

Octocrylene, an Emerging Photoallergen

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Background: Octocrylene is a new emerging photoallergen. We report and discuss 50 cases of photoallergic contact dermatitis from octocrylene use and/or positive photopatch test reactions to this UV filter and draw attention to the unexpected association in adults with a history of photoallergic contact dermatitis from ketoprofen.

Observations: Patients were divided in 3 groups: group A comprised 11 children; group B, 28 adults with a history of photoallergy from sunscreen products; and group C, 14 adults systematically tested with octocrylene because of a history of photoallergy from ketoprofen. All patients but 3 in group C had positive test reactions to octocrylene. Ten of 11 children in group A and 9 of 28 adults in group B had positive patch test reactions to octocrylene. One child in group A, the other 19 adults in group B, and 11 of 14 adults in group C had positive pho-

topatch test reactions to octocrylene. All adults in group C and 24 of 28 adults in group B had a history of photoallergy from ketoprofen and positive patch test or photopatch test reactions to other allergens that are often positive in patients with photoallergy from ketoprofen, especially fragrance components.

Conclusions: Octocrylene appears to be a strong allergen leading to contact dermatitis in children and mostly photoallergic contact dermatitis in adults with an often-associated history of photoallergy from ketoprofen. Patients with photoallergy from ketoprofen frequently have positive photopatch test reactions to octocrylene. These patients need to be informed of sunscreen products not containing octocrylene, benzophenone-3, or fragrances.

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PREVENTION OF PHOTOAGING and photocarcinogenesis has resulted in a huge increase in the use of sunscreen products. Sunscreens have traditionally been divided into chemical absorbers that mainly reflect or scatter UV rays and physical blockers that mainly absorb high-intensity UV rays. These very chemically reactive UV filters are well known for inducing allergic contact dermatitis as well as photoallergic contact dermatitis (PACD), even if such reactions remain uncommon.¹ Nevertheless, sunscreen chemicals are, along with drugs, the most common causes of PACD.¹⁻⁴ New UV filters have been introduced to replace allergenic ones, especially benzophenone-3, and to enhance the prevention of sun-induced skin damage. Octocrylene is one of those new UV filters. It is an ester formed by the condensation of a diphenylcyanoacrylate with 2-ethylhexanol and is considered to belong to the family of cinnamates. It was introduced in sunscreen products approximately 10 years ago and is increasingly used because of its spectrum efficiency, covering mostly UV-B but also short UV-A wavelengths.⁵ It is often used in combination with other UV absorbers, especially cinnamates and butyldibenzoylmethane, to achieve a higher sun protection factor (SPF) and to also add to their overall stability and water resistance.

The first cases of PACD from octocrylene were reported in 2003 by Carrotte-Lefebvre et al,⁶ and since then, only 4 cases have been reported in 2 other articles.^{7,8} However, very recently, a study on photopatch testing in Italy reported 19 cases of positive photopatch test reactions to octocrylene.³ Our objective was to report and discuss 50 cases of photoallergic contact dermatitis from octocrylene and/or positive photopatch test reactions to this UV filter gathered in France and Belgium by the REVIDAL⁹ (Réseau de Vigilance en Dermato-Allergologie) over a period of 2 years. Furthermore, we would also like to draw attention to the unexpected association of PACD from both octocrylene and ketoprofen.

METHODS

Thirty-nine patients were photopatch tested because of adverse skin reactions from sunscreen products. They were divided into 2 age-based groups. Group A included 11 children (8 girls and 3 boys), with a mean (range) age of 7 (2-16) years (**Table 1**). Of these 11 children, 4 had a history of atopy and 7 had the first skin manifestations before the age of 3 years. Group B comprised 28 adult patients (10 men and 18 women) with a mean (range) age of 40 (18-69) years (**Table 2**). Of these 28

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Table 1. Allergic Contact Dermatitis From Octocrylene in Sunscreen Products in Children (Group A)

