

Contact and photocontact sensitivity to sunscreens

Review of a 15-year experience and of the literature

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This review summarizes published and unpublished data of our 15-year experience with sunscreen allergy and photoallergy. From 1981–1996, 402 patients with suspected clinical photosensitivity were patch and photopatch tested with the commercial sunscreens and facial cosmetics that they had used and with chemical UV absorbers, fragrance materials, preservatives, and emollients. 80 patients (20%) (28 men, 52 women) demonstrated allergic and/or photoallergic contact dermatitis to 1 or more UV absorber(s). In 47 patients with photodermatoses or photo-aggravated dermatoses and in 33 subjects with normal photosensitivity, 91 allergic and 84 photoallergic reactions to UV filters were observed. Over the years sunscreens were added to the test series, which since 1989 comprised the following 10 UV absorbers and which induced allergic (a) and photoallergic (pa) reactions (number, type of reaction): 4 UVA absorbers – isopropylidibenzoylmethane (30a/32pa); butyl methoxydibenzoyl-methane (15a/13pa); benzophenone-3 (3a/9pa); benzophenone-4 (0a/0pa); and 6 UVB absorbers – PABA (2a/2pa); octyl dimethyl PABA (1a/2pa); methylbenzylidene camphor (32a/5pa); octyl methoxycinnamate (3a/4pa); isoamyl p-methoxycinnamate (4a/10pa); and phenylbenzimidazole sulfonic acid (1a/7pa). The frequent (photo)sensitization to isopropylidibenzoylmethane was the reason that its production was discontinued in 1993. 47 patients reacted to fragrance materials, 11 to preservatives and 2 to lanolin alcohol. These constituents were contained in the commercial sunscreens and cosmetics that they had used. Continuous revision of the UV absorber photopatch test series was necessary to be closer to the real frequency of exposure and of reported (photo)allergy to newer sunscreens. Clinicians should consider contact and photocontact allergy, especially in patients with photodermatoses and photo-aggravated dermatoses, and they should perform photopatch testing. Once the culprit has been identified, its INCI (International Nomenclature Cosmetic Ingredients) designation should be given to the patient, who must be warned to avoid products containing the (photo)allergen.

Key words: sunscreens; UV absorbers; allergic contact dermatitis; photoallergic contact dermatitis; dibenzoylmethanes; benzophenones; PABA derivatives; cinnamates; cosmetics; allergen replacement; prevention. © Munksgaard, 1997.

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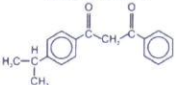
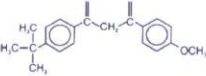
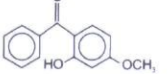
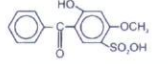
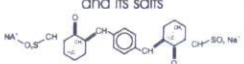
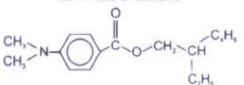
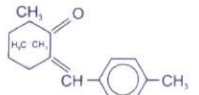
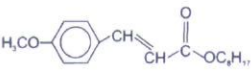
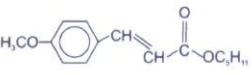
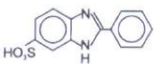
Active sunscreen constituents are of 2 basic types: chemical agents that absorb ultraviolet radiation (UVR) and reflectant sunscreens that act as a physical barrier to UVR (1). Chemical UV absorbers can broadly be divided into those which offer some protection to UVA (320–400 nm) (e.g., dibenzoylmethanes, benzophenones) and those which protect against UVB (290–320 nm) (e.g., PABA derivatives and cinnamates) (Table 1) (2).

Whereas physical sunscreens are chemically and biologically inert and hence do not cause irritation, sensitization and phototoxicity or photoallergy, chemical UV absorbers can elicit such adverse reactions (22). Contrary to UV absorbers, the concentration of physical sunscreens in a formulation is not regulated in the European Union (Table 1). Chemical UV absorbers are increasingly

being used, not only in sunscreens for protection of photosensitive patients and for prevention from the carcinogenic effects of solar radiation, but also in facial cosmetics and toiletries to protect the skin against photoaging and also to increase the shelf-life of the products by protecting against photodegradation. This extensive use has led to an increased frequency of UV absorber allergy and photoallergy. Publications on this issue range from case reports to multicenter studies and surveys (9, 10, 18, 20, 23–34). This review summarizes the results from our photobiology unit (1981–1996) on 80 patients with UV absorber allergy and photoallergy, 47 of them with concomitant photodermatoses or photo-aggravated dermatoses.

Adverse reactions to sunscreens have been thoroughly reviewed up to 1989 (24, 25). We will there-

Table 1. Description and characteristics of the chemical UV absorbers that were tested – regulatory update 1997

