



Sunscreen allergy and its investigation

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Abstract Allergic reactions to sunscreens are relatively rare. However, as the public become more conscious of the dangers of excessive sunlight exposure, the use of sunscreens is increasing. They are also being incorporated into general cosmetics on a more frequent basis. Sunscreens contain a variety of potential sensitizers which may lead to contact and/or photocontact allergic dermatitis, and as pharmaceutical companies continue to manufacture and incorporate new UV filters it is crucial that we remain up to date and aware of these agents to include in patch and photopatch testing batteries. Furthermore, the creation of a European consensus statement regarding methodology in photopatch testing has enabled greater standardization and comparison of patch test results across centers.

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Introduction

Sunscreens contain ultraviolet (UV) filters that help protect against the acute and chronic damaging effects of UV radiation (UVR), including sunburn, skin pigmentation, skin carcinogenesis, and photoaging. UV filters are also important for the protection of patients with photosensitive dermatoses and are used to protect manufactured products from photodegradation, with recent applications in the clothing and fabric industries.

As the public has become increasingly aware of the dangers of excessive sun exposure, the use of sunscreens has also increased. Although these are predominantly in the form of specific sunscreen products, they are also being regularly incorporated into the formulations of other personal care products.

UV filters: Absorbers and reflectors

Sunscreen products usually contain one or more UV filters that can be classified into organic or physical agents, according to their mechanism of action. Organic or chemical UV filters absorb UVR, whereas physical UV filters act as a barrier and reflect UVR. The physical UV filters include titanium dioxide and zinc oxide, which are chemically and biologically inert and are unlikely to cause irritation or skin sensitization. Because these physical agents have an opaque appearance on the skin, chemical UV filters are generally considered more cosmetically acceptable and are, therefore, more commonly used in personal care products. Chemical UV filters can be further subdivided into UVA protectors (operating in the 320–400 nm range of wavelengths) or UVB protectors (operating in the 290–320 nm range of wavelengths). These can potentially cause allergic or photoallergic contact dermatitis, or both, in contrast to physical UV filters. A summary of the chemical UV filters and their spectrum of action is presented in [Table 1](#).

Allergic contact dermatitis is a type IV cell-mediated hypersensitivity reaction after exposure to an allergen. In photoallergic contact dermatitis, the allergen is produced

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Table 1 Examples of chemical ultraviolet (UV) filters and their ultraviolet absorption spectrum

Class of compound	INCI name	UV absorption
Dibenzoylmethanes	Isopropyl-dibenzoylmethane	UVA
	Butyl-methoxy-dibenzoylmethane	UVA
Benzophenones	Benzophenone-3	UVB + slight UVA
	Benzophenone-4	UVB + slight UVA
Para-aminobenzoic acid	PABA	UVB
Cinnamates	Octocrylene	UVB
	Isoamyl-p-methoxycinnamate	UVB
	Ethylhexyl-methoxycinnamate	UVB
Salicylates	Ethylhexyl salicylate	UVB
Camphor derivatives	4-Methylbenzylidenecamphor	UVB
Other	Phenylbenzimidazole sulfonic acid	UVB

INCI, International Nomenclature of Cosmetic Ingredients.

after UV exposure, resulting in a photoactivated chemical or photoproduct. The sun-exposed sites are predominantly involved in the initial stages, but dermatitis may subsequently include covered sites due to the presence of circulating activated T lymphocytes.

The incidence of photoallergic contact dermatitis for sunscreens is unclear, although it has been reported to vary from 1% to 40% in patients with a history of photosensitivity.¹⁻⁴ This variation in the reported incidence of photoallergy may result from differences in patient selection, photopatch testing methodology, the test battery that is used, and interpretation of test results. The reported causes of photoallergic contact dermatitis have also changed over time. The main causes in the 1960s included the topical antimicrobials based on tetrachlorosalicylanilides and the fragrance chemicals (musk ambrette and 6-methylcoumarin). At present, sunscreen chemicals are the most common cause of photoallergic contact dermatitis in the UK.⁴

In addition, the incidence of photoallergic contact dermatitis and the causative allergens is also likely to evolve, as new UV absorbers are introduced. One can neatly trace the evolution of allergy and photoallergy to sunscreens in the patch test literature. In the 1930s and 1940s, sulfonic acid and para-aminobenzoic acid (PABA) were widely used to protect against the adverse effects of UVB, but as the effects of UVA also became apparent in the 1970s and 1980s, benzophenones and dibenzoylmethanes were introduced to provide combined UVA and UVB photoprotection. An investigation describing the organic UV filters and summarizing when they were used in Europe, correlated with corresponding reports of contact and photocontact allergic reactions, demonstrated a variable time delay from duration of use in Europe to reported adverse skin reactions.⁵

Concerns in the 1980s, regarding the allergic and photoallergic potential to PABA and its derivatives, led to a general reduction in its use, although PABA can still be found in some sunscreen products across Europe. A recent published case report documented the development of photocontact allergy to PABA, highlighting the need for continued vigilance.⁶

In the 1990s, benzophenone-3 was recognized as the most common sunscreen photoallergen. A meta-analysis documented 64 unpublished exaggerated-use studies testing sunscreens containing benzophenone-3 (also known as oxybenzone, with concentrations of 1%-6%) on healthy individuals with no history of skin conditions or photosensitivity.⁷ This testing was performed in 10 laboratories from 1992 to 2006, and the studies were sponsored by industry. The analysis concluded that allergic contact reactions to sunscreens were more commonly due to the presence of other excipient components, such as fragrances and preservatives.

