29 Photopatch Testing

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Contents

29.1 Introduction

Photopatch testing combines the techniques of two subspecialties in Dermatology, patch testing for allergic contact dermatitis and phototesting for photodermatology. Due to difficulties in having both technologies together (a patch test clinic and an UV irradiation source), or because photoallergic contact dermatitis is uncommon [1], this technique is not so widely performed. In a survey by Lehmann in the beginning of 2000, only a few dozens of clinics in Europe were performing photopatch testing and only two centres tested more than 50 patients/year [2].

Also, in photopatch testing, apart from the inherent temporal and regional variability of skin reactivity, many variables have to be dealt with: allergen concentrations and vehicles, test series and reading of tests results from allergic contact dermatitis, UV source, UV spectrum, UV irradiance and UV dose reaching the skin from photodermatology, and, then, the common final interpretation of test results. Therefore, there has been some difficulty in standardizing procedures. But, photodermatologists and contact dermatologists met in Amsterdam, in 2002 and 2007, and agreed upon a consensus methodology, allergen series and interpretation of test results [2]. Also, thereafter, several studies are being performed in order to strengthen and improve this consensus methodology [3–5].

Core Message

› Photopatch testing is probably underused and photoallergic contact dermatitis is presumed to be uncommon.

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29.2 Indications for Performing Photopatch Tests

29.2.1 Main Indication

The primary indication for photopatch testing is to confirm a diagnosis of photoallergic contact eczema / photoallergy and find the responsible allergen. It can also contribute to distinguish photoallergic from phototoxic reactions, although this is not always easy. This distinction may be important as photoallergic reactions are usually more severe, with increasing intensity on further exposures, with the possibility of progressing to persistent photosensitivity and reactivity to cross-reactive chemicals. Therefore, recognizing and avoiding the allergen is crucial for the prognosis of the dermatitis.

Clinical manifestations of photosensitivity are very polymorphic, sometimes with difficulty in distinguishing photoallergy from phototoxicity – acute or chronic eczema, urticarial, lichenoid and pigmented reactions, erythema multiforme, exaggerated sunburn, etc. (see Chap. 18 for details). In photosensitivity from systemic agents, lesions are usually localized on a symmetrical distribution, on the face, neck, V-area of the upper chest, forearms, back of the hands and legs, whereas in photoallergic contact dermatitis, lesions occur in the areas of concomitant application of a photosensitizer and UV exposure (Fig. 29.1a, b). But there are less obvious patterns of photoallergy: the eczematous reactions, sometimes associated with targetoid lesions of erythema multiforme, can also involve some shaded areas [6]; the allergen may, inadvertently, be transported by hands to areas other than the one of primary application, as for ketoprofen (ectopic dermatitis) [6–8]; only part of the exposed skin may be involved, e.g. cheilitis as a manifestation of photoallergy from a systemic photosensitizer [9] or cheilitis and chin dermatitis from a mouth wash containing benzydamine [10]; sometimes lesions spare the area of application and occur at a distance, as in the case of hand dermatitis from using a vaginal wash containing benzydamine [11] and connubial photoallergic contact dermatitis can also occur [7, 12, 13] (Fig. 29.1a, b).

Also, the relation to sunlight exposure may not be so evident for the patient, as most reactions do not occur immediately on sun exposure, some involve non-exposed areas or have an asymmetric distribution, namely in car drivers who expose mainly one arm/forearm.