Patient No./ Sex/Age	History	Eczema	PT With Octocrylene ^a	Other Positive PT Reaction	PT With Sunscreens Used (Manufacturer)
1/F/7		Face	++		Vichy Capital soleil lait enfant IP 60++ (Vichy Laboratories, Vichy, France)
2/M/11	Atopy	Generalized	++		Avène spray SPF 50++ and Avène spray enfant SPF 40+ (Avène Laboratories, Avène, France)
3/M/4		Treated areas	++		Photoderm AKN Avène 50++ (Bioderma Laboratories, Lyon, France)
4/F/8 ^b		Cheeks	++	Butyl methoxydibenzoyl methane (at day 7)	Photoderm SPF 40++ (Bioderma Laboratories)
5/F/10 ^b		Face	++	Benzophenone-4	Different sunscreens
6/F/2 ^b		Face, forearms	++		Avène spray enfant SPF 40+ (Avène Laboratories)
7/F/16 ^c	Atopy	Treated areas	++		Different sunscreens
8/M/6 ^b	Atopy	Face	++		Lait Vichy 50+ (Vichy Laboratories); Lait Ambre Solaire SPF 30 (Garnier Laboratories, Paris, France)
9/F/3 ^b		Sun-exposed areas	Neg but PPT+		Photoderm max 50+ (Bioderma Laboratories)
10/F/3 ^b		Treated areas	++		Anthelios 50+ enfant (La Roche Posay Laboratories, La Roche Posay, France); Uriage SPF 50 (Uriage Laboratories, Uriage, France)
11/F/10 ^b	Atopy	Treated areas	++		Ombra lait solaire (unknown)

Abbreviations: Neg, negative; PPT, photopatch test; PT, patch test; SPF, sun protection factor.

^aSee "Methods" section for explanation of plus signs.

^bBeginning before the age of 3 years.

^cBeginning in childhood.

Table 2. Photoallergic Contact Dermatitis From Octocrylene in Sunscreen Products in Adults (Group B)

Patient No./ Sex/Age	History of PACD From KP	Localization	Particularity	Sunscreen Product Used
1/M/31	Yes	Neck, forearms	Recurrence from passive transfer	Avène spray SPF 40 (Vichy Laboratories, Vichy, France); Photoderm SPF 50 (Bioderma Laboratories, Lyon, France)
2/F/18	Yes	Face		Minesol SPF 30 (RoC Laboratories, Paris, France)
3/F/37	Yes	Face	Hand transfer	Ambre Solaire Clear Protect SPF 20 (Garnier Laboratories, Paris)
4/F/29	Yes	Sun-exposed areas		Vichy Capital Soleil SPF 20 (Vichy Laboratories); Anthelios SPF 40 (La Roche Posay Laboratories, La Roche Posay, France); Ambre Solaire UV ski IP 25 (Garnier Laboratories)
5/M/53	Yes	Face		Avène spray SPF 50 (Avène Laboratories, Avène, France)
6/M/43	Yes	Hands		Photoscreen 50 (Ducray Laboratories, Pierre Fabre Dermocosmetics, Castres, France)
7/F/57	Yes	Neck		Anthelios XL lait 40 (La Roche Posay Laboratories)
8/M/54	Yes	Face		Vichy Capital Soleil (Vichy Laboratories)
9/F/21	Yes	Face, forearms		Avène SPF 50 (Vichy Laboratories); Photoderm max (Bioderma Laboratories); Ambre Solaire SPF 10 (Garnier Laboratories)
10/M/37	Yes	Face		Ambre Solaire 50+ UV sensitive (Garnier Laboratories); Vichy Capital Soleil 50+ (Vichy Laboratories)
11/F/32	Yes	Sun-exposed areas		Anthelios XL and Anthelios S40 enfant (La Roche Posay Laboratories); Spray solaire L'Oréal SPF 20 (L'Oréal, Paris, France)
12/F/30	Yes	Sun-exposed areas		Anthelios crème 50+ and Lait 40 (La Roche Posay Laboratories)
13/M/34	Yes	Treated areas		Ambre solaire lait enfant SPF 60 (Garnier Laboratories)
14/F/50	Yes	Treated areas		Dermactive 50+ Sogiphar (Sogiphar cooperative, Grandvilliers, France)
15/M/49	Yes	Face, forearms		Avène 50+ Spray (Vichy Laboratories)
16/F/56	Yes	Face, neck		Anthelios XL 50+ and Anthelios XL 60 (La Roche Posay Laboratories)
17/F/35	Yes	Face		Different sunscreens
18/F/30	Yes	Face		Different sunscreens
19/F/57	Yes	Arms, legs		L'Oréal Solaire Expertise 50+ (L'Oréal)
20/F/32	Yes	Face, hands		Lait Avène 50+ (Avène Laboratories, Avène)
21/F/51	No	Face		Anthelios Fluide Extreme SPF 40 (La Roche Posay Laboratories)
22/M/40	No	Legs		Vichy Capital Soleil SPF 20 (Vichy Laboratories)
23/F/44	No	Total body		Vichy Capital Soleil SPF 20, 50, 60 (Vichy Laboratories)
24/F/42	Yes	Sun-exposed areas		Anthelios XL enfant (La Roche Posay Laboratories)
25/M/35	Yes	Sun-exposed areas		Anthelios XL 50+ lait enfant (La Roche Posay Laboratories); Sun All Day Widmer SPF 20 (Louis Widmer Laboratories, Schielren, Switzerland)
26/M/69	Yes	Face, forearms, hands		Minesol RoC 50+ fluide (RoC Laboratories)
27/F/42	Yes	Sun-exposed areas		Anthelios XL, Uriage 50 (La Roche Posay Laboratories)
28/F/41	Yes	Face		Anthelios Sunspray SPF 20 (La Roche Posay Laboratories); Estée Lauder Daywear SPF 30 (Estée Lauder Inc, New York, NY)

