Contact and photocontact allergy to octocrylene: a review

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Summary

Octocrylene is an ultraviolet (UV)B and UVAII absorber that was introduced some 15 years ago, and is now widely used in sunscreen agents and skin care cosmetics. Since 2003, several studies, notably from France, Belgium, Spain, and Italy, have reported an increasing number of patients with photocontact allergy to octocrylene. This reaction is seen mainly in adult patients who have previously used topical products containing the non-steroidal anti-inflammatory drug ketoprofen. Photosensitization to ketoprofen leads, in many cases, to photocontact allergy to octocrylene; the mechanism of this reaction is unknown. Contact allergy to octocrylene also occurs, but is far less frequent, and is seen, in most cases, in children, resulting from the use of octocrylene-containing sunscreen products. In this article, (photo)contact allergy to octocrylene is fully reviewed.

Key words: benzophenone-3; contact allergy; ketoprofen; octocrylene; photocontact allergy; photopatch tests; photo-cross-reactivity; sunscreen; UVA-absorber; UVB-absorber.

The rise in public awareness of the harmful effects of the sun's ultraviolet (UV) radiation, such as sunburn, skin cancer, and photoaging, has led to an increase in the use of sunscreen products. Octocrylene is a relatively new UV-filter that was introduced in sunscreens and daily care cosmetic products in the late 1990s. Since 2003, several studies have indicated that octocrylene not infrequently causes photocontact allergy/photoallergic contact dermatitis, notably in adult patients previously photosensitized to ketoprofen in topical medications. Allergic contact dermatitis is seen to a lesser degree, usually in children, and is caused by sensitization to octocrylene in sunscreen products.

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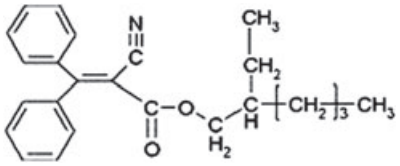
Profile of Octocrylene

The UV-absorber octocrylene is an ester formed by the condensation of diphenylcyanoacrylic acid with 2-ethylhexanol, and is considered to belong to the family of cinnamates. Some of its characteristics are shown in Table 1.

The action spectrum of octocrylene (290–360 nm, peak absorption at 303 nm) covers mostly UVB wavelengths, but also short UVA wavelengths (UVAII) (1–4). However, it is not a very effective filter, and for this reason octocrylene is usually combined with other UVB agents to increase the sun protection factor (SPF) of a sunscreen product, notably other cinnamates (1). Octocrylene has excellent photostability (5), and is used as a stabilizer for other photo-unstable UV-filters (1, 5, 6), and to also improve their overall stability and water resistance (3). This applies particularly to the widely used UVA-filter butyl methoxydibenzoylmethane, which suffers from substantial decomposition under sunlight exposure, leading to a decrease in the photoprotective efficacy of the cosmetic formulations that use it (7). Octocrylene is miscible with many cosmetic oils; it is one of the few UV-filters that can easily be incorporated into gel sunscreens (1).

Table 1. Characteristics of octocrylene

CAS	6197-30-4
EINECS	228-250-8
IUPAC name	2-Ethylhexyl 2-cyano-3,3-diphenylprop-2-enoate
Synonyms	2-Cyano-3,3-diphenylacrylic acid 2′-ethylhexyl ester; 2′-ethylhexyl 2-cyano-3-phenylcinnamate; 2-ethylhexyl-2-cyano-3,3-diphenylacrylate
Trade names examples	Escalol® 597 (Ashland); Eusolex® OCR (Merck); Maxgard® DPA-8 (Syrgis); Neo Heliopan® 303 (Symrise); Parsol® 340 (DSM); Seesorb® 502 (Shipro); Uvinul® 539 T (BASF)
Absorption spectrum	290–360 nm (UVB, UVAII) (1, 2)
Peak absorption λ_{max}	303 nm (2)
Critical wavelength λ_c[a]	356 nm (1)
Molecular formula	$C_{24}H_{27}NO_2$
Molecular weight	361.5
Structural formula	

[a]λ_c critical wavelength: the wavelength below which 90% of the sunscreen's ultraviolet absorbance occurs (1).

This UV-absorber is used not only in sunscreen preparations, but also in skin care cosmetics (daily skin care products), such as day creams and anti-ageing creams, to retard photodegradation of the product, extend its shelf-life, and protect the consumer from UV-damage (3). Octocrylene is permitted in both the EU (8) and the United States (9) as a UV-absorber (United States: light stabilizer) and a UV-filter (United States: sunscreen agent) up to 10% in sunscreens and (other) cosmetics. Another application is in the protection of plastics, coatings and adhesives from UV radiation (www.syrgis.com).