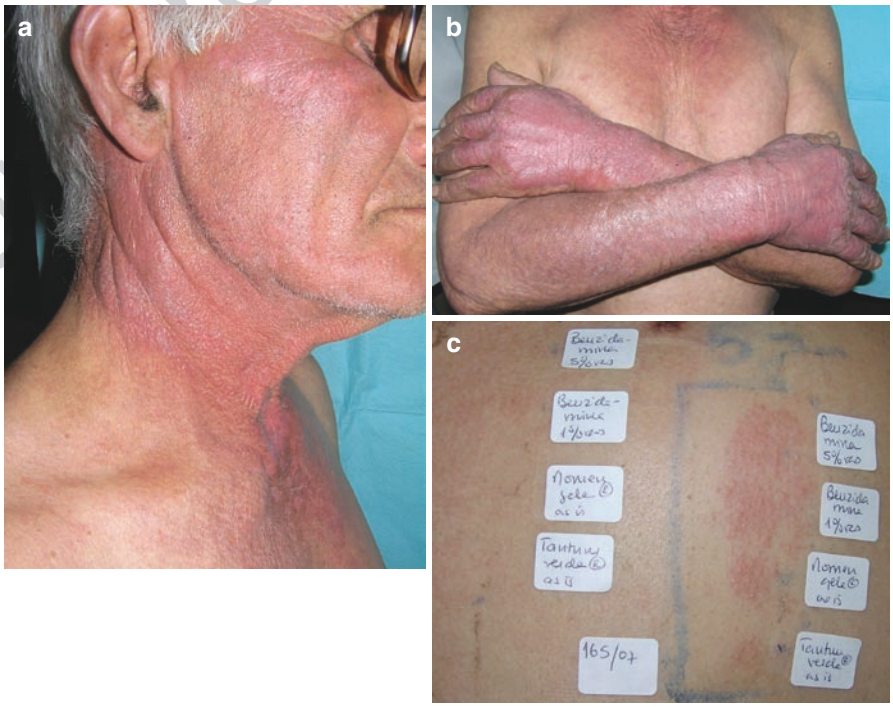

Fig. 29.1 (**a**, **b**) Chronic photoallergic contact dermatitis from benzydamine contained in Momem gele®, which the patient applied regularly to his wife. The distribution of lesions is similar to systemic photosensitivity, probably due to systemic transcutaneous absorption of the NSAID. (**c**) Positive photopatch tests to benzydamine at 1 and 5% pet. irradiated with 5 J/cm^2 of UVA and to the drugs containing the drug (Tantum verde® and Momem gele®) (*right side*), with negative reactions in the left, non-irradiated area

Core Message

› Photopatch testing is mainly indicated for the study of photoallergic contact dermatitis/photoallergy, but many other patients may benefit from photopatch testing.

29.2.2 Other Indications for Photopatch Testing

Apart from patients with suspected photoallergic contact eczema / photoallergy, others can also benefit from this study, namely any patient with a dermatitis that mainly affects the exposed sites (Table 29.1).

Photopatch testing may be important to distinguish an airborne allergic contact dermatitis from photosensitivity. Both involve the face, neck, V-area of the upper chest, dorsum of the hands, forearms and the legs, and even though shaded and hairy areas, e.g. upper eyelid, retroauricular folds and submandibular area, are classically spared in photosensitivity and involved in airborne dermatitis, this difference is not always so evident [7]. Also, photoallergic contact dermatitis can occur from an airborne allergen, as olaquindox, present in pig feeds [14].

Facial dermatitis, suspected to be cosmetic dermatitis, can be due to a photosensitizer in a cosmetic, e.g. UV filters, which are frequently responsible for allergic and photoallergic contact dermatitis in cosmetics [15–18]. Facial, hair and nail cosmetics usually contain UV filters, both to prevent photoaging and skin cancer in the users and also to photostabilize the product and increase its shelf life.

UV filters, both in cosmetics and sunscreens, are the main cause of photoallergic contact dermatitis (Fig. 29.2a). Therefore, any suspicion of skin intolerance to a sunscreen deserves photopatch testing. Patients with idiopathic photodermatoses (chronic actinic dermatitis, polymorphic light eruption) or other types of chronic photosensitivity (photosensitive atopic dermatitis, lupus erythematosus) are particularly prone to develop photoallergic contact dermatitis from UV filters, as they have to use sunscreens daily to prevent photosensitivity [1, 16, 17]. Therefore, this is another indication to perform photopatch testing, most particularly when these patients present with an eczematous reaction or there is an unexpected cutaneous response to therapy.

When, in the investigation of photosensitivity, the patient refers exposure to a known phototoxic agent, particularly if it occurs with a slight sun exposure or little contact with the phototoxic substance, photopatch testing may also reveal photoallergy. Photoallergy to psoralens can develop during PUVA therapy or from contact with plants containing psoralens [19]. These patients react to very low concentrations of psoralen (down to 0.0001%) in the photopatch test [20] or, both in the patch and photopatch test, therefore, associating both allergic and photoallergic contact dermatitis [21, 22]. Also, for known phototoxic drugs like promethazine, chlorpromazine, benzydamine, lomefloxacin and tiaprofenic acid, cases of photoallergy have been diagnosed by photopatch testing [23, 24].

In patients with photosensitivity from systemic agents, particularly drugs, photopatch testing has shown to be positive in several instances [10, 25–27], namely for piroxicam [28–32], ketoprofen and carprofen [26], fenofibrate [10, 31], lomefloxacin (Fig. 29.3) [23, 24, 33], ciprofloxacin [24], flutamide [34, 35], carbamazepine [27] and efavirenz [36], among others. Nevertheless, in this setting, photopatch tests are more frequently negative and the study has to proceed with other tests. Systemic photoprovocation (irradiation of a small area of the normal back skin with increasing doses of UVA (1–5 J/cm^2) and/or UVB after drug intake) and the determination of the minimal erythema dose (MED) in UVB and UVA, before and after exposure to the drug, can be important to confirm the participation of the drug in the photosensitive reaction [26, 37].