Colipa no. CAS no.	Structural formulas of chemical UV absorbers	CTFA / INCI designation	Trade names (suppliers) Allowed in Europe	Spectral efficacy	Regulated maximum concentration (%) warnings	Solubility	Classification of allergic and photoallergic reactions First report
CAS no. 63250-25-9	1-[4'-Isopropylphenyl]-3-phenyl-1,3-propanedione 	Isopropyl- dibenzoyl- methane	Eusolex 8020 (Merck) 1979-1993	UVA	5 production discontinued in 1993	lipophilic	AL3° English et al. 1986 (3) PA3° Schauder et al. 1986 (4)
S 66 CAS no. 70356-09-1	1-[4-tert.-Butylphenyl]-3-(4-methoxyphenyl)-1,3-propanedione 	Butyl methoxy- dibenzoyl- methane	Parsol 1789 (Givaudan), Eusolex 9020 (Merck) since 1981	UVA	5	lipophilic	AL2 Schauder et al. 1986 (4) PA2 Schauder et al. 1986 (4)
S 38 CAS no. 131-57-7	2-Hydroxy-4-methoxy- benzophenone 	Benzo- phenone-3	Eusolex 4360 (Merck), Neo Heliopan (H&R), Uvinul M40 (BASF) etc. since 1980	UVA	10 if >0.5 warning: contains Oxybenzone	lipophilic	AL3 Pariser 1977(5) Thompson et al. 1977 (6) PA3 Hölzle et al. 1982 (7)
S40 CAS no. 4065-45-6	2-Hydroxy-4-methoxy- benzophenone 5-sulfonic acid and its Na salt 	Benzo- phenone-4	Uvinul MS-40 (BASF) etc.	UVA	5 (expressed as acid)	hydrophilic	AL1 Baer et al. 1971(8) PA1 Menz et al. 1988 (9)
S 71 CAS no. 90457-82-2	3,3'-(1,4-Phenylenedimethylene) bis (7,7-dimethyl-2-oxo-bicyclo[2.2.1] heptane-1-methane sulfonic acid and its salts 	Terephthal- ylidene dicamphor sulfonic acid	Mexoryl SX (Chimex) since 1993	UVA	10 (expressed as acid)	hydrophilic	AL 0 PA 0 Léonhard et al. (10)
S 1 CAS no. 150-13-0	4-Aminobenzoic acid 	PABA	4-Aminoben- zoic acid (Merck) since 1948	UVB	5	hydrophilic	AL3 Marmelzat et al. 1980 (11) PA 3 Horio et al. 1978 (12)
S 8 CAS no. 21245-02-3	2-Ethylhexyl-p-dimethyl- aminobenzoate 	Octyl dimethyl PABA	Escalol 507 (Van Dyk), Eusolex 6007 (Merck) etc. since 1984	UVB	8	lipophilic	AL2 Thune et al. 1984 (13) PA 1 Weller et al. 1984 (14)
S 60 CAS no. 36861-41-9	3-(4'-Methylbenzylidene)-camphor 	4-Methyl- benzylidene camphor	Eusolex 6300 (Merck), Neo Heliopan MBC (H&R) etc. since 1984	UVP	6	lipophilic	AL2 Hunloh et al. 1983 (15) PA 1 Schauder et al. 1988 (16)
S 28 CAS no. 5466-77-3	2-Ethylhexyl-p-methoxycinnamate 	Octyl methoxy- cinnamate	Neo Heliopan AV (HR), Parsol MCX (Givaudan) Eusolex 2292 (Merck) etc. since 1970	UVB	10	lipophilic	AL1 Helsing et al. 1991(17) PA 1 Freeman et al. 1990 (18)
S 27 CAS no. 71617-10-2	Isoamyl-p-methoxycinnamate 	Isoamyl p-methoxy cinnamate	Neo Heliopan E1000 (H&R) since 1976	UVB	10	lipophilic	AL1 Fagerlund et al. 1983 (19) PA 1 Schauder 1991(20)
S 45 CAS no. 27503-81-7	2-Phenylbenzimidazole-5-sulfonic acid and its K-, Na-, and TEA- salts 	Phenyl- benzimidazole sulfonic acid	Eusolex 232 (Merck) Neo Heliopan Hydro (H&R) etc. since 1933	UVB	8 (expressed as acid)	hydrophilic	AL1 Schauder et al. 1986 (4) PA 1 Fagerlund et al. 1983 (19)

* (Photo)allergy rates (0-3) (21)

AL0,PA0 (photo)allergic reaction unknown or extremely rare,
AL1,PA1 (photo)allergic reaction occasionally reported,AL2,PA2 (photo)allergic reaction may occur,
AL3,PA3 (photo)allergic reaction known.

fore only refer to first reports of a UV absorber (photo)allergy and to publications from 1990 onward (Table 1).

The aims of our study were to investigate:

- incidence and frequency of relevant allergic and photoallergic contact dermatitis to UV absorbers in a selected group of patients with suspected clinical photosensitivity;
- incidence and frequency of additional contact and photocontact sensitization to fragrances, preservatives, and emollients;
- factors promoting or masking sunscreen allergy and photoallergy;
- means to improve diagnostics and to prevent further contact with the (photo)allergen in commercial sunscreens and cosmetics;
- consequences of adjusting the sunscreen photopatch test series to the frequency of exposure and of reported (photo)allergy to newer UV absorbers;
- influence of our findings on the producers of UV absorbers, of commercial sunscreens and cosmetics, and of standard photopatch test series.

Patients and Methods

Patients

From 1981–1996 we performed patch tests and photopatch tests on a consecutive series of 402 patients referred to our photobiology unit with suspected clinical photosensitivity. The minimal erythema doses (MEDs) for UVA and UVB were established for each patient before photopatch testing.

Light sources

UVB: Osram Ultra Vitalux 300 W high pressure mercury lamps with incoherent emission spectrum at 313, 365, 406, 436, 446 and 580 nm (Osram, München, Germany). This lamp, which had been prescribed by the Deutsches Institut für Normung, was used until 1996 to establish the MED UVB in unprotected and in sunscreen-protected skin to determine the sun protection factor (35). Dosimetry: Centra UV-Meßgerät (Osram, München, Germany). UVA: Waldmann UV-Test unit equipped with Philips TL-K 40 W/09 N fluorescent tubes (emission spectrum 315 to 395 nm, maximum at 355). Dosimetry: PUVA meter (Waldmann, Villingen-Schwenningen, Germany).