Extent of the Usage of Octocrylene

In 2001, 75 sunscreen products, creams and lotions from 30 cosmetic manufacturers in Europe and the United States and collected from Danish retail outlets were analysed for the presence of a number of UV-absorbers, including octocrylene. Octocrylene proved to be present in 17 of 75 products (23%). The concentration range was 1.2–10.4% (mean 7.7%, median 9.2%). Only two other UV-absorbers were identified more often: ethylhexyl methoxycinnamate (49%) and butyl methoxydibenzoylmethane (44%) (10).

Of 35 cosmetic products purchased in 2008 in perfume stores and pharmacies in France claiming to have an SPF between 4 and 30 (six day creams, eight anti-aging creams, 10 tinted face creams and foundations, six self-tanning lotions, one skin-lightening cream, two anti-redness creams, and two spot remover creams), 10 (29%) contained octocrylene (11).

In the United States, the combination of octocrylene and butyl methoxydibenzoylmethane was not present in any of 48 commercial sunscreens purchased in 1999 in Cincinnati, Ohio (12). In 2003, these UV-filters were identified in 12% of 118 products, and in 2009, over half (54%) of 141 commercial sunscreens were found to contain octocrylene + butyl methoxydibenzoylmethane. In the same period, the frequency of their combined presence in cosmetic products not specifically intended for protection against UV, such as moisturizers, colour cosmetics, foundations, eye creams, and lip balms, rose from 0% to 23% (12).

In the United Kingdom in 2010, 91% of 337 sunscreens (316 for the skin, 18 for the lips alone, and three for a combination of both) were found to contain octocrylene (13). In a similar UK study performed in 2005, the proportion was only 36% (14), which represents a 2.5-fold increase in the use of octocrylene in sunscreen products available in the United Kingdom between 2005 and 2010 (13, 14).

In Switzerland, in 2011, 33 of 39 sunscreens (85%) contained octocrylene, and the UV-filter was present in 17 of 77 (22%) other cosmetic products. Concentrations ranged from 1.03% to 9.86%, with a mean and median of ~6%; similar results were obtained for sunscreens and other cosmetics intended for daily use. This means that the latter, widely used, product category may be an important source of exposure to octocrylene (15). In The Netherlands, in 2013, > 80% of 50 sunscreens randomly collected by the Netherlands Food and Consumer Product Safety Authority proved to contain octocrylene (DE Hissink, unpublished data, written communication, November 2013).

Thus, it appears that, generally speaking, the use of octocrylene in sunscreens and skin care cosmetics has

increased rapidly since the beginning of this century. At present, in the United States and European countries, the majority (in some countries, > 80%) of sunscreens may contain octocrylene; also, this UV-absorber may be present in > 20% of daily skin care cosmetics.

Contact Allergy

Sensitizing potency

The sensitizing potency of octocrylene has been assessed in the murine local lymph node assay (16). Octocrylene was shown to be a moderate sensitizer, with an EC3 value of 7.7% or 0.21 M (17). This chemical has been shown to react with the amines benzylamine and *N*α-acetyl-L-lysine methyl ester at room temperature via an initial Michael-type addition, followed by a reaction sequence corresponding to a retro-aldol reaction. It has been suggested that octocrylene's reactivity towards amines is the explanation for its ability to cause contact allergy (17).

Patch testing in groups of patients

There are no studies in which octocrylene has been routinely patch tested in (unselected) patients suspected of having allergic contact dermatitis. Some investigators, however, have reported their results of testing octocrylene in groups of selected patients, for example with a history of sunscreen intolerance, with exposed site dermatitis, with suspected photosensitivity, or with a history or suspicion of adverse reactions to ketoprofen gel (17–21). The results are shown in Table 2. From 0.7% to 5% of the patients investigated had positive reactions to octocrylene. It should be noted, however, that the higher rate of 4.4% was found in a study with some weaknesses in its design (19), and that the percentage of 5% was found in a very small study with only 1 patient reacting to octocrylene in the patch test (18).

Contact allergy case series and case reports

Case series. From 2007 to 2012, 131 positive patch tests and photopatch tests were notified to the French network Réseau de Vigilance en Dermatoallergologie/Groupe d'Etudes et de Recherche en Dermatoallergologie (REVIDAL/GERDA) (22). Approximately 20% were in young children who mostly suffered from allergic contact dermatitis caused by octocrylene in sunscreens (80% of the 131 reactions were photoallergic). Other clinical data were not provided (23). These data probably include patients from previously published communications (3, 24–27).

In 2010, 10 children were described who had suffered from allergic contact dermatitis caused by sunscreens containing octocrylene (3). There were 7 girls and 2 boys aged 2–16 years who had been collected in a 2-year period in Belgium and France by REVIDAL/GERDA members (22). All had positive patch test reactions to octocrylene and one or more of the sunscreens containing octocrylene used by them (3). In the same study, 6 adults with contact allergy to octocrylene were described: 3 had photo-augmentation, 1 had contact allergy, and in 2 photopatch testing had not been performed. Four of the 6 patients had also photocontact allergy to ketoprofen; in the other 2 this had not been tested. All reactions, both in children and in adults, were clinically relevant (3).