A recent multicenter prospective study in the UK and the Netherlands tested 1155 patients to 11 established organic sunscreen agents and 1 commercial sunscreen applied "as is,"⁴ including test allergens recommended by the British Photodermatology Group (Table 2) and the common UV absorbers used across Europe. The study identified that 4.4% of tested patients had sole photoallergic contact dermatitis, 5.5% had allergic contact dermatitis, and 1.3% had concomitant photoallergic and allergic contact dermatitis to sunscreen chemicals. Multiple photoallergies, in addition, were observed in some individuals.⁴ The most common was benzophenone 3, followed by butylmethoxydibenzoylmethane. A newly emerging photoallergen—octyl triazone (also known as

Table 2 Sunscreen agents in the photopatch testing battery as recommended by the British Photodermatology Group in 1997

Test compound	Patch test concentration
PABA	5%, 10%
Octyl dimethyl PABA	2%, 10%
2 ethylhexyl-p-methoxycinnamate	2%, 10%
2-hydroxy-4-methoxybenzophenone ^a	2%, 10%
4-tert-butyl-4'-methoxydibenzoylmethane	2%, 10%
Musk ambrette	1%, 5%
Patient's own product	Diluted as appropriate

PABA, para-aminobenzoic acid.

^a Benzophenone 3, oxybenzone.

octocrylene)—was also highlighted as being of interest. Octyl triazone has been separately reported as a strong sensitizer causing allergic contact dermatitis in children and photoallergic contact dermatitis in adults, particularly in those with a history of photoallergy to ketoprofen.^{8,9} This demonstrates the importance of being aware of new sunscreen filters that can lead to photoallergic contact reactions.

Isopropylidibenzoylmethane was withdrawn from the market in 1993, having been identified as a common cause of photoallergic contact dermatitis in the 1980s to 1990s. A 15-year retrospective review of 402 German patients with clinical photosensitivity who were patch and photopatch tested to 11 UV absorbers (German, Austrian, and Swiss photopatch test series)¹⁰ reported that 20% had an allergic or photoallergic contact dermatitis to UV absorbers. The most frequent photosensitizer was isopropyl dibenzoylmethane, and a smaller proportion of patients also had allergic or photoallergic reactions to benzophenone 3 and PABA.¹⁰ As a consequence, 4-tert-butyl-4'-methoxydibenzoylmethane (also known as avobenzone or butyl methoxydibenzoylmethane) has become more widely used. This compound has recently been shown to photodegrade to benzils and arylglyoxals. The latter compound is a strong skin sensitizer, and photocontact allergy to dibenzoylmethanes may therefore be due to the formation of arylglyoxals in skin.¹¹

A retrospective review of a 13-year period in the US reported that 11.2% of individuals with a "photosensitivity disorder" had definite relevant photoallergic contact dermatitis. The photoallergens tested were subdivided into seven categories including sunscreens, antimicrobial agents, medications, fragrances, plants, pesticides, and other substances. The main photoallergens reported were sunscreen chemicals and the antimicrobial agent, fentichlor.¹² The most common sunscreen allergens identified included PABA (5.8%), octyl dimethyl PABA (3%), 4-tert-butyl-4'-methoxydibenzoylmethane (4.3%), benzophenone 3 (4.3%), and benzophenone 4 (4.3%).¹² Benzophenone-4, which is becoming increasingly incorporated into personal care product formulations as well as in sunscreens produced the most positive patch test results when tested alongside other UV filters, including benzophenone-3.¹³

Cinnamates have largely replaced PABAs as UVB absorbers. They are poorly soluble in water, and reported photoallergic reactions to cinnamates continue to be relatively uncommon.^{14,15} Similarly, salicylates, which are weak UVB absorbers are also rarely associated with allergic and photoallergic contact dermatitis and are popular for use in sunscreens due to their safety, solubility, and stability. A recent report, however, documented the development of allergic contact dermatitis to octyl salicylate (also known as 2-ethyl-hexyl-salicylate) which was found in the patient's moisturizer.¹⁶