Minimal erythema dose

The MED for each patient was determined by applying graded doses of UVA and UVB to unexposed skin of the lower back. The following UVA

doses were used: 0.4, 0.6, 0.9, 1.3, 1.9, 2.8, 4.2, 6.3, 9.5, 14, and 20 J/cm². Starting from a dose of 20 J/cm², each successive dose is equal to roughly 66% of the previous dose. The following UVB doses were applied: 8.5, 12.5, 17, 25, 35, 50, 70, 100, 140, and 200 mJ/cm². Beginning with an initial dose of 8.5 mJ/cm², each successive dose is equal to approximately 140% of the previous dose (35). The dose that produced a minimally perceptible, sharply confined erythema at the test site 1 day after irradiation was defined as the MED UVA or MED UVB. The normal range for the MED UVA was taken to be 20 J/cm² and greater, depending on the skin type (36), and for the MED UVB 100 mJ/cm² and greater. The test sites were observed for up to 8 days after irradiation for evaluation of eczematous transformation.

Test substances

UV absorbers (Table 2), commercial sunscreens, facial cosmetics, the German, Austrian, Swiss photopatch test series (Hermal, Reinbek, Germany) (37) for photopatch testing, and the various series of the German Contact Dermatitis Research Group (DKG) (Hermal) for patch testing. To assess the problem of contact and photocontact allergy fully and to determine the frequency of photoallergy to newer UV absorbers, our sunscreen series was updated in 1984, 1986, 1987, 1989, 1995 and 1996 (Table 2).

Photopatch testing

From 1981 to June 1986 a UVA dose of 5 J/cm² and from July 1986 to 1996 a UVA dose of 10 J/cm² was used for photopatch testing when the MED UVA was within the normal range. If the MED was diminished, a suberythemalogenic UVA dose (66% of the MED UVA) was applied. Since July 1986 the procedure corresponded to that of the German, Austrian, and Swiss photopatch test group (26). A delayed erythematous and/or papular reaction at the non-irradiated sites was defined as an allergic reaction even if there was an increase in strength of the reaction at the irradiated sites.

Patch testing

Patch tests were performed according to the guidelines of the ICDRG which correspond to those of the DKG (38, 39). *Skin type* was determined according to Fitzpatrick (36). *Atopic disposition of the skin*: The proposal of Diepgen and Fartasch (40) was used to evaluate atopic disposition of the skin.

Table 2. Different photopatch test series of UV absorbers from 1981 to 1996

Period of investigation (mo/year)	3/81-2/84	3/84-6/86	7/86-12/86		1/87-7/89		8/89-12/94	1/95-6/96	7/96-12/96
UV absorbers	Own series conc. (% pet.)	Own series conc. (% pet.)	Own series conc. (% pet.)	Standard ^{a)} conc. (% pet.)	Own series conc. (% pet.)	Standard conc. (% pet.)	Standard conc. (% pet.)	Standard conc. (% pet.)	Standard conc. (% pet.)
isopropylidibenzoyl-methane	10	5, 10	10	5	0.05, 0.5, 2, 10	5	10	10	10
butyl methoxydi-benzoylmethane	—	10	10	—	2, 5, 10	—	10	10	10
benzophenone-3	—	—	—	10	—	2	10	10	10
benzophenone-4	—	—	—	—	—	—	—	—	10
terephthalylidene dicamphor sulfonic acid	—	—	—	—	—	—	—	1 (aqueous, own series)	1 (aqueous, own series)
PABA	—	—	—	5	—	5	10	10	10
octyl dimethyl PABA	—	—	—	—	—	—	10	10	10
methylbenzylidene camphor	3, 10	3, 10	3, 10	—	3, 10	5	10	10	10
octyl methoxy-cinnamate	—	—	undiluted	—	undiluted	—	10	10	10
isoamyl p-methoxy-cinnamate	—	—	undiluted	—	undiluted	—	10	10	10
phenylbenzimidazole sulfonic acid	—	1 (aqueous)	1 (aqueous)	—	1 (aqueous)	—	10	10	10

^{a)} Contained in the German, Austrian, and Swiss photopatch test series and since 1993 in the photopatch test series (Hermal; Trolab) (26).

Results

Of the 402 patients studied, 80 patients (20%) presented with relevant allergic or photoallergic contact dermatitis to UV absorbers. Age and sex distribution of this subgroup is given in Fig. 1.

Reasons for contact with UV absorbers – clinical data (Table 3)

33 patients had normal photosensitivity and used UV absorbers to prevent sunburn, some of them

employed facial cosmetics containing sunscreens for lip and skin care. 9 of these presented with signs of atopic disposition of the skin. 47 patients used UVA and UVB absorbers in high concentrations because of polymorphic light eruption (PLE), chronic actinic dermatitis (CAD) or other photodermatoses and photo-aggravated diseases. Age and sex distribution was typical for PLE and CAD (Fig. 1) (2, 41, 42). 12 of 18 PLE patients presented with signs of atopic skin disposition. Some of them used skin care products containing UV absorbers to combat dry skin and lips or to prevent herpes solaris. In 26 patients the MEDs for UVB and/or UVA were below normal.