From January 2000 to December 2010, 959 ingredients of cosmetics were identified as the cause of allergic cosmetic dermatitis in Leuven, Belgium. In 10 of the 959, octocrylene was the allergenic cosmetic ingredient. There were also 28 photocontact allergic reactions to octocrylene in this period. Clinical data were not provided (28); some of these patients have probably been presented in an earlier study (3).

Case reports. Case reports of contact allergy to octocrylene are summarized in Table 3.

Photocontact Allergy

Photocontact allergy/photoallergic contact dermatitis is the most frequent adverse effect of octocrylene, accounting for ~ 80% of all reactions (23). As will be discussed below, most such cases are probably secondary to previous photosensitization to ketoprofen (mostly from topical preparations).

Photosensitizing capacity

In its UV-induced excited state, octocrylene has the ability to form hapten–protein complexes, which may constitute the basis of photocontact allergic reactions to octocrylene (4). There is a dissimilarity between the hapten–protein complexes formed by octocrylene in its ground state and those formed in its excited state, which may explain why photocontact allergic patients do not usually show a positive patch test reaction in the absence of UV (4).

Photopatch testing in groups of patients

There have been several studies in which groups of selected patients have been routinely photopatch tested with octocrylene (17, 18, 20, 21). Selection criteria have been (combinations of) exposed site dermatitis, history or

Table 2. Patch testing of octocrylene in groups of selected patients

Years and country	Test concentration and vehicle	No. of patients tested, no. positive (%)	Selection of patients (S), relevance (R), comments (C)	References
2008–2011, 12 European countries	10% pet.	1031, 7 (0.7)	S: patients with exposed site dermatitis or history of a reaction to a sunscreen or topical NSAID. R: not specified	(21)
2001–2010, Canada	Not stated	160, 7 (4.4)	S: patients with suspected photosensitivity and patients who developed pruritus or a rash after sunscreen application. R: not stated. C: weak study – inadequate reading of test results, erythema only was considered to represent a positive patch test reaction; of the 7 patients, 1 had photo-aggravated allergic contact dermatitis	(19)
2000–2010, Belgium	10% pet.	172, 5 (2.9)	S: patients with (suspected) adverse reactions to sunscreen products and/or ketoprofen. R: all had sunscreen intolerance and 2 of 5 had previously used ketoprofen gel. C: 1 of the 5 patients had photo-aggravation from octocrylene, and 2 were photoallergic to ketoprofen (2 others were not tested with ketoprofen) and benzophenone-3 (the 2 who had used ketoprofen gel); 2 children (3, 11), 3 adults	(17)
2004–2006, Italy	5% pet.	1082, 9 (0.8)	S: patients with histories and clinical features suggestive of photoallergic contact dermatitis; R: 18%; all 9 were cases of photoaggravated contact allergy	(20)
2004, Belgium	10% pet.	20, 1 (5)	S: patients suspected of having sunscreen allergy. R: 100%	(18)

NSAID, non-steroidal anti-inflammatory drug.

suspicion of a reaction to a sunscreen or to a topical non-steroidal anti-inflammatory drug (NSAID), and histories and clinical features suggestive of photoallergic contact dermatitis. The relevant data are shown in Table 4. The largest recent study was performed by the European Multicentre Photopatch Test Study (EMCPPTS) Taskforce (21). Between 2008 and 2011, 1031 patients were patch and photopatch tested with a series of 19 UV-filters (including octocrylene and benzophenone-3) and five NSAIDs (including ketoprofen) in 30 centres across 12 European countries. The patients included had at least one of the following four indications for performing photopatch tests: (i) an exposed site dermatitis during the summer months; (ii) any exposed site dermatitis; (iii) history of a sunscreen reaction; or (iv) history of a topical NSAID skin reaction. Most positive photopatch test reactions were observed with the NSAIDs ketoprofen (n = 128) and etofenamate (n = 59), followed by the UV-filters octocrylene (n = 41), benzophenone-3 (n = 37), and butyl methoxydibenzoylmethane (n = 18). Of the 41 reactions to octocrylene, 22 (54%) were considered to be of current relevance, 14 (34%) to be the result of a 'cross-reaction to another agent', and 6 (15%) to be of unknown relevance (totals are not correct). A similar relevance distribution was given for the 37 benzophenone-3 reactions. The reactivity rate to octocrylene was as high as 4% (41/1031). However, it should be appreciated that there were large differences between countries, ranging from 0% (The Netherlands, Greece, Portugal, and Poland) to an estimated (Appendix 4 of the study) 5% (Spain), 9% (Italy), 23% (Belgium), and 32% (France). In the last four countries, high rates of photoreactivity to ketoprofen were also observed [Italy, 63%; France, 42%; Belgium, 38%; Spain, 18% (estimated from Appendix 4)]. In general, high frequencies of reactions to octocrylene were accompanied by high frequencies of reactivity to ketoprofen. The differences between countries are probably attributable to differences in the regional availability of topical ketoprofen preparations and usage patterns, but differences in subject recruitment may also – albeit to a lesser degree – play a role (21). A very high rate of positive photopatch tests (20%) was observed in Belgium, probably because of strict selection of patients for photopatch testing (17).