Table 29.1 Indications for performing photopatch tests

Photoallergic contact dermatitis
Photosensitive eczematous eruptions
Any dermatitis predominant on exposed sites (suspected airborne dermatitis)
Facial dermatitis (suspected cosmetic dermatitis)
Skin intolerance to sunscreens
Idiopathic photodermatosis (chronic actinic dermatitis, polymorphic light eruption) or diseases with chronic photosensitivity (atopic dermatitis, lupus erythematosus), with worsening of photosensitivity or no response to adequate therapy
Systemic drug photosensitivity
Dermatitis suspected from a phototoxic substance, when occurring with a low UV dose and slight contact

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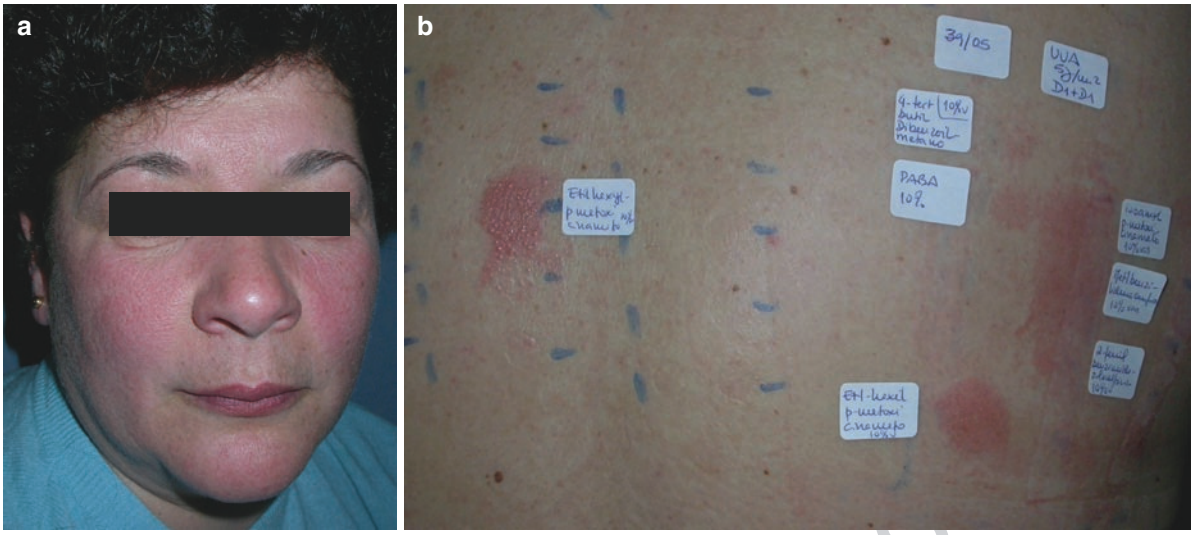

Fig. 29.2 Allergic and photoallergic contact dermatitis of the face from sunscreens (**a**), with positive patch tests to ethylhexyl methoxycinnamate (equal reaction score in the irradiated and non-irradiated areas), and positive photopatch tests to the other UV filters, namely butilmetoxydibenzoylmethane, PABA, isoamyl-*p*-metoxycinnamate, methylbenzyliden camphor and phenylbenzimidazol sulphonic acid (1+ or 2+ reactions, only in the irradiated set of allergens, on the *right*) (**b**)

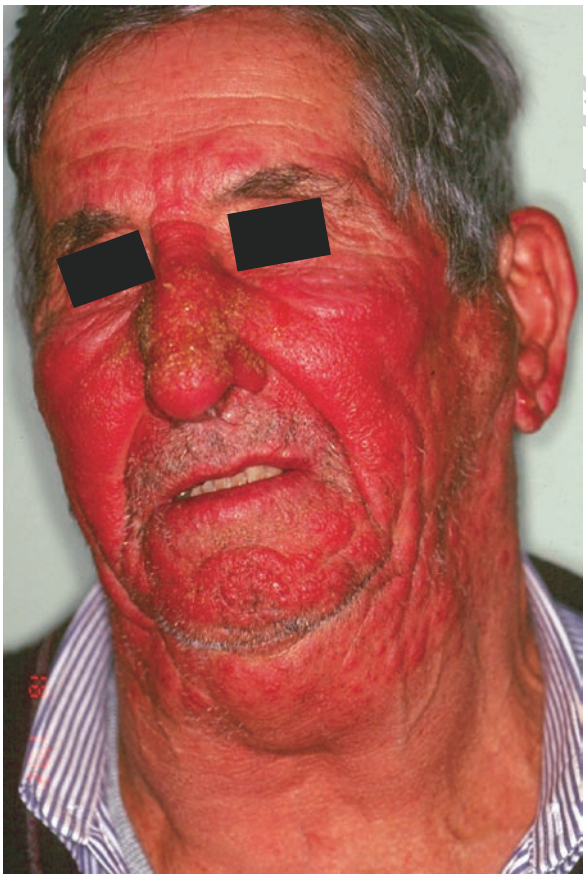

Fig. 29.3 Photoallergic reaction from oral lomefloxacin, with positive photopatch tests to lomefloxacin

Even though all these are indications for photopatch testing, this procedure is not performed very frequently; therefore, it certainly is underused, both in Europe and in the rest of the world [2, 31]. This and, eventually, a wrong choice of photoallergens may explain the presumed low prevalence of photoallergy [1, 38]. But, in a recent Italian study, photoallergic contact dermatitis represented 10% of all photodermatosis [31], which probably means that this is not such a rare problem, at least in geographical areas with high sun exposure.