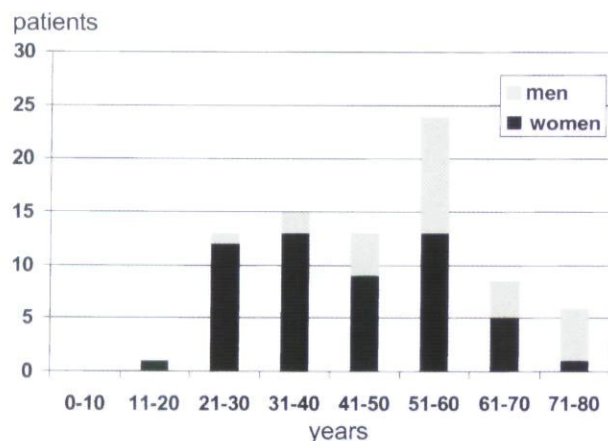


Fig. 1. Ages of 28 men and 52 women sensitive to UV absorbers.

Photopatch test reactions to UV absorbers (Table 4)

80 patients demonstrated positive patch or photopatch tests to sunscreens, of which 102 were to UVA absorbers and 73 to UVB absorbers. UVA filters elicited more allergic (48a) and many more photoallergic (54pa) reactions than UVB filters (43a/30pa). The ratio of 80 subjects to 152 reactions entails that numerous patients had an allergy or photoallergy to more than one sunscreen agent. A total of 84 photoallergic reactions were observed, which would have been missed on simple patch testing. This underlines the importance of including photopatch testing in the investigation of adverse reactions to UV absorbers.

Dibenzoylmethanes

The dibenzoylmethane group (isopropylidibenzoylmethane, butyl methoxydibenzoylmethane) gave rise to most positive results. Overall, isopropylidibenzoylmethane was the most frequent (photo)sensitizer, accounting for 30 allergic and 32 photoallergic reactions. This agent has been used in Europe since 1979 as a UVA filter in medically recommended sunscreens for patients with photodermatoses but also in facial cosmetics. Our patients with increased photosensitivity often used this UVA filter in maximum concentration on damaged skin and were thus particularly prone to develop (photo)allergy to this agent (Table 1). The structurally related butyl methoxydibenzoylmethane was a less common (photo)sensitizer, with 15 allergic and 13 photoallergic reactions (Table 1). A cross-(photo)sensitization reaction between these 2 dibenzoylmethanes can be assumed in 15 patients who had contact with isopropylidibenzoylmethane but not with butyl methoxydibenzoylmethane. None of the patients had an isolated reaction to butyl methoxydibenzoylmethane.

Benzophenones

Benzophenone-3 has been used in Europe since 1980 as a UVA sunscreen. Though it was included in our photopatch test series in December 1986, only 3 allergic and 9 photoallergic reactions to this agent were observed, and none to benzophenone-4, which has been tested since July 1996. Although in 1996, 20–30% of commercial sunscreens on the German market contained benzophenone-3, less than 5% contained benzophenone-4 (43).

Terephthalylidene dicamphor sulfonic acid

Terephthalylidene dicamphor sulfonic acid is also known by its trade name Mexoryl SX and was included in our sunscreen series in January 1995 (Table 2). No allergy nor photoallergy to this new UVA absorber has been observed in our patients (Tables 1, 4). However, 1 case of photoallergy has been reported (10).

Aminobenzoates

PABA and octyl dimethyl PABA accounted for 3 allergic and 4 photoallergic reactions. The well-known sensitization and photosensitization properties of PABA and its derivatives have led to a switch to PABA-free sunscreens considered to be safer. PABA has not been encountered in sunscreens and cosmetics on the German market since 1988 (43). In 1996, only 3% of these commercial products

Table 3. Reason for contact with UV absorbers – clinical data

	Low MED and/or UVB/UVA		Atopic disposition of the skin
	m	w	
<i>Normal photosensitivity</i>			
sun, vacation, skin type I, II skin and lip care	9	24	–
Total	9	24	–
<i>Photodermatoses and photo-aggravated diseases</i>			
polymorphic light eruption	–	18	2
chronic actinic dermatitis	16	1	17
drug photosensitivity	–	2	2
phytophotodermatitis	–	1	–
photo-aggravated atopic dermatitis	–	3	2
discoid lupus erythematosus	1	–	–
herpes solaris	–	1	–
vitiligo	1	–	–
photosensitivity, cause unknown	1	2	3
total	19	28	26

contained octyl dimethyl PABA compared to 15% in 1988. The low incidence of positive reactions to aminobenzoates is probably related to the low frequency of exposure to these agents.

Methylbenzylidene camphor

Methylbenzylidene camphor was commonly used together with isopropylidibenzoylmethane to photostabilize this UVA absorber. This combination is known as Eusolex 8021. The high incidence of 32 allergic and 5 photoallergic reactions to methylbenzylidene camphor must be considered together with the frequent (photo)sensitization to isopropylidibenzoylmethane. Most patients with positive reactions to methylbenzylidene camphor demonstrated concomitant (photo)sensitization to isopropylidibenzoylmethane. After isopropylidibenzoylmethane was removed from the market, only 2 allergic reactions to methylbenzylidene camphor were observed in our patients.