Photocontact allergy case series and case reports

Case series. From 2007 to 2012, 131 positive patch tests and photopatch tests were notified to the REVIDAL/GERDA (22). Approximately 80% were in adult patients with a history of photoallergic contact dermatitis caused by ketoprofen and who mostly suffered from photoallergic contact dermatitis caused by octocrylene (20% of the 131 were young children, who mostly

Table 3. Case reports of contact allergy to octocrylene

Year and country	Patient data	Patch test data and other information	References
2013, Spain	F, 5 years	Eruption after sunscreen application; positive patch test reactions to sunscreen andoctocrylene	(29)
2013, Spain	M, 1 year	Eruption after the use of two sunscreens; positive patch tests to the two commercial products butyl methoxydibenzoylmethane and octocrylene	(30)
	Child, 1 year	Eruption 2 hr after application of sunscreen; positive patch test reactions to the commercial sunscreen, octocrylene, and butyl methoxydibenzoylmethane	
2012, Belgium	F, 4 years	Eruption on the face after sunscreen application; positive patch test reactions to octocrylene, four sunscreens containing octocrylene, fragrance mix I, sorbitan sesquioleate, and benzophenone-3; photopatch tests were negative	(31)
2007, United Kingdom	F, 37 years	Eruption after using sunscreen and exposure to sun; positive patch test reactions to octocrylene, two sunscreens, lanolin alcohols, Amerchol® L101; no photo-augmentation in photopatch tests	(32, 33)
	M, 8 years	Eczematous rash after application of sunscreen; positive patch test reactions to octocrylene and two sunscreens containing octocrylene	
2007, France	M, 31 years	Skin eruption after application of sunscreen; history of eczema caused by ketoprofen gel; positive patch test reactions to octocrylene and positive photopatch test at a lower concentration	(26)
2006, Belgium	F, 7 years	Acute eruption after sunscreen application; positive patch test reactions to octocrylene and two sunscreens; photopatch tests were negative	(18)
2005, United Kingdom	M, 3 years	Eruption after sunscreen application; positive patch test reactions to octocrylene, sunscreen, lanolin alcohols, and Amerchol® L101; photopatch tests negative; 3 years later, acute eruption of the face where his aunt had kissed him 1 day earlier; she wore a moisturizer containing octocrylene but no lanolin; patch test with the moisturizer was positive	(34)
	M, 10 years	Eruption after application of sunscreen lotion; positive patch test reactions to octocrylene, fragrance mix I, and budesonide; no photopatch tests performed	

F, female; M, male.

had allergic contact dermatitis caused by octocrylene in sunscreens). Other clinical data were not provided (abstract) (23). These data probably include patients from previously published communications (3, 24–27).

In 2010, 22 adult patients were described, aged 18–69 years (mean 40 years), who nearly all had a history of ketoprofen photoallergic contact dermatitis (3). They had been collected in a 2-year period in Belgium and France by REVIDAL/GERDA members (22). All had positive photopatch test reactions to octocrylene, and 12 (55%) had positive photopatch test reactions to one or more of the sunscreens containing octocrylene used by them (3). The other 10 had a history of sunscreen intolerance, so all 22 photopatch test reactions were considered to be relevant (3). One 3-year-old girl had an eruption on sun-exposed areas with a positive photopatch test reaction to octocrylene, but a positive contact allergic reaction to the sunscreen used (3).

From January 2000 to December 2010, 959 ingredients of cosmetics were identified as cause of (photo)allergic cosmetic dermatitis in Leuven, Belgium. In 28 of the 959, octocrylene was the photoallergenic cosmetic ingredient. There were also 10 contact allergic reactions to octocrylene in this period. Clinical data were not provided (28); some of these patients have probably been presented in an earlier study (3).

Four patients with positive photopatch test reactions to octocrylene and benzophenone-3, 3 of whom also photo-reacted to ketoprofen, were reported from Spain. Only one reaction to octocrylene was clinically relevant; other clinical data were not provided (35). In a group of 15 patients with reactions to ketoprofen gel in Italy (1 contact allergy, 2 photo-aggravated contact allergy, and 12 photocontact allergy), 3 (20%) had positive photopatch test reactions to octocrylene. No clinical data or comments on relevance of these reactions were given (8). Other studies in which positive photopatch test reactions to octocrylene have been reported in relation to ketoprofen photosensitization are shown in Table 5.