Abbreviations: KP, ketoprofen; PACD, photoallergic contact dermatitis.

adults, 24 had a history of PACD from ketoprofen. Later, we added a third group (group C) comprising 14 adult patients (7 men and 7 women) with a mean (range) age of 47 (29-72) years, who underwent testing because of acute eczema following topical application of a ketoprofen gel (**Table 3**). However, they did not report any history of skin reactions from sunscreen products.

Whenever possible, patch tests with the patients' personal sunscreen product used were also performed with the European baseline series (in France, Chemotechnique [Chemotechnique Diagnostics, Vellinge, Sweden], or in Belgium, Trolab [Hermal AG, Reinbeck, Germany]). One child (group A, patient 4) had patch tests only with her own products. The patch test materials used were Haye's Chambers (Haye's Service B.V., Alphen aan den Rijn, the Netherlands) in France, Finn Chambers (Epitest Ltd Oy, Tuusula, Finland) in France and Belgium, and Van der Bend Chambers (Van der Bend, Brielle, the Netherlands) in Belgium, with 2 readings, the first on day 2 or 3 and the second on day 3 or 4 and sometimes also on day 7. Additional patch tests were performed with the ingredients of the sunscreen products provided by the manufacturers, and every patient underwent patch tests with octocrylene (10% concentration in petroleum) (Chemotechnique). Four children (group A, patients 4 and 8-10) and all adult patients (groups B and C) but 2 (group B, patients 9 and 14) underwent photopatch testing with octocrylene. Patients 6 to 11 and 15 to 28 in group B and all patients in group C but 4 (patients 2-4 and 14) also had photopatch tests with the European baseline photopatch tests series. Patients 1 to 5 (group B) and 2 to 4 and 14 (group C) had photopatch tests with the ingredients of the commercial ketoprofen-containing gel and also benzophenone-3 and fenticlor. Duplicate allergens were applied to the mid-upper back, and 1 set was irradiated on day 1 with 5 J/cm² of fluorescent UV-A using PUVA 800 Waldmann (Herbert Waldmann GmbH & Co KG, Villingen-Schwenningen, Germany), in France, Alfasun (BLS Light System Products, Wolveterm, Belgium) in Belgium, and Philips Performance UVA 100-W-R lamps (Philips International B.V., Amsterdam, the Netherlands) in France and Belgium. Readings were performed after removal of the control set on days 2 and 3 after irradiation and sometimes also on day 7 after irradiation. According to the criteria of International Contact Dermatitis Research Group, + indicates weak positive reaction with erythema and edema; ++, true-positive reaction with erythema, edema, and vesicles; and + + +, strong positive reaction spreading locally with sometimes bullae.

RESULTS

All patients but 3 (group C, patients 3, 11, and 12) showed an allergic reaction to octocrylene. A positive patch test reaction to octocrylene was found in all the children but 1 (group A, patient 9; Table 1) and in 9 adults, 5 of whom showed a photoaugmentation, as they presented with a stronger reaction after irradiation (Table 3 and **Table 4**). All other adult patients and 1 child showed a positive reaction only on the photopatch test with octocrylene. All positive patch and photopatch test reactions to octocrylene in group B were relevant, since all the patients had positive patch test or photopatch test reactions to their own octocrylene-containing sunscreen products or reported a history of adverse reactions to them. However, no relevance could be determined for the positive photopatch test reactions to octocrylene in the group C patients.