29.3 Photopatch Testing Technique

29.3.1 How to Perform Photopatch Tests

A standardized amount of the allergens, diluted on the most convenient vehicle, is applied on the chambers as for patch testing, e.g. 15, 20 and 25 μL for liquids, respectively in Finn Chambers® (Epitest Ltd Oy, Tuusula, Finland), van der Bend Chambers® (van der Bend, Brielle, the Netherlands) and large IQ chambers (Chemotechnique Diagnostics, Malmö, Sweden), and 20 mg for petrolatum in 8 mm Finn Chambers®, which correspond to a string across the chamber or a small pile in the middle [39, 40]. For photopatch testing, two equal sets of allergens are prepared and applied on

symmetrical areas of the back, avoiding the central vertebral groove. Occlusion is best maintained for 2 days, but the variation of results is not very significant in case patches are removed after 1 day, the usual procedure in photodermatology units as it is the time to read photo tests performed simultaneously [3].

A first reading should be performed after removing the patches to detect contact reactions present before irradiation. Then, while one set is shield from light with a UV opaque material, the other is irradiated with 5 J/cm^2 of UVA.

A reading within 30 min after irradiation should be performed, in order to detect immediate urticarial reactions.

At least one other reading should be performed 2 or 3 days after irradiation (D3/D4), to detect allergic and photoallergic reactions (Table 29.2).

29.3.2 When to Perform Photopatch Tests

Photopatch testing should be performed, whenever possible, when there are no active lesions. How long after their resolution is not known, but it is advised at least 2 weeks after stopping a local or systemic steroid [2]. If it is not possible, at least the back has to be clear of lesions, but more false positive reactions can be expected.

As that for patch testing, it is not adequate to perform photopatch testing after sunburn or after an important sun exposure on the back. The immunosuppressive effect of UV light is known for the sensitization phase of allergic contact dermatitis and although not so well studied, this effect may be extensive to the elicitation phase [41]. Therefore, due to transient modifications of the antigen presenting capacity of the skin induced by UV, it is probably advised to postpone the tests, for 3–4 weeks, after sunburn.

29.3.3 Irradiation Source and UV Dose

The dose of 5 J/cm^2 of UVA, tolerated by most individuals, including those with lower phototypes, is now consensual. Irradiation with 10 J/cm^2, or more, is responsible for more phototoxic reactions and, although some photoallergic reactions occur after 1–2 J/cm^2 of UVA, some false negatives might occur with this low UV dose [42].

There are several possible sources for UV irradiation, as long as the spectrum is broad-band UVA (320–400 nm), and a dose of 5 J/cm^2 delivered at the skin surface can be adequately measured. Usually fluorescent UV lamps are used, like those used for PUVA therapy (both for whole body or hand and feet irradiation). They emit a reproducible and stable-wide UVA spectrum and are easily accessible.

For regular photopatch testing monochromator is not adequate. Also, UVB lamps are not used on a regular basis. Most photopatch tests reactions occur also with UVA, even if the photoallergen absorbs mainly in UVB, as sulfonamides and diphenhydramine [7]. Only in exceptional cases UVB irradiation was needed to prove photosensitivity, like in a case of systemic photosensitivity from ambroxol [43]. But, probably, there

Table 29.2 Timings for occlusion, irradiation and reading of photopatch tests

Procedure	D0	D1	D2	D3	D4	D5/6
A	Apply two sets of allergens		Remove allergens Irradiate UVA			
			Reading 1 (a,b)	Reading 2 (optional)	Reading 3	Reading 4 (optional)
B	Apply two sets of allergens	Remove allergens Irradiate UVA				
		Reading 1 (a,b)	Reading 2 (optional)	Reading 3	Reading 3/4	Reading 4 (optional)

Two accepted procedures, type A, used most frequently in contact dermatitis clinics and type B, mainly in photodermatology units
Reading 1 includes a reading before and another immediately after irradiation (a,b)
Reading 2 is optional. Its main interest is to distinguish crescendo from decrescendo reactions, considered respectively photoallergic and phototoxic
Reading 3 is the most important. It is usually performed at D4 (procedure A), but can be done either at D3 or D4 in procedure B
Reading 4 is optional, but could be interesting to detect late reactions and, also, to evaluate crescendo or decrescendo reactions

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are not enough data on the regular photopatch testing with UVB [44].

Core Message

› Photopatch tests are irradiated with 5 J/cm^2 of UVA, or 50–75% of the MED in patients with UVA photosensitivity.

29.3.4 Photopatch Testing in Particular Cases (Immunosuppression and Photosensitivity)

It is usually advised not to test patients on immunosuppressive drugs, but it may not be possible to stop them, as in patients under immunosuppression for solid organ transplantation. Photopatch tests can be positive in this setting but, of course, more false negative reactions can be expected. If the patient is under transient treatment with corticosteroids, it is advised to wait, at least, 2 weeks after its suspension or to its reduction to a dose equivalent to10 mg prednisolone/day.