Case reports. Case reports of photocontact allergy to octocrylene are summarized in Table 6.

Table 4. Photopatch testing in groups of patients

Years and country	Test concentration and vehicle	No. of patients tested, no. positive (%)	Selection of patients (S), relevance (R), comments (C)	References
2008–2011, 12 European countries	10% pet.	1031, 41 (4.0)	S: patients with exposed site dermatitis or history of a reaction to a sunscreen or topical NSAID. R: 54% current relevance, 34% attributable to ketoprofen photosensitivity, 15% unknown relevance. C: rates ranged from 0% to 32% in different countries; most frequent photocontact allergen among the UV-filters	(21)
2000–2010, Belgium	10% pet.	90, 18 (20)	S: patients with (suspected) adverse reactions to sunscreen products and/or ketoprofen. R: 15 of 18 had sunscreen intolerance, of who 12 had previously used or reacted to ketoprofen gel; 3 had reacted to ketoprofen previously, but had no known sunscreen intolerance. C: 15 of 18 patients also had a positive photopatch test to ketoprofen (3 were not tested) and 13 of 18 had a positive photopatch test to benzophenone-3	(17)
2004–2006, Italy	5% pet.	1082, 14 (1.3)	S: patients with histories and clinical features suggestive of photoallergic contact dermatitis. R: 18%. C: most frequent photocontact allergen among the UV-filters; there were an additional 9 cases of contact allergy with photo-aggravation	(20)
2004, Belgium	10% pet.	20, 1 (5)	S: patients suspected of having sunscreen allergy. R: 100%; the patient was also photoallergic to ketoprofen	(18)

NSAID, non-steroidal anti-inflammatory drug.

Relationship between octocrylene, ketoprofen, and benzophenone-3

Some patients in early reports on photoallergic contact dermatitis caused by octocrylene-containing sunscreens (18, 44) reported a history of reactions to ketoprofen gel, and the possible relationship was first discussed in 2008 by Devleeschouwer et al. (38), and later confirmed (3). Ketoprofen gel is an NSAID with sprains and contusions as the primary indications, because of its analgesic and anti-inflammatory actions. Commercial topical products (in various countries) include Fastum® gel, Kétum® gel, Profenid® gel, Lasonil® gel, Artrosilene® gel, and Oruvail® gel; they usually contain 2.5–5% ketoprofen. Topical ketoprofen products have caused many cases of photoallergic contact dermatitis, notably in France, Spain, Italy, and Belgium (20, 21, 38, 39, 45), countries where these products are widely used (An Goossens, Leuven, Belgium, Email communication, 4 November 2013). In a considerable number of patients with a history of reactions to ketoprofen and/or who have a positive photopatch test reaction to this NSAID, concomitant photo-reactions to octocrylene and – to a lesser degree – benzophenone-3 have been observed. The relevant data are summarized in Table 5. In the studies shown there, 27–80% of patients who were photoallergic to ketoprofen co-reacted to octocrylene and 17–64% co-reacted to benzophenone-3.

Even more interesting is how many patients with a positive photopatch test reaction to octocrylene co-react to ketoprofen. The relevant data are shown in Table 7. In the study performed by the EMCPPTS Taskforce (21), the rate of co-reactivity to ketoprofen was 83% in the group of 41 patients with positive octocrylene photopatch test reactions. Of 15 octocrylene-photosensitive patients seen in Belgium who were also tested with ketoprofen, all 15 (100%) co-reacted to the NSAID (17), and in a study from Belgium and France there was also a 100% score (3). Although there is the possibility that patients who are primarily photosensitized to octocrylene become sensitized to ketoprofen by the photosensitization event (4), it appears far more likely that a great majority, and possibly > 80%, of all cases of photosensitization to octocrylene are induced by primary ketoprofen sensitization. It can also be seen that 44–72% of patients who are photoallergic to octocrylene co-react to benzophenone-3 (Table 7). Interestingly, at present, both in Belgium and in France, far fewer patients who are photoreactive to ketoprofen co-react to octocrylene than before; an explanation is currently lacking (An Goossens, Leuven, Belgium, Email communication, 4 November 2013).

