Workshop report
Photopatch testing – methods and indications

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Summary
This workshop report aims to provide a concise and up to date summary of the clinical use and methodology of photopatch testing. Specific recommendations are made concerning a standard series of six potential photoallergens.

Photoallergic dermatitis reactions are considered to be a form of cell-mediated hypersensitivity in which a photo-activated chemical or a photoproduct acts as a hapten or a complete antigen. Ultraviolet exposure is required both for induction and elicitation of the immune response. In contrast, phototoxic (or 'photooeritirant') reactions are not considered to be immunologically mediated, and will occur in all subjects given sufficient exposure to the photosensitizer and ultraviolet radiation. The acute reactions to porphyrins and psoralens are examples of phototoxicity. Some compounds, for example chlorpromazine, can induce both phototoxic and photoallergic reactions. A further complication is that many photoallergens can, in some subjects, also induce allergic contact reactions without ultraviolet activation.

Photopatch testing is used to diagnose and investigate photoallergic contact dermatitis. Other than confirming that a substance has photosensitizing potential, photopatch testing is not useful for suspected phototoxic skin reactions.

There are widespread differences in the practice of photopatch testing, both within the U.K. and in other countries. This is a report of a British Photodermatology Group workshop on photopatch testing, held in Newcastle upon Tyne in November 1995. The main purpose of the workshop was to discuss the indications, technique and interpretation of results of photopatch testing, in order to provide a list of photoallergens of current clinical relevance and to give guidance on technique.

Clinical indications
Photopatch testing is used principally to investigate patients with an eczematous eruption predominantly affecting light exposed sites, and in whom a history of worsening following sun exposure may be obtained.

Chronic actinic dermatitis, persistent light reaction and other photosensitive disorders

The terms chronic actinic dermatitis and photosensitivity dermatitis/actinic reticuloid syndrome are used synonymously to describe an eczematous disorder, characterized by generalized photosensitivity with abnormal responses to ultraviolet B (UVB), UVA and sometimes to visible light. Photoallergic contact dermatitis may clinically resemble chronic actinic dermatitis but can be distinguished by the finding of normal phototest responses in the absence of the allergen. Although positive photopatch tests have been reported in patients with chronic actinic dermatitis, there are considerable difficulties in testing patients with generalized sensitivity to UVA (see below). It is likely that many of the positive results are phototoxic reactions of uncertain clinical relevance. Nevertheless, clinically important sunscreen photoallergy may occur in this group of patients.

In 1961, Wilkinson reported contact and photocontact allergy to tetrachlorosalicylanilide (TCSA), an antibacterial added to soaps. The dermatitis resolved in most cases once contact with the allergen had ceased, but, despite this, a few patients apparently developed persistent and generalized photosensitivity and were described as having persistent light reactivity. Since
then, numerous photoallergens have been said to cause ‘persistent light reactivity’, including musk ambrette and hexachlorophene. However, in many of the cases reported, the diagnosis was based on a positive photo-patch result in patients with generalized photosensitivity but without a clear history of a preceding acute, localized photococontact reaction. There is little evidence that photoallergens have a causal role in the majority of cases of generalized photosensitivity.

Photocontact allergy, particularly to sunscreen products, may also occur in patients with other photosensitivity or photoaggravated disorders, such as polymorphic light eruption.

### Technique and equipment

#### Action spectrum

The wavelength-dependence in photoallergic contact dermatitis has been studied for very few allergens, several of which are no longer clinically relevant. Radiation from 320 to 400 nm (UVA) is effective in producing photocontact reactions and, over this spectral region, the most effective wavelength correlates reasonably well with the in vitro absorption maxima for TCSA and other salicylanilides. However, these substances and many other photosensitizers often show greater absorbance at wavelengths less than 320 nm. It seems likely that positive photopatch reactions can only, in practical terms, be induced by UVA radiation because of the normal erythemal response: at shorter wavelengths, even if the allergen shows strong absorption, the dose required to achieve photoallergy will still be greater than that required for a normal ‘sunburn’ response.