A similar problem may arise when photopatch testing HIV-positive patients with severe immunosuppression. Nevertheless, these patients still develop contact hypersensitivity reactions [45] and patch and photopatch tests can be positive independent of the CD4 count. In a recent case of efavirenz photosensitivity, photopatch tests were positive in a patient with a high number of circulating viral copies and with a very low CD4 cell count (56 CD4/μL) [36].

In these settings, a positive test can be validated, but no definite conclusion can be taken on negative photopatch tests.

When testing a UVA photosensitive patient, like a patient with chronic actinic dermatitis, it is better to evaluate the threshold of reactivity to UV beforehand, that is perform phototests to evaluate MED. Irradiation for the phototests can be done, on Day 0, simultaneous with the application of the patches. Then, after reading the phototests and determining the MED (Day1), choose only a dose of 50–75% of the MED for irradiating the photopatch tests. In the interpretation of the test results, more false positive results can be expected, as when testing patients with active lesions elsewhere.

29.4 Reading and Interpretation of Test Results

29.4.1 Timing of the Readings

Readings have, obligatorily, to be performed immediately before and after UV irradiation, and 2 or 3 days after the irradiation. Some variability on the timing of the readings is admitted and has to do with the occlusion time and, consequently, the day of irradiation (procedure A and B – see Table 29.2).

After irradiation, it would be interesting to perform readings for 3 or more consecutive days, in order to evaluate the crescendo or decrescendo pattern interpreted, respectively, as a photoallergic or phototoxic pattern, but this is not practical. Moreover, this crescendo/decrescendo pattern has been questioned and is not uniformly consistent with these two mechanisms of photosensitive reactions [46].

Readings performed before and immediately after UV irradiation (D1 or, preferably D2) are necessary, respectively, to record reactions present before irradiation and those that appear immediately thereafter.

The most important obligatory reading for evaluating delayed photoallergic reactions is performed 2 or 3 days after irradiation (D3, D4 or D5). This interval is necessary for the development of the T-cell-mediated hypersensitivity reaction to the new photoproduct formed during UV irradiation. In this reading, it is important to compare reactions in the irradiated and non-irradiated panel of allergens, to distinguish contact allergy (positive in both sets) from photoallergy (positive only in the irradiated set) (Table 29.3). At this time, irradiated areas contiguous to those of allergen application are used as a control for evaluating skin reactivity to UVA with no allergen. Reaction in this control area may occur in chronic actinic dermatitis or another photosensitive dermatosis or if the patient is, inadvertently, taking a systemic photosensitive drug (amiodarone, chlorpormazine or thioridazine, fluorquinolone, NSAID, fenofibrate, etc.).

29.4.2 Scoring of the Reactions

Reactions should be scored according to the International Contact Dermatitis Research Group (ICDRG), as

Table 29.3 Interpretation of photopatch test results

Reading 1		Reading 2		Reading 3[a]		Test results	Interpretation of positive reactions
No UV	UVA	No UV	UVA	No UV	UVA		
–	–	–	+ to +++	–	+ to +++	+ Photopatch test	Photoallergy or phototoxicity
+	+	++	++	++	++	+ Patch test	Contact allergy
+	+	+	++ or +++	+	++ or +++	Photo-aggravated + patch test	Photo-augmented contact allergy/or allergic+photoallergic contact dermatitis
++	++	++	– or +	++	– or +	Photo-inhibition[b]	

[a]Optional

[b]The meaning of this type of reaction is not completely understood

[AU3] "–" (negative), "+?" (doubtful, only with faint erythema), "+" to "+++" (faint to strongly positive reactions, namely with erythema, infiltration and possibly papules for 1+, erythema, infiltration, papules and possibly vesicles for 2+ and erythema, infiltration and coalescent vesicles or a bulla for 3+), "IR" (irritant), and NT (not tested) [2].

Core Message

› A photopatch test is positive when the reaction to the allergen occurs only in the irradiated set of allergens. Most often, on a single reading, it is not possible to distinguish definitively photoallergy from phototoxicity.

29.4.3 Interpretation of Test Results: Allergy or Photoallergy

A photopatch test is positive when it occurs only in the irradiated set of allergens. When 2+ or 3+ reactions are observed interpretation is easy, but a doubtful or weak 1+ reaction occurring only in the irradiated area can be more difficult to interpret. It can be due to the additional effect of UV irradiation on a subclinical allergic or irritant patch test [4].

When reading immediately after irradiation, an urticarial reaction to an allergen exclusively in the irradiated area can be due to immediate hypersensitivity, as in photoallergic contact urticaria, which has been described with oxybenzone [47] and chlorpromazine [48].

A transient macular erythema that regresses within 24 h, sometimes with residual hyperpigmentation, attributed to phototoxicity, occurs very occasionally with NSAIDs (benoxaprofen and tiaprofenic acid), promethazine and some UV filters [5, 46, 49, 50].