Regarding benzophenone-3, of 37 patients with a positive photopatch test reaction to benzophenone-3, 7

Table 5. Co-reactivity to octocrylene and benzophenone-3 in patients with positive ketoprofen photopatch tests

Year and country	Number of patients with positive photopatch tests (% related to ketoprofen)			Comments	References
	Ketoprofen	Octocrylene	Benzophenone-3		
2008–2011, 12 European countries	128	34 (27)	22 (17)	It can be estimated (Appendix 4) that the rates of positive reactions to octocrylene in countries with many reactions to ketoprofen ranged from < 14% (Italy) to a maximum of 76% (France)	(21)
2008–2009, France, Belgium	14	10 (71)	No data	Patients had suffered from acute dermatitis after application of ketoprofen gel, but had no history of sunscreen intolerance; 2 of the 10 reacting to octocrylene had photo-augmentation; of the remaining 4, 3 were entirely negative and 1 had allergic contact dermatitis caused by octocrylene; none had a history of sunscreen intolerance	(3)
1994–2010, France	11	7 (64)	No data	There were 148 photo-reactions to ketoprofen, but only 11 patients were photopatch tested with both ketoprofen and octocrylene	(36)
2008, France	8	6 (75)	No data	Four of the patients had a history of sunscreen intolerance	(37)
1993–2007, Belgium	33 5	No data 4 (80)	19 (58) No data	It is not absolutely sure that all 33 resp. 5 patients were indeed photoallergic to ketoprofen	(38)
1998–2002, France	18	NT	6 (33)	All 18 patients had suffered from photoallergic contact dermatitis caused by ketoprofen gel	(39)
1996–1997, France	12	NT	3 (25)	–	(40)
Other, older studies	59 (18, 19, 22)	NT	(25, 21, 64)	Literature summarized in (39)	–

NT, not tested.

co-reacted only to ketoprofen, 3 only to octocrylene, and 15 to both ketoprofen and octocrylene. Only 12 of 37 patients (32%) reacted exclusively to benzophenone-3, which may indicate that the majority of reactions to benzophenone-3 do not – at least in countries with high rates of ketoprofen photosensitization – result from primary sensitization to this UV-absorber (21), and that these reactions are – as with octocrylene – frequently the result of primary ketoprofen photocontact allergy, in this case from photo-cross-reactivity. However, another explanation may be concomitant sensitization to ketoprofen and benzophenone-3, as the UV-filter may be present in ketoprofen preparations as a photostabilizer to protect the product from being degraded by sunlight (46).

From these data, it can be concluded that ketoprofen photosensitivity, in a considerable number of the patients, leads to octocrylene (27–80%) and benzophenone-3 (17–64%) photocontact allergy. Conversely, octocrylene photocontact allergy is, in the great majority (probably > 80%) of cases, the result of ketoprofen photosensitization.

Some patients with contact allergy or photo-aggravated contact allergy to octocrylene were also photoallergic to ketoprofen (3, 17, 24).

Mechanism of co-reactivity. Patients who have positive photopatch test reactions to ketoprofen often show co-reactions not only to octocrylene and benzophenone-3, but also to numerous other chemicals. These include other NSAIDs, such as etofenamate, suprofen, and tiaprofenic acid (40), the lipid-lowering drug fenofibrate (40), and photoallergens such as fenticlor, chlorpromazine, triclosan, bithionol, and tetrachlorosalicylanilide; such reactions are usually not relevant (38, 39). Co-reactivity to benzophenone-3 and fenofibrate is often considered to be photo-cross-reactivity, as these chemicals share a benzophenone moiety (double benzene rings linked by a ketone group; Fig. 1) (38, 40), and the major photodegradation product formed from ketoprofen (in

Table 6. Case reports of photocontact allergy to octocrylene

Year and country	Patient data	Photopatch test data and other information	References
2013, Spain	F, 4 years	Eruption after application of sunscreen; positive photopatch test reactions to the commercial sunscreen and to octocrylene	(29)
2013, Spain	F, 29 years	Hand dermatitis resulting from photocontact allergy to benzophenone-3 in printing ink; the patient had previously suffered from reactions to ketoprofen gel and a sunscreen, and had positive photopatch test reactions to ketoprofen and to octocrylene	(41)
2010, Italy	F, 40 years	Dermatitis on the hand, waist and back resulting from photo-aggravated contact allergy to ketoprofen gel, used by a student dance partner; positive patch test reaction to fragrance mix and photopatch test reactions to octocrylene, benzophenone-10, and fentichlor	(42)
2009, Spain	F, 57 years	Eruption after application of sunscreen and intense sun exposure; history of skin reactions after oral ketoprofen intake; positive photopatch test reaction to octocrylene	(43)
	F, 35 years	Eruption after application of sunscreen and moderate sun exposure; history of skin rashes after sun exposure; positive photopatch test reactions to octocrylene, ketoprofen, and butyl methoxydibenzoylmethane	
2007, France	M, 31 years	Skin eruption after application of sunscreen; history of eczema caused by ketoprofen gel; positive photopatch test reactions to octocrylene, and positive patch test reactions to octocrylene at higher concentrations	(26)
2006, Belgium	M, 48 year	Recurrent demarcated eruption on the face after sun exposure; history of cutaneous allergic reactions after topical use of ketoprofen; positive photo-patch test reactions to ketoprofen, commercial sunscreen, and octocrylene	(18)
2003, France	M, 55 years	Clinical reaction to sunscreens; positive photopatch test reactions to octocrylene, benzophenone-3, fragrance mix, two commercial sunscreens, and three non-relevant photoallergens	(44)
	M, 31 years	Photodistributed reaction to sunscreens; history of cutaneous allergic reactions after topical use of ketoprofen; positive photopatch test reactions to octocrylene, a commercial sunscreen, ketoprofen, and four non-related photoallergens; contact allergy to the fragrance mix	