Cinnamates

Octyl methoxycinnamate is the most commonly used UVB absorber in sunscreens and cosmetics. From 1989–1996, 60 to 65% of the sunscreen products on the German market contained this filter (43). Compared to the frequency of exposure the incidence of allergic (3a) and photoallergic (4pa) reactions was low. Isoamyl p-methoxycinnamate is less common in sunscreens and gave rise to 4 al-

Table 4. Allergic and photoallergic reactions to UV absorbers per year from 1981–1996

Year	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96															
Type of reaction	a pa	a pa	a pa	a pa	a pa	a pa	a pa	a pa	a pa	a pa	a pa	a pa	a pa	a pa	a pa	a pa															
<i>UVA absorbers</i>																															
isopropylidibenzoylmethane	1	—	—	2	1	1	1	—	2	—	2	3	—	8	10	6	8	2	2	4	1	2	3	1	1	—	1	—	—	—	
butyl methoxydi-benzoylmethane	nt	nt	nt	2	—	—	1	1	1	1	—	5	5	2	3	2	1	1	1	1	—	—	1	—	—	—	—	—	—	—	
benzophenone-3	nt	nt	nt	nt	nt	—	—	—	—	1	2	2	2	—	—	—	—	—	—	1	—	1	—	1	—	1	—	1	—	1	
Total UVB	1	—	—	2	1	3	1	—	3	1	3	4	—	14	17	10	13	4	3	5	2	3	4	1	3	—	2	—	1	—	1
<i>UVB absorbers</i>																															
PABA	nt	nt	nt	nt	nt	—	—	—	—	1	1	—	—	—	—	—	1	1	1	—	—	—	—	—	—	—	—	—	—	—	
octyl dimethyl PABA	nt	nt	nt	nt	nt	nt	nt	nt	1	1	—	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—	—	
methylbenzylidene-camphor	—	—	—	1	—	1	2	—	—	3	1	11	3	8	1	1	—	2	—	1	—	1	—	1	—	1	—	—	—	—	
octyl methoxycinnamate	nt	nt	nt	nt	nt	—	1	—	1	—	1	—	—	—	—	—	—	2	—	—	—	1	1	—	—	—	—	—	—	—	
isoamyl p-methoxycinnamate	nt	nt	nt	nt	nt	1	1	1	1	—	1	1	—	—	—	—	1	1	—	2	—	2	—	1	—	—	—	—	—	1	
phenylbenzimidazole sulfonic acid	nt	nt	nt	—	—	1	—	—	—	—	1	—	2	—	2	—	—	—	1	—	—	—	1	—	—	—	—	—	—	—	
Total	—	—	1	—	1	3	—	1	2	4	4	12	9	9	3	1	—	4	4	4	2	1	4	2	1	—	—	—	—	—	
no. patients tested	5	8	11	13	10	11	28	59	68	44	28	45	21	20	22	19															
no. patients positive	1	0	3	3	2	4	6	21	16	5	7	5	3	2	1	2															
no. patients reported							7	7+25			32+24																				
reference							(4)	(16)			(20)																				

a=no. of allergic reactions.

pa=no. of photoallergic reactions.

nt=not tested.

lergic and 10 photoallergic reactions. Cross-reactions to both cinnamates were seen in 6 patients. 1 patient with photoallergy to isoamyl p-methoxycinnamate demonstrated allergic reactions to cinnamic alcohol and cinnamic aldehyde, 1 to cinnamic aldehyde, and 1 to balsam of Peru. Both cinnamates were included in our UV absorber series in January 1987 (Table 2).

Phenylbenzimidazole sulfonic acid

Phenylbenzimidazole sulfonic acid is, like terephthalylidene dicamphor sulfonic acid and like benzophenone-4, hydrophilic (Table 1). It elicited 1 allergic and 7 photoallergic reactions. Though this UVB absorber has been on the market since 1933, and was contained in more than 20% of sunscreens on the German market between 1988 and 1996, reports of allergy or photoallergy from phenylbenzimidazole sulfonic acid are rare (Table 1) (10, 33, 43).

Photopatch test reactions to commercial sunscreens and UV-absorbing cosmetics (Table 5)

Of the 80 patients sensitive to UV absorbers, 62 provided the commercial sunscreen products and

facial cosmetics that they had used for patch and photopatch testing. Here, 89 different commercial sunscreens and 15 different UV-absorbing cosmetics were found to elicit 88 allergic and 57 photoallergic reactions. Of these reactions, 64 were caused by a medically recommended sunscreen (Contralum ultra/Hermal) with Eusolex 8021 in maximum concentration (Table 1). Many of the patients reacted to 3 or more commercial sunscreens. In 1987, we first observed a photoallergic contact dermatitis from isopropylidibenzoylmethane in a cosmetic preparation. Since then, special attention has been paid to UV absorbers in cosmetics. Claims such as "protects against environmental damage" refer indirectly to UV filters

Table 5. Summary of positive photopatch tests to 89 different commercial sunscreens and 15 different UV-absorbing cosmetics of 62 patients sensitive to UV absorbers

Commercial products	Reactions	
	allergic (no.)	photoallergic (no.)
sunscreens	72	47
cosmetics	16	10
total	88	57

that absorb solar radiation. The majority of the CAD and PLE patients were unaware of their sunscreen (photo)allergy and considered the flare-up of exposed-site dermatitis as a reason to apply sunscreens with higher sun protection factors. Photoallergic contact dermatitis from UV absorbers in cosmetics remained undiscovered until these commercial products were photopatch tested.

Patch and photopatch test reactions to fragrance materials, preservatives and lanolin alcohol (Table 6)

Although our objective was to investigate sensitization to UV absorbers, it is important to emphasize

that contact and photocontact allergy can also be caused by other ingredients included in formulations.