When reading 1 or more days after irradiation, if an allergen reacts on both sets of tests, with a similar intensity, this is contact dermatitis, allergic or irritant. Probably, at D2, when removing the patches, this reaction was already present (Fig. 29.2b).

When a reaction, graded as 1+ to 3+, occurs only in the irradiated set of allergens it is a positive photopatch test (Fig. 29.1c and 29.2b). A simple observation does not discriminate definitively between a phototoxic and a photoallergic reaction. In a phototoxic reaction, the [AU4] test is usually more uniform, with erythema, sometimes with infiltration and with sharp limits, and tends to regress more quickly (peak intensity by 24 h), and this reaction occurs in a high percentage of individuals tested under the same circumstances. A typical photoallergic reaction is more pruritic, with papules or vesicles, which sometimes goes beyond the strict area of contact with the allergen, and tends to increase in intensity with a peak in 48 or 72 h after irradiation. Another argument to support photoallergy is the absence of this reaction in control patients and maintenance of the positive reaction with serial dilutions of the allergen and with lower UV doses of irradiation. Spongiotic dermatitis with no sunburn cells, on histology, also suggests photoallergy.

Other combinations of reactions can occur, namely negative reactions on both sides, irritant reactions on both sides, eventually with photo-augmentation (photo-augmented irritation, probably not relevant),

a photo-augmented or photo-aggravated allergic contact reaction or a photo-inhibited or photo-suppressed allergic contact reaction (Table 29.3).

By definition, a photo-aggravated allergic contact reaction is considered when, in the irradiated set, it is graded with at least one "+" more than in the non-irradiated site. This can occur with contact allergens that also have some photoactive potential, like etofenamate, ketoprofen, UV filters and perfumes [7]. It can represent the association of allergic and photoallergic contact dermatitis or a photo-augmentation of contact allergy [4].

Photo-inhibition or photo-suppression, with reduction in the intensity or complete suppression of an allergic contact reaction on the irradiated site, is seldom observed. This may not be relevant or it can be due to UV-induced immunosuppression or variability of the cutaneous response in different areas of the back [4].

Also, in the interpretation of the results, it is important to have in mind a possible technical error, namely with inadvertent UV exposure in the set of allergens that was supposed to be shielded.

29.4.4 Relevance of Positive Reactions

To determine reaction relevance, a good detailed questionnaire with recent and past history has to be done very carefully with the patient. Positive reactions may explain the present dermatitis (current relevance) or be due to a past exposure, with or without lesions, representing past or old relevance or, simply, previous exposure [2].

Also, it is important to know that many photoallergens cross-react with contact allergens or other photoallergens, which can explain some positive reactions. Photoallergy to ketoprofen is associated with positive photopatch tests to other NSAIDs of the arylpropionic acid group that share the benzophenone moiety (tiaprofenic acid and suprofen), to benzophenone UV filters, mostly oxybenzone, and to the lipid lowering drug, fenofibrate [6, 8]. More frequently, these patients also have positive photopatch tests to fentichlor [51] and positive patch tests to balsam of Peru and fragrance mix I, probably due to the similarity to cinnamic aldehyde [52]. Fluorquinolones can cross-react within the group (lomefloxacin, ciprofloxacin) [23], like the phenothiazines used as neuroleptics (chloropromazine and thioridazine), topical antihistamines (promethazine) or muscle relaxants (chlorproethazine) [53]. Positive photopatch tests to piroxicam occur in patients with previous contact allergy to thiomersal and its moiety thiosalicylic acid [10, 54]. Therefore, in the rare situations of a negative photopatch test to piroxicam and a very typical history of photoallergic contact dermatitis or systemic photoallergy from this drug, a positive patch test to thiosalicylic acid (0.1% pet.) can be a good indication that piroxicam was responsible [32, 55].

Core Message

› The recommended Basic tray of allergens for photopatch testing has to be dynamic. At present, it is recommended to include UV filters and some NSAIDs, namely ketoprofen. Regional additions are necessary to adapt it to the population habits.

29.5 Allergens for Photopatch Testing (Basic and Additional Series)

The allergens used in photopatch testing are very different from centre to centre, but there is usually a common group of allergens responsible for most positive reactions. Therefore, for detecting the most common allergens and comparing results among centres, a recommended basic list of photoallergens should be used for regular photopatch testing [2], with the additions of regionally prevalent allergens [10, 16, 31, 56, 57] (Table 29.4).

A photoallergen basic tray of allergens has to be dynamic and subject to temporal changes (additions and removals). Along the last decades, the main allergens responsible for photoallergic contact dermatitis were identified and removed from the market, therefore, they became "historical" photoallergens and, for the moment, they have no place in a basic tray of photoallergens. These are musk ambrette, prohibited in perfumes, the UVA filter isopropyl-dibenzoylmethane, withdrawn in 1994, the antibiotic olaquindox, a swine feed additive banned, in 1998, by the European Commission [14], and the halogenated salicylanylides, removed from disinfectants and hygiene products in most countries, since 1976.

