Antaron® VP-660, Ganex VP-660, Ganex V-230, Unimer U-6 et Agent® ACP-1009), sometimes mixed with titanium oxyde (Utinamer T-40) is found in 26 SP. Despite this widespread use in SP, these copolymers rarely cause contact dermatitis to SP. Two cases were reported with PVP/eicosene copolymer, the first one by Smith [64], the other by Le Coz [65] and we personally saw widespread acute eczema in a 48-year-old female patient after she had used two different SP containing it. To our knowledge, only one case with PVP/triacontene has been published, by Stone [66] in a 3-and-a-half-year-old girl.

Conclusion

Allergic contact dermatitis to SP remains rare in view of their widespread use. It develops in small "epidemics" that follow the launching of new filters and we are currently witnessing an octocrylene "epidemic". Diagnosing contact allergy is sometimes difficult as the responsible allergens are photoreceptive chemical filters that usually cause photoallergic reactions. To detect contact allergy, patch tests with the SP as well as its components must be exposed to a UVA dose of 5 J/cm², failing which there might be false negatives. Similarly, it is important to test all the ingredients, which necessitates close collaboration with the manufacturers. Finding the precise aller-

gen responsible enables the patient to effectively avoid it. Many excipient components as well as chemical filters can be found in other types of cosmetics and the patient has to be able to identify them. In France we also usually notify these cases to the AFSSAPS (Agence Française de Sécurité Sanitaire des Produits de Santé) cosmetovigilance commission which in return decides what possible measures should be taken, according to the number of cases and/or how serious they are. ■

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