The summary of patch test and photopatch test reactions to indicators of fragrance (photo)allergy, fragrance materials, preservatives, and lanolin alcohol of patients sensitive to UV absorbers is given in Table 6. In 47 patients, a total of 178 allergic and 14 photoallergic reactions to fragrance materials were observed. 7 patients reacted to perfume oil in commercial sunscreens that they had used. In most cases it was not possible to obtain the complete composition of the perfume oil from the more than 100 commercial products that the

Table 6. Positive patch test and photopatch test reactions to indicators of fragrance (photo)allergy, fragrance materials, preservatives, and emollients of patients sensitive to UV absorbers

Substance	Conc. (%) and Vehicle ^a	No. patients tested	Reactions	
			allergic (no.)	photoallergic (no.)
<i>Indicators of Perfume (photo)allergy</i>				
wood tar	3 pet	59	10	—
colophony	20 pet	59	15	—
balsam of Peru	25 pet	59	23	—
turpentine	10 pet	42	4	ni ^b
<i>Fragrance materials</i>				
fragrance mix	8 pet	59	25	6
α -amyl-cinnamatic aldehyde	1 pet	41	3	—
oak moss	1 pet	41	17	—
eugenol	1 pet	41	6	—
geraniol	1 pet	41	1	—
hydroxycitronellal	1 pet	41	2	—
isoeugenol	1 pet	41	7	—
cinnamic alcohol	1 pet	41	10	—
cinnamic aldehyde	1 pet	41	6	2
musk ambrette	5 pet	59	—	1
α -amyl-cinnamic alcohol	2 pet	20	2	ni
anise oil	10 Ipm	36	4	ni
bergamot oil	25 Ipm	36	18	ni
jasmine oil	30 oo	36	2	ni
peppermint oil	2 pet	36	4	ni
rose oil (natural)	30 oo	36	9	ni
rose oil (artificial)	30 oo	36	6	ni
<i>Perfume oil in commercial sunscreens</i>				
Anthélios products	0.2 par	4	2	2
Contralum Ultra cream	1 pet	5	2	1
Ombra sun milk SPF4	0.2 par	2	—	2
<i>Total</i>			178	14
<i>Preservatives</i>				
formaldehyde	1 aqua	59	3	ni
2-bromo-2-nitropropane-1,3-diol	0.5 pet	59	2	ni
quaternium 15	1 pet	59	1	ni
imidazolidinyl urea	1 pet	59	1	ni
methyl(chloro)isothiazolidine	0.01 aqua	59	8	ni
triclosan	2 pet	59	7	3
methyldibromoglutaronitrile	0.5 pet	59	1	ni
paraben mix	1 pet	59	1	ni
<i>Total</i>			24	3
<i>Emollient</i>				
lanolin alcohol	30 pet	55	2	ni

^a Abbreviation used for the vehicles are as follows: IPM=isopropylmyristate; oo=olive oil; par=liquid paraffine, pet=petrolatum.

^b not irradiated.

patients had provided for testing. Nonetheless, we regard most of the reactions to fragrance materials as being relevant and advised the patients to use fragrance-free sunscreens and cosmetics. 1 woman developed CAD after photoallergy to the perfume oil in Contralum ultra (Table 3 and 5), as a result of our adverse reporting, from 1988–1996 the proportion of fragrance-free commercial sunscreens on the German market increased from 10 to 19% and that of such cosmetics from 7 to 25% (43).

In 11 patients, 24 relevant allergic reactions to preservatives were observed. Since triclosan is not contained in suncreening cosmetics, the 3 photoallergic reactions are not considered relevant. From 1988–1996 the proportion of preservative-free sunscreens on the German market increased from 12 to 27% and that of such cosmetics has remained at about 9% (43). This reflects the need for preservative-free products. Only 2 patients reacted to lanolin alcohol. Since contact and photocontact allergy to multiple cosmetics ingredients is a common feature in CAD patients, they should be advised to use a broad-spectrum barrier preparation without fragrance, preservatives and emollients (2, 42, 44, 45).

Allergen and photoallergen identification and prevention

Whereas at the beginning of this study it was often difficult to obtain information on all ingredients of a product to which a patient showed positive (photo)patch tests, this has become easier over the years with increasing labeling of all ingredients on a voluntary basis. From 1988–1996 the proportion of sunscreens and cosmetics on the German market that list all constituents on the label has increased from 11 to 87% in sunscreens and from 27 to 73% in cosmetics. Thus it has become easier to identify the ingredients that cause the (photo)allergic reaction of a commercial product (43).

Once the culprit has been identified, its INCI designation should be given to the patient, who must be warned to avoid products containing the (photo)allergen (46). The listing of all ingredients in sunscreens and cosmetics according to the INCI declaration has become mandatory in the European Union in 1997. It replaces the nomenclature according to the Cosmetic, Toiletry and Fragrance Association (CTFA) (47) (Table 1).

Discussion and Conclusion

Definition of allergic and photoallergic reactions

Photopatch testing is thought to be an integral part of the work-up of the photosensitive patient (48). However, differences in technique and evalu-

ation make direct comparison between different centers difficult (27). In the present study, a delayed erythematous and/or papular reaction at the non-irradiated sites was defined as an allergic reaction, even if there was an increase in strength of the reaction at the irradiated sites. In the literature this phenomenon is sometimes regarded as concomitant allergic and photoallergic reaction, whereas we consider these reactions consistent with photoaggravation rather than true photoallergy (24, 25). According to our definition of contact and photocontact allergy, 1 patient presented only 1 of these reactions to any given UV absorber.