Octocrylene was the only allergen in the group A children except 2 who had a positive reaction to other UV

Table 3. Results of PTs and PPTs With Octocrylene in Ketoprofen Photoallergic Patients (Group C)^a

Patient No./ Sex/Age, y	Ketoprofen		Octocrylene ^b	
	PPT		PT	PPT
1/M/67	++		Neg	++
2/F/32	++		Neg	++
3/M/29	++		Neg	Neg
4/M/72	++		Neg	++
5/F/43	++		+	+
6/F/36	++		+	++ ^c
7/M/51	++		+?	++ ^c
8/M/41	++		Neg	++
9/M/49	++		Neg	+
10/F/58	++		Neg	++
11/F/38	++		Neg	Neg
12/F/53	++		Neg	Neg
13/F/39	++		Neg	+
14/F/54	+++		Neg	+

Abbreviation: Neg, negative; PPT, photopatch test; PT, patch test.

^a See "Methods" section for explanation of plus signs. +? indicates doubtful reaction.

^b No relevance for positive test reactions to octocrylene.

^c Photoaugmentation.

filters—butylmethoxydibenzoylmethane (patient 4) and benzophenone 4 (patient 5). All patients with a history of PACD from ketoprofen had positive patch test and/or photopatch test reactions to 1 or more of the different allergens that are usually positive in such patients, in particular, fragrance components (Table 4).¹⁰

COMMENT

The occurrence of allergic contact dermatitis and PACD from octocrylene has been increasing over the past 2 years, along with the increase of its inclusion in sunscreen formulas (**Figure**). Six cases of PACD were published between 2003 and 2006⁶⁻⁸—3 children with severe allergic contact dermatitis, one of them after passive transfer,⁷ who strongly reacted to patch tests with octocrylene, and 3 adults who had PACD and strongly reacted to photopatch tests with octocrylene. Two of them had also a history of PACD from ketoprofen.

Our experience and the published cases lead us to outline striking findings. First, octocrylene seems to be a strong allergen because allergic dermatitis can be induced by passive transfer. Second, it seems that allergic reactions to this UV filter are age dependant: all 11 children except 1 had allergic contact dermatitis, whereas adults mainly presented with PACD. Third, among the adults, we observed a very high incidence (more than 80%) of an associated history of PACD from ketoprofen, which was confirmed by positive photopatch test reactions to this non-steroidal anti-inflammatory drug. Furthermore, the most recent reviews on PACD from ketoprofen¹¹⁻¹³ showed that positive photopatch test reactions to octocrylene (as well as to benzophenone-3, fenticlor, or fenofibrates) were frequently observed in such patients. This also applies to 11 of the 14 patients in group C, in whom the positive photopatch test reactions to octocrylene were not relevant, since these patients had never used nor experienced any ad-

Table 4. Results of PTs and PPTs in Adult Patients in Group B^a

Patient No.	Sunscreen Product		Octocrylene		Ketoprofen	Other Positive PT Reactions	Other Positive PPT Reactions
	PT	PPT	PT	PPT	PPT		
1	Neg	+++	Neg	+++	+++	FM, MP	
2	Neg	+++	Neg	++	++	FM, MP	FT
3		Neg	Neg	+	++	FM, MP	FT
4	Neg	++	Neg	++	+++	FM, MP	FT, O
5	+	+	Neg	+	++	FM, MP	FT
6	Neg	++	+	+++ ^b	++	FM, MP, MCB	FN, O
7	Neg	++	Neg	++	+++	FM, MP	FN, O
8	Neg	++	Neg	++	++		
9		Neg	Neg	+	++	FM, IAM	
10		ND	Neg	+	++		FT
11	++	ND	Neg	+	ND	FM, MP	FT, O
12		ND	Neg	+++	ND		FT, O
13	++	ND	++	ND	ND		ND
14	++	ND	++	ND	ND	FM, MP	ND
15	Neg	++	Neg	++	++	FM	O
16	++	++	++	+++ ^b	+++	FM, MCB	FN
17		ND	Neg	++	+++		O
18		Neg	+	+++ ^b	+++	FM	B, O
19	Neg	++	Neg	++	ND	FM	B, FN, O
20		ND	++	++	+++	B, FM, FN, O	
21	Neg	+	Neg	+	ND		
22		ND	Neg	++	ND		
23		ND	Neg	++	ND		
24		ND	Neg	++	++	FM, MP	IDB, O
25	Neg	++	Neg	+++	+++	FM, MP	IDB, O
26	Neg	+	Neg	++	++	FM	
27		ND	Neg	++	+++	FM	O
28	+	++	Neg	++	+++	FM	