F, female; M, male.

neutral aqueous media) is 3-ethylbenzophenone (47). Indeed, photo-cross-sensitization to benzophenone in primary ketoprofen photosensitization has been observed in animal experiments in all six photosensitized animals (46).

Ketoprofen and octocrylene, at first sight, appear to have little structural similarity, as octocrylene does not have the benzophenone substructure. However, aminolysis and hydrolysis of octocrylene in the skin may lead to benzophenone (4), so, if the 'benzophenone' hypothesis were valid, the frequent co-reactivity to octocrylene might also be explained as cross-sensitivity.

The chemical basis of photo-cross-reactivity among the NSAIDs is not clear. The frequent co-reactivity to tiaprofenic acid [up to 100% (40)] and other NSAIDs, such as suprofen, in ketoprofen-photosensitized subjects is sometimes also explained as cross-reactivity (39, 40), although these chemicals do not have the benzophenone moiety. Nevertheless, in animal experiments, photo-cross-sensitization between ketoprofen, tiaprofenic acid, suprofen and benzophenone in animals photosensitized to ketoprofen has been convincingly shown, and the benzoyl substructure ArCO was suggested to be the key structure for photosensitivity and photo-cross-reactivity (46). Although tiaprofenic acid and suprofen do not have the benzophenone moiety, they do have an ArCOAr substructure, where one of the R groups is a thiophene ring and the other a benzene ring. Possibly, the presence of a diaromatic ketone ArCOAr substructure (this includes compounds in which one of the Ar groups is a thiophene ring and the other is a benzene ring) is an important factor in photo-cross-reactivity (38, 46). This ArCOAr substructure is not present as such in octocrylene, but can be generated from it by aminolysis

Table 7. Co-reactivity to ketoprofen and benzophenone-3 in patients with positive octocrylene photopatch tests

Year and country	Number of patients with positive photopatch tests (% related to octocrylene)			Comments	References
	Octocrylene	Ketoprofen	Benzophenone-3		
2008–2011, 12 European countries	41	34 (83)	18 (44)	–	(21)
2008–2009, Belgium, France	22	16 (100[a])	10 (45)	Only 16 of the 22 patients who were photoallergic to octocrylene were photopatch tested with ketoprofen; all 16 reacted to ketoprofen, hence the 100% score	(3)
2000–2010, Belgium	18	15 (100[a])	13 (72)	Only 15 of the 18 patients who were photoallergic to octocrylene were photopatch tested with ketoprofen; all 15 reacted to ketoprofen, hence the 100% score	(17)

[a]See comments in this table.

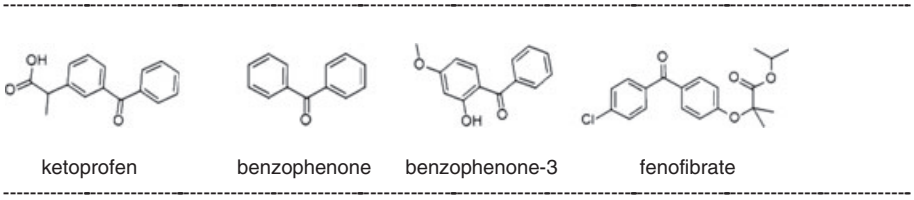


Fig. 1. Chemical structures of ketoprofen, benzophenone, benzophenone-3, and fenofibrate.

and hydroysis (17), which would enable otocrylene to give photo-cross-reactions in ketoprofen-sensitized subjects. The mechanistic role played by this ArCOAr substructure will be discussed elsewhere.

Other explanations for the co-reactivity to octocrylene, etofenamate and the many other photoallergens in ketoprofen-photosensitized individuals have included: (1) hyper-photosusceptibility to non-relevant allergens, with a possible role for a benzoyl substructure ArCO (38); and (2) co-sensitization (which we interpret as either concomitant sensitization or prior or subsequent *de novo* photosensitization) instead of cross-sensitization (39, 45). For a number of non-relevant co-reactions, however, contact with the pertinent chemicals is almost impossible, as some were removed from consumer products in Europe several decades ago, for example halogenated salicylanilides; this would make co-sensitivity resulting from primary sensitization to these chemicals highly unlikely.