On the other hand, as new UV filters have been introduced in the market – Mexoryl SX (terephtalydene

Table 29.4 Allergens for photopatch testing, to be included in a basic tray (*) and in an extended tray for photopatch testing, according to geographical variations (+) and for aimed testing

INCI/INN	CAS	Vehicle
UV filters		
*Butyl methoxydibenzoylmethane/avobenzone	70356-09-1	10% pet.
*Benzophenone-3/oxybenzone	131-57-7	10% pet.
*Benzophenone-4/sulisobenzone	4065-45-6	2% pet.
*Ethylhexyl methoxycinnamate	71617-10-2	10% pet.
*Isoamyl-*p*-methoxycinnamate	71617-10-2	10% pet
*PABA/aminobenzoic acid	150-13-0	10% pet.
*Octyl dimethyl PABA	21245-02-3	10% pet.
*4-methylbenzylidene camphor	27503-81-7	10% pet.
*Phenylbenzimidazole sulfonic acid	27503-81-7	10% pet.
+Benzophenone-10/mexenone	1641-17-4	10% pet.
+Homosalate	8045-71-4	5% pet.
+Octyl salicylate/2-ethylhexyl salicylate	118-60-5	10% pet.
+Octocrylene/ethyl-hexyl-cyano-diphenylacrylate	6197-30-4	10% pet.
+Octyltriazone/ethylhexyl triazone	88122-99-0	10% pet.
+Drometrizole trisiloxane (Mexoryl XL)	155633-54-8	10% pet.
Terepthalylidene dicamphor sulphonic acid (Mexoryl SX)[a]	92761-26-7	10% H_20
Bis-ethylhexyloxyphenol methoxyphenol triazine (Tinosorb S)[a]	187393-00-6	10% pet.
Methylene-*bis*-benzotriazolyl tetramethylbutylphenol(Tinosorb M)[a]	103597-45-1	10% pet.
Diethylamino hydroxybenzoyl hexyl benzoate (Uvinul A Plus)[a]	302776-68-7	10% pet.
Disodium phenyl dibenzimidazole tetrasulfonate(NeoheliopanAP)[a]	180898-37-7	10% pet.
Diethylhexyl butamido triazone (Uvasorb HEB)[a]	154702-15-5	10% pet.
Drugs		
*Ketoprofen	22161-86-0	1% pet.
+Diclofenac sodium	15307-79-6	5% pet.
+Ibuprofen	15687-27-1	5% pet.
+Naproxen	22204-53-1	5% pet.
+Etofenamate	30544-47-9	2% pet.
+Piroxicam	36322-90-4	1% pet.
+Benzydamine	642-72-8	1-5% pet.
+Chlorpromazine	50-53-3	0.1% pet.
+Promethazine	60-87-7	0.1% pet.
Other allergens		
Fentichlor	97-24-5	1% pet.
Bithionol	97-18-7	1% pet.

(continued)

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Table 29.4 (continued)

INCI/INN	CAS	Vehicle
Hexachlorophene	70-30-4	1% pet.
6-Methylcoumarin	92-48-8	1% pet.
Quinine sulphate	6119-70-6	1% pet.
Diphenhydramine	58-73-1	1% pet.
"Historical" photoallergens		
Tetrachlorosalicylanilide/benzamide	1154-59-2	0.1% pet.
Tribromosalicylanilide/tribromsalan	1322-38-9	1% pet.
5-Bromochlorosalicylanilide	3679-64-9	1% pet.
Triclocarban	101-20-2	1% pet.
Olaquindox	23696-28-8	1% pet.
Musk ambrette	83-66-9	5% pet.
Isopropyl-dibenzoylmethane	63250-25-9	10% pet

t4.39 *INCI* international nomenclature of cosmetic ingredients; *INN* international nonproprietary names; *CAS* chemical abstracts service

t4.40 [a]New UV filters that may be included in a photopatch test series, mainly for research purposes

dicamphor sulfonic acid), Tinosorb M (methylene-*bis*-benzotriazolyl tetramethylbutylphenol), Tinosorb S (*bis*-ethylhexyloxyphenol methoxyphenyl triazine), Uvinul A Plus (diethylamino hydroxybenzoyl hexyl benzoate), Neoheliopan AP (disodium phenyl dibenzimidazole tetrasulfonate) and Uvasorb HEB (diethylhexyl butamido triazone), it may be adequate to add some of these molecules to a photopatch test tray [5], even though they are more photostable and, for the moment, there are no or very few references to contact dermatitis [58, 59].