Abbreviations: B, benzophenone-10; FM, fragrance mix; FN, fenofibrate; FT, fenticlor; IAM, isoamyl methoxycinnamate; IDB, isopropyl dibenzoylmethane; MCB, methylbenzylidene camphor; MP, *Myroxylon perairae*; ND, not done; Neg, negative; O, benzophenone-3; PPT, photopatch test; PT, patch test.

^aSee "Methods" section for explanation of plus signs.

^bPhotoaugmentation.

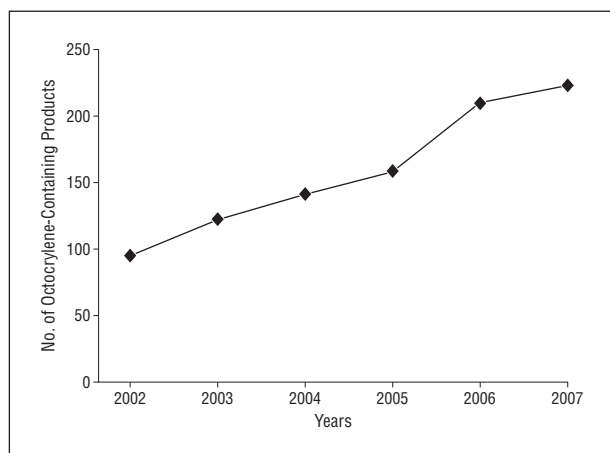


Figure. Increasing number of octocrylene-containing sunscreen products in France from 2002 to 2007.

verse effect from a sunscreen product. The explanation for this frequent association remains unclear.

Indeed, octocrylene has no chemical similarities with ketoprofen, nor with fenticlor, that also frequently produces a positive photopatch test reaction in patients with PACD from ketoprofen. Recently, Foti et al¹³ published the results of a study that aimed to identify the substances most often associated with PACD from ketoprofen and to evaluate, by means of computerized conforma-

tional analysis, if this association could be due to cross-allergy. All patients had positive patch test reactions to cinnamyl alcohol, which is a component of fragrance mix, and 67% reacted to fragrance mix, which is similar in our study, since 20 of 28 subjects (71%), reacted to it (Table 4). Positive reactions on photopatch tests were also found with fenticlor (27%), octocrylene (20%), and benzophenone-10 (20%). The computerized conformational analysis showed a strong similarity between the standard structure of cinnamyl alcohol and the UV-A-excited ketoprofen structure. On the contrary, benzophenone-10 and hydrolyzed octocrylene showed weaker similarity. According to the article by Foti et al,¹³ these findings suggest that there is a cross-allergy between cinnamyl alcohol and ketoprofen but not with benzophenone-10, octocrylene, or fenticlor. However, fenticlor is no longer used in cosmetics because it has been prohibited in Europe since the 1970s, together with other halogenated salicylanilides.⁹ More studies on the chemical structure and the chemical reactivity of these molecules, especially octocrylene, need to be performed to achieve an exact explanation of these clinical findings. Finally, in contrast to octocrylene and fenticlor, the UV filters benzophenones and fenofibrates have a chemical structure close to the one of ketoprofen; hence, cross-reaction mechanisms may be able to explain the frequently associated positive photopatch tests results to these UV filters.¹⁴

In conclusion, our observations, which are in agreement with other recent studies,¹⁰⁻¹² give rise to some recommendations. Octocrylene may induce severe allergic contact dermatitis in children, which should warn us to be more cautious in the use of octocrylene-containing sunscreens in young individuals. In adults, octocrylene more often causes PACD, which is frequently associated with a history of PACD from ketoprofen. Moreover, patients with PACD from ketoprofen very often present with positive photopatch test reactions to octocrylene. Hence, they need to be aware of this risk and avoid sunscreen products containing octocrylene, benzophenone-3, and fragrances.

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