Incidence of sunscreen allergy and photoallergy

The high incidence of (photo)contact dermatitis from UV absorbers in the present report may be due to the selection of patients and to the frequently applied Eusolex 8021. Of 402 patients with suspected photosensitivity, 80 subjects (20%) demonstrated positive (photo)patch tests to 1 or more UV absorber(s). This incidence of 20% is comparable to that reported by Jeanmougin et al. (33) (25%) and higher than that reported by Menz et al. (9) (10%), de Leo et al. (48) (6%), Gonçalo et al. (31) (1.2%), Léonard et al. (10) (10%), Pakzad et al. (31) (3%), and Pigatto et al. (34) (3%). They also carried out photopatch tests on a selected group of patients with suspected photosensitivity, but their UV absorber series, the concentration of the chemicals, and the sunscreens to which the patients were exposed differed considerably. Freeman et al. (18) reported positive (photo)patch tests to UV absorbers in 10 of 14 patients with suspected sunscreen agent intolerance. This corresponds to an incidence of 71%. As in other studies, most of our cases resulted from photoprotection with high SPF sunscreens but daily cosmetics, which often contain UV absorbers to prevent skin photodamage, have also been found responsible (Table 5).

Sex and age distribution – concomitant photodermatoses

Photobiological investigation was necessary to ensure accurate diagnosis, since sunscreen contact or photocontact allergy may simulate, mask or reinforce photosensitivity eruptions (Table 3). The predominance of 24 females out of 33 patients with normal photosensitivity is explained in that women use more sunscreen products and cosmetics than men. The difference was not as large among patients with photodermatoses and photo-aggravated dermatoses. CAD contributed to the high proportion of 16 men out of 19 and PLE to that

of 18 women out of 28. Another explanation for the predominance of women is that women are more eager to look for dermatological advice than men (25, 31). Age and sex distribution among patients with photodermatoses is explained by the fact that PLE is common among women between 20 and 40 years and CAD is mostly seen in elderly men (Fig. 1) (2, 41, 42).

Atopic skin disposition was registered in 9 out of 33 patients with normal photosensitivity (Table 3). Some of them used skin care products containing UV absorbers to combat dry skin and herpes solaris. The high incidence (66%) of atopic disposition in PLE patients is greater than would be expected (49). 6 out of 16 CAD patients had a history of atopic dermatitis. This disease may precede CAD (41).

Prevalence of allergy and photoallergy to different UV absorbers in the course of time

The high number of positive reactions to isopropyl-dibenzoylmethane, butyl methoxydibenzoylmethane, and methylbenzylidene camphor is explained by cross-reactions between the dibenzoylmethanes and by coupled reactions to Eusolex 8021 (isopropyl-dibenzoylmethane and methylbenzylidene camphor) (Table 4). Many of our patients with photosensitivity diseases used Eusolex 8021 in broad-spectrum sunscreens. The high incidence of positive patients and of positive (photo)patch tests to sunscreens in 1988 and 1989 was induced by the combination of concomitant and coupled (photo)allergy to Eusolex 8021 and to butyl methoxydibenzoylmethane (Table 4). With adverse reporting, commercial sunscreens and cosmetics that contain the strongest (photo)sensitizer isopropyl-dibenzoylmethane decreased to almost zero in 1993, when Merck/Darmstadt stopped the production of this UVA absorber (43). Meanwhile the proportion of butyl methoxydibenzoylmethane increased from 20% in 1988 to 55% in 1996, and that of methylbenzylidene camphor remained steady over the years at about 30% in commercial sunscreens on the German market (43). Nevertheless, from 1994 on, adverse reactions to these 2 UV absorbers, but also to other UV filters have become rare (Table 4).

Dual contact or photocontact allergy to Eusolex 8021 and coupled (photo)allergy to both dibenzoylmethanes has frequently been reported (10, 24, 27, 33, 50, 51, 53).

An isolated photoallergy to butyl methoxydibenzoylmethane has not been observed in our patients. It has been seen in the US and Australia, where isopropyl-dibenzoylmethane has not been on the market (18, 54, 55). According to our recent

experience, it is not likely that it will become a major sensitizer in the US even with more widespread use.

Contrary to our results, allergy and photoallergy from dibenzoylmethanes have been less often reported than from benzophenones (2, 10, 18, 27, 31, 33, 56–62). With the combination of up to 4 UV absorbers in sunblockers, relatively high concentrations (up to 40%) of active ingredients are applied topically. As with other chemicals, increasing the concentration of active ingredients also increases the likelihood of (photo)sensitization, especially, if applied on damaged skin (24). The high concentration of UV absorbers in sunblockers may account for the fact that many of our patients had an allergy or photoallergy to more than one UV filter.

The photopatch test series of UV absorbers, as well as the positive reactions in the present study and the reports in the literature, reflect the history of sunscreen (photo)allergy (Tables 2, 4) (24, 25). Increasing awareness of the public of (photo)sensitization to PABA and its derivatives has encouraged the use of PABA-free sunscreens in the US, Europe, Japan, and Australia. However, as benzophenone-3 (oxybenzone) has been used extensively as an alternative to PABA, reports of allergic and photoallergic reactions have increased (18, 26, 27, 29–31, 34, 48, 61, 63–73). Oxybenzone has to be labeled on the packaging as a warning (Table 1). The current shift from PABA-free to oxybenzone-free sunscreens has led to a third wave of (photo)allergy to dibenzoylmethanes. Before terephthalylidene sulfonic acid came on the market, dibenzoylmethanes were the only potent UVA absorbers. Although the benzophenones have an absorption spectrum that extends into the UVA range, they cannot be considered as very efficient UVA filters. Since UVA radiation elicits or aggravates photodermatoses, photosensitive patients were advised to use UVA absorbers. These sunscreens have also been incorporated in facial cosmetics to prevent photoaging. With increasing use of dibenzoylmethanes, especially of isopropyl-dibenzoylmethane, (photo)allergies to these agents have been increasingly reported. They have been the 2nd most common cause of sunscreen (photo)allergy in other reports (3, 24, 27, 30, 31, 74) and the commonest in the present and 2 multicenter studies (26, 75). Now that the strong (photo)sensitizer isopropyl-dibenzoylmethane has been removed from the market, (photo)allergies to butyl methoxydibenzoylmethane have become rare (33).