Methylene bis-benzotriazolyl tetramethylbutylphenol is a new-generation broad-spectrum hybrid UV filter produced as microfine particles, and therefore, it absorbs UV but also scatters and reflects UV. This UV filter is being increasingly

used, but as yet, only three case reports of allergic contact dermatitis have been published.^{17,18}

Patch testing

Over the years, there has been considerable variation in the methodology used for photopatch testing, the allergens tested, and the interpretation of results such that a comparison of data from published studies is difficult. This lack of standardization in methodology was summarized in a review that highlighted differences in irradiation wavelengths, UVA dosage, duration of test allergen application, and postirradiation reading times.⁵

In 2004, a group of European contact dermatologists and photobiologists produced a consensus statement regarding methodology, test allergens, and interpretation of test results.¹⁹ This has standardized the recommended photopatch testing procedure across Europe and should enable comparison of the prevalence of different photoallergens across different test centers. Because consumer use of products continuously changes and specific formulations of these products evolve, they recommend that test allergens should be regularly reviewed to detect and demonstrate the real frequency of photoallergy to sunscreens.

The current recommended photopatch test series focuses on organic sunscreens and testing to the patient's own products.^{19,20} The list is detailed in Table 3 and includes the

Table 3 Sunscreen agents in the photopatch testing battery as recommended by the European Consensus Group in 2004

Test compound	Patch test concentration
Petrolatum (control)	
Octyl methoxycinnamate	10%
(2-ethylhexyl-p-methoxycinnamate, Parsol MCX, Eusolex 2292)	
Benzophenone-3 (2-hydroxy-4-methoxy benzophenone, Oxybenzone, Eusolex 4360)	10%
Octyl Dimethyl PABA	10%
(2-ethylhexyl-p-dimethyl-aminobenzoate, Escalol 507, Eusolex 6007)	
PABA (4-Aminobenzoic acid)	10%
Butyl methoxydibenzoylmethane (Parsol 1789, Eusolex 9020)	10%
4-methylbenzylidene Camphor (Eusolex 6300, Mexoryl SD)	10%
Benzophenone-4	10%
(2-hydroxy-4-methoxy-benzophenone-5-sulfonic acid, Uvenyl MS-40)	
Isoamyl p-methoxycinnamate (Neoheliopan, E1000)	10%
Phenylbenzimidazole sulfonic acid (2-phenyl-5-benzimidazolsulphonnic acid, Eusolex 232)	10%

sunscreen chemicals previously also recommended by the British Photodermatology Group in 1997.^{19,21}

At present, the concentration of test allergens is recommended to be at 10% in petrolatum. An investigation of the frequency of irritant reactions to the organic sunscreen filters that are in current use and tested concentrations of 2%, 5% and 10% in petrolatum (except terephthalylidene dicamphor sulfonic acid which was diluted in water) concluded that photopatch testing to these allergens at a 10% concentration was suitable for all sunscreen filters except benzophenone-4, which should be tested at a 2% concentration because 5% and 10% concentrations led to irritant reactions.²² The application of test allergens for 48 hours, in addition, provided a greater sensitivity, and 47% of all photoallergic reactions would have been missed if only occluding for 1 day.²³

After removal of the test allergens, the European consensus recommends that one set is covered with UV opaque material and the other is irradiated with 5 J/cm² of UVA. UVA, rather than UVB, is preferred, because the UVB dose that is required to produce photoallergy is likely greater than that leading to a sunburn response.²⁴ Because the action spectrum of some compounds is in UVB wavelengths and certain UV filters absorb UVB only, a photoallergic reaction caused by UVB could be missed. A recent study investigated 118 patients with suspected photoallergic contact dermatitis by applying suspected photoallergens in triplicate. One set was irradiated with UVA (5 J/cm²), another set irradiated with UVB (10 mJ/cm²), and one set was used as a non-irradiated control. The study found that there were no positive reactions that did not react to UVA, thus providing support for irradiating with UVA.²⁵

Sunscreen chemicals need to be present in the skin at the time of irradiation to lead to a positive photoallergic contact reaction, possibly due to the short half-life of the photoallergen that is produced. Irradiation of sunscreen chemicals before skin application did not lead to any positive patch test reactions.²⁶

Patch test readings taken at 72 and 96 hours after irradiation are generally thought to be desirable and helpful in distinguishing allergic from nonallergic reactions with respective crescendo and decrescendo reaction patterns. One group extended the follow-up period of their photopatch test patients to 5 days after irradiation but concluded that there was no additional advantage in extending the reading time beyond 2 days after irradiation.²⁵

Conclusions

The continual development of new sunscreen filters means one must remain vigilant and include these on patch and photopatch test series. The literature also highlights the necessity to continue to test patient's own

products to detect new sunscreen allergens and photoallergens. Feedback of patch and photopatch test data to industry remains essential to reduce the effect of allergic and photoallergic contact dermatitis to sunscreen chemicals. This should ensure the development of safer products for the future.

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