Patch testing and photopatch testing with octocrylene

Octocrylene 10% in petrolatum is commercially available from Chemotechnique Diagnostics (www.chemotechnique.se) and Allergeaze (www.allergeaze.com). A joint taskforce group of the European Society of Contact Dermatitis and the European Society for Photodermatology has recently recommended the inclusion of octocrylene in a 'European photopatch test baseline series' containing 20 photoallergens, which also includes ketoprofen and benzophenone-3 (48). Although no advice was given on the selection of patients to be photopatch tested with this series, patients suspected of having photoallergic contact dermatitis, reactions to topical NSAIDs and reactions to sunscreens should certainly be included.

Should the use of octocrylene be restricted or should octocrylene be banned?

At present, the number of reported cases of allergic contact dermatitis caused by octocrylene that result from sensitization to a sunscreen preparation appears to be small in relation to the widespread use of octocrylene in sunscreen products and in daily-use cosmetics. Also, most cases, probably > 80%, of the far more frequently occurring photocontact allergic reactions are probably not induced by octocrylene itself, but by ketoprofen as a result of previous photosensitization to this topical NSAID, and cases are largely restricted to France, Belgium, Italy, and Spain (21). In addition, octocrylene is very useful as photo-stabilizer of butyl methoxydibenzoylmethane, which is one of the few available efficient UVA

absorbers. Currently, therefore, restrictions on its use (49) may be premature. For prevention of octocrylene photoallergy, restrictions on ketoprofen would be more logical and probably more efficacious. In fact, in 2009, concerns about interactions with octocrylene led regulatory authorities in France to suspend all marketing authorizations for topical ketoprofen. This, in turn, led to a risk–benefit analysis by the European Medicines Agency. Although a 'positive benefit balance' was given, it can, since 2010, be prescribed only by clinicians, and patients are given more warnings about the risk of developing photoallergic contact dermatitis (50). At present, it is too soon to evaluate whether this restriction is adequate and will result in less photosensitization to ketoprofen gel and octocrylene. In the most recent relevant study (21), ketoprofen was the most important photocontact allergen, especially in Italy, France, Belgium, and Spain. In these countries, high rates of positive photopatch test reactions to octocrylene were observed, whereas, in countries with low rates of reactivity to ketoprofen, reactions to octocrylene were few or absent (21). However, these patients were tested between 2008 and 2011, whereas the new regulations were implemented in 2010, and some of the more recent cases may have been sensitized before that. Should future studies again yield high rates of ketoprofen photosensitivity, a reappraisal of the 'pros and cons' for the use of topical ketoprofen preparations by the regulatory authorities will be indicated, as the problem of octocrylene photosensitivity is probably, in > 80% of all patients, related to ketoprofen.

Conclusions

Octocrylene is a UVB and UVAII absorber that was introduced 15 years ago. It is an important photo-stabilizer of the UVA filter butyl methoxydibenzoylmethane. In the United States and European countries, octocrylene may be present in the majority of sunscreen preparations and in > 20% of cosmetic care products for daily use. Since 2003, many studies have reported patients with photocontact allergy and – to a lesser degree – contact allergy to octocrylene in sunscreens. Contact allergy is observed mainly in children, who become sensitized to this UV-filter from its presence in sunscreens. Reported patients with photoallergic contact dermatitis caused by sunscreens and positive photopatch tests are adults, mainly in France, Belgium, Italy, and Spain. The majority (> 80%) of these reactions are probably not caused by photosensitization to octocrylene itself, but result from previous photocontact sensitization to topical ketoprofen preparations. Despite the apparent lack of structural similarity between ketoprofen and octocrylene, there are experimentally demonstrated chemical mechanisms whereby the two substances can give rise to very similar photoallergenic benzophenone-type chemicals. However, at present, it cannot be definitively stated whether or not the reactions are attributable to cross-sensitization.

Many patients who are photoallergic to octocrylene co-react to benzophenone-3; a number of the cases may be attributable to ketoprofen photosensitization, and can be explained by photo-cross-reactivity to this NSAID. The most effective way to decrease the number of octocrylene photoallergic contact reactions is by reducing the number of reactions to ketoprofen. Whether new European legislation, implemented in 2010 and specifying that ketoprofen can now only be prescribed by clinicians and that patients should be given more warnings about the risk of developing photoallergic contact dermatitis, is effective and adequate cannot be confirmed (or denied) at present.

Routine patch testing of octocrylene 10% pet. (www.chemotechnique.se; www.allergeaze.com) in unselected and selected patient groups and routine photopatch testing of octocrylene in selected populations is advised to evaluate the magnitude of the (photo)allergenic problems with octocrylene and to better identify patients at risk.

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