29.5.1 UV Filters in the Basic and Additional Tray for Photopatch Testing

In most studies, including those from outside Europe [60, 61], UV filters are the most frequent photoallergens. In European studies they were responsible for 5.6–80% of the positive photopatch tests or photoaggravated reactions and, when considering all patients tested, positive photopatch reactions to UV filters occurred in 5.7–21.8% [10, 15, 16, 31, 56, 57, 62]. Therefore, UV filters have to be the main constituents of a photoallergen series [2, 16], even though, which ones can be a subject of discussion. It is consensual to include, in a basic series, the following UV filters: the benzophenones, oxybenzone and sulizobenzone, the dibenzoylmethane, butyl methoxydibenzoylmethane, the cinnamates, isoamyl-*p*-methoxycinnamate and ethylhexyl methoxycinnamate, *p*-aminobenzoic acid and its analogue, octyl-dimethylPABA, 4-methylbenzylidene camphor and phenylbenzimidazole sulfonic acid. The recommended concentration for testing these molecules is 10% pet. (equal to the maximum allowed concentration for most UV filters in sunscreens), except for benzophenone 4/sulizobenzone for which 2% pet. is advised [5]. Other UV filters that have been responsible for photoallergic reactions can be tested in an extended series, namely mexenone (benzophenone 10), octocrylene, drometrizole trisiloxane, homosalate, ethylhexyl salicilate and ethyl hexyl triazone [56, 63–65]. At present, the newer UV filters are being, prospectively, evaluated in an European multicentre photopatch study to decide, whether or not, to include in a photopatch test tray. (Table 29.4)

29.5.2 Drugs in the Basic and Additional Tray for Photopatch Testing

With the wide use of topical NSAIDs and their frequent responsibility in cases of photoallergic contact

dermatitis, some of them quite severe, it is also mandatory to include some of these molecules in a basic photopatch test series. The most important candidate is ketoprofen [2, 6, 8, 66, 67], which is the most frequent photoallergen in recent Italian, French and Spanish studies [31, 56, 57] and also quite frequent in Belgium and Sweden [6, 66]. Other NSAIDs, recently proposed to be included in the basic series, as naproxen, diclofenac and ibuprofen [2], are not so frequently responsible for photoallergy.

Apart from a basic series, recommended for all photopatch tests, regionally prevalent allergens should be added adequately [10, 16, 31, 56, 57]. This is the example of drugs used more frequently in some countries where they are responsible for a large number of photoallergic reactions, namely the NSAID piroxicam, used both topically and by systemic administration, in Portugal, Spain and Italy [10, 31, 57], benzydamine, used as a topical NSAID or a mouth or vaginal wash, in Portugal and Spain [10, 12, 57], the topical antihistamine, promethazine, widely used in Portugal and Greece [10, 68] or its analogue chlorproethazine, used in France as a muscle relaxant [53, 56] or the neuroleptic chlorpromazine that can induce photoallergic contact dermatitis in health care workers or relatives of patients who smash the pills before administration [10, 69].

29.5.3 Other Allergens for Photopatch Testing

Also, we must take into account the "historical" photosensitizers. Some are not available anymore, like musk ambrette and isopropyl-dibenzoylmethane, and, therefore, it is not probable that new cases of photoallergy are diagnosed. On the other hand, other "historical" photoallergens, like olaquindox and halogenated salicylanilides, are still used in countries outside Europe, and some "imported" products can be responsible for new cases of photoallergy [14]. Occasional relevant reactions are still found with other halogenated antimicrobials, like fentichlor and bithionol [31, 70], but they occur more often in patients with photoallergy from other causes, like that from ketoprofen [51, 66]. The photosensitizer, 6-methylcumarin, an ingredient of perfumes not allowed in Europe, was recently responsible for facial pigmentation in a patient from Thailand [71]. PABA, which was frequently responsible for photoallergic contact dermatitis in the 60s and therefore was almost completely removed from sunscreens, was responsible for a recent case of photoallergic contact dermatitis from a sunscreen market in the UK until recently [72]. Therefore, these historical allergens can still be used in aimed photopatch testing.

Also, it is important to photopatch test patient's own products, namely cosmetics, sunscreens, drugs or occupational material. New or hidden photoallergens may be discovered in these products. Even though there is an increased concern on pretesting the phototoxic/photoallergic potential of new cosmetics, UV filters and drugs before the introduction in the market, there is always the chance of finding a new photoallergen.

Core Message

› It can be important to photopatch test with patient's own products, e.g. cosmetics, sunscreens, drugs, etc.

29.6 Conclusions

Although there is still some variation in the procedures and, particularly, in allergens used for photopatch testing, we are nearer to standardization which will allow a more regular use of this procedure and comparison of results between centres. As we have shown, the technique is not so difficult to perform and probably many more patients, than those with typical photoallergic contact dermatitis, can benefit from it.

It is important to publish regularly the results of multicentre studies to know the more prevalent photoallergens and cross-reactive substances in order to take measures to reduce their expression in the market, as has occurred with the "historical" photoallergens. Local or regional studies are also important to adapt photopatch test trays to the population that is the object of the study.

If we perform this technique more often, under standardized procedures, we may, probably, get to the conclusion that photoallergy and, particularly, photoallergic contact dermatitis, is not so uncommon.

29

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[AU5]

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