In recent years, cinnamates have emerged as an alternative to PABA and benzophenones in Europe, the US, Japan, and Australia (76). However, with increasing use, evidence has emerged

that they too elicit (photo)allergy. We found 7 allergic and 14 photoallergic reactions to cinnamates in our patients. Considering the widespread use of cinnamates in about 70% of commercial sunscreens on the German market, reports of allergy and photoallergy are rare. Therefore these filters may be regarded as relatively weak photosensitizers (Table 1) (2, 10, 27, 31–33, 77–79). Cross-sensitizations between different cinnamates were seen in our patients. Compounds that have been reported to cause such reactions with isoamyl p-methoxy-cinnamate include cinoxate, balsam of Peru, benzyl cinnamate, cinnamic alcohol, and methylcinnamate (24). Cinnamates were not included in the standard photopatch test trays (Hermal/Trolab) before 1993 (Table 2). This may have contributed to the rare reports of (photo)allergy to these UV absorbers.

We found no instance of CAD from UV absorbers. However, 1 woman developed CAD after photoallergy to perfume oil in the commercial sunscreen Contralum ultra (Tables 3, 6). This was the reason for removing fragrance from this medically approved sunscreen.

Sunscreen photopatch test trays in Europe and in the United States

Prompted by our 1st reports of (photo)allergy to isopropylidibenzoylmethane, butyl methoxydibenzoylmethane, and methylbenzylidene camphor, and based on our findings with octyl methoxycinnamate, isoamyl p-methoxycinnamate, and phenylbenzimidazole sulfonic acid in different test concentrations and vehicles, these UV filters have been included in the German, Austrian, and Swiss photopatch test series and later in the standard photopatch test tray (Hermal/Trolab) (Table 2) (20). By the end of 1997, isopropylidibenzoylmethane will be replaced by terephthalylidene sulfonic acid in this standard series. The suggested UV absorbers for photopatch testing in the UK will be the same as those in the coming sunscreen series in Germany, except for benzophenone-4, terephthalylidene dicamphor sulfonic acid, methylbenzylidene camphor, isoamyl p-methoxycinnamate, and phenylbenzimidazole sulfonic acid, which will not be tested in the UK (80, 81). Whereas in Germany a UVA dose of 10 J/cm² is used for photopatch testing, in the UK a UVA dose of 5 J/cm² is recommended (26, 81).

In Italy, the same UV absorbers as in Germany are included in the actual photopatch test tray, except for phenylbenzimidazole sulfonic acid (34). Compared to the future German UV absorber series, the French test tray contains, in addition, benzophenone-10 (10). In the US, octyl methoxy-

cinnamate, benzophenone-4, octyl salicylate, and homosalate have recently been added to PABA, octyldimethyl PABA, benzophenone-3, and butyl methoxydibenzoylmethane (48, 55). This new series reflects their real exposure. The frequency of sunscreen use in 1996, as reported in the FDA voluntary reporting database, was for octyl methoxycinnamate 688, benzophenone-4 462, benzophenone-3 402, octyl dimethyl PABA 327, PABA 42, butyl methoxydibenzoylmethane 30, octyl salicylate 95, and DEA-methoxycinnamate 56 (54).

Improving prevention

In Germany, UV absorbers have become the most important, relevant photoallergens in recent years (26, 37). However, diagnosis may not always be obvious to the physician or to the patient photosensitized by sunscreen products or cosmetics containing UV absorbers. Until 1997, manufacturers in Europe changed sunscreen constituents without changing label information. Now that complete ingredient labeling according to INCI has become mandatory in the EU, diagnosis and prevention has become easier, provided that careful patch and photopatch testing is performed and that the physician as well as the patient know the INCI designation of the (photo)-allergenic ingredient (s) and of the product that should be avoided (Table 1). Reporting of adverse reactions and cooperation between physicians and manufacturers of sunscreens has resulted in increased product safety.

Producers of commercial sunscreens have been encouraged to incorporate micronized, physical UV blockers either to replace or to reduce chemical absorbers. From 1988–1996, the proportion of sunscreens and cosmetics on the German market that contain physical UV blockers has increased from 8 to 60% in sunscreens and from 16 to 48% in cosmetics (43). Some sunscreen products with SPF up to 50 are exclusively based on TiO₂ and ZnO (43). Since 1995, coated micronized TiO₂ and ZnO are provisionally allowed as sunscreens in the EU (82). These ingredients are a safe alternative to UV absorbers, especially for patients with damaged skin.

The establishment of a registry for adverse reporting of sunscreen agents would help to characterize the (photo)sensitization rate, adapt the photopatch test tray, and provide more safety by removing and replacing frequent (photo)sensitizers (34).

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