#### Radiation source

The ideal radiation source for photopatch testing should: (i) allow spatially uniform irradiation of different field sizes as required clinically; (ii) have broad, continuous emission within the UVA region; (iii) have high irradiance so that long exposures can be avoided; (iv) have a stable and well-characterized emission. In practice, either fluorescent UVA lamps, metal halide lamps or a xenon arc lamp coupled to an irradiation monochromator are used for photopatch testing.

The irradiation monochromator is usually only suitable for exposure of small areas (perhaps up to 10 cm²) so that individual patch-test sites will require irradiation in turn. However, as this instrument allows a precise dose and waveband to be chosen, investigation of wavelength-dependence and other characteristics of the response is possible. Use of an irradiation monochromator is likely to be restricted to those centres with facilities for diagnostic phototesting.

UVA lamps of the sort used for psoralens and ultraviolet A (PUVA) are suitable sources. Conventional PUVA equipment can be used, either the whole-body irradiation units, or the small-area units designed for hand/foot irradiation (see below for details of testing). The irradiance from these lamps should be measured using a calibrated UVA meter, and doses prescribed in radiometric units (J/cm²).

Another lamp which is suitable for photopatch testing is the fluorescent ‘Blacklight’. This has a UVA spectrum very similar to that from PUVA lamps, but incorporates a filter to remove visible light.

Sources which largely meet the criteria are optically filtered metal halide and xenon arc lamps (the latter is often referred to as a solar simulator). However, their high cost precludes them as recommended sources for centres which do not have a specialist interest in photobiology. Sources which are not suitable for photopatch testing include Wood’s lamps and mercury arc lamps (for example, the Alpine sunlamp).

#### Ultraviolet dose

The UVA dose for photopatch testing needs to be sufficient to activate the photoallergic response without inducing either an erythemal response attributable to the radiation itself, or a phototoxic reaction likely to be of little clinical significance. UVA doses ranging from 5 to 10 J/cm² are widely used in published reports.

Phototoxic responses are more likely to develop with UVA doses that approach the minimal erythema dose (MED). The UVA dose for just perceptible erythema from PUVA lamps in unacclimatized white skin on the upper part of the back is around 15–20 J/cm² (95% confidence interval 8–40 J/cm²). Thus, positive photopatch responses to promethazine (likely to be phototoxic) were reported in 34–45% of patients tested at 10 J/cm², but only in 1.8% of patients tested at 5 J/cm². In these reports, the proportion of patients reacting to musk ambrette and para-aminobenzoic acid (more likely than promethazine to induce true photoallergic reactions) showed no significant differences according to the UVA dose used. In the absence of published data to suggest that clinically important reactions are revealed only with a UVA dose of 10 J/cm², it seems reasonable to recommend the use of 5 J/cm² for routine testing.
is limited evidence that smaller doses may be sufficient for certain allergens. 20, 21

**Test procedure**

Conventional patch-test techniques are used, except that the allergens are applied in duplicate (one set for irradiation, one as the non-irradiated control), usually to the back on either side of the midline but avoiding the immediate paravertebral skin. Three protocols appear to be in use (Table 1) but no information exists as to which is more reliable or discriminatory. Protocols (1) and (3), favoured by units with an interest in investigation of patients with suspected photosensitivity, allow the patient to be phototested and the 24-h MEDs known at the time of irradiation of the photopatch tests. Phototesting is considered to be essential if there is any clinical suspicion of generalized photosensitivity.

The allergens and applicator chambers are removed and discarded at the time of irradiation. The allergen sites are irradiated in turn if a small-area light source is used (such as an irradiation monochromator), or with a single exposure to the relevant part of the back if a wide-area source (such as PUVA equipment) is used. PUVA equipment designed for hand/foot treatment is a convenient light source when mounted vertically on a wall. The irradiance from these units is highly dependent on the distance from the lamps. It is recommended that the patient’s back is 15 cm from the front panel of the lamps, when a relative change of ±5 cm (for example, due to curvature of the back) gives an error in dose of within ±12%.

**Reading and interpretation of results**

A positive response at the irradiated allergen site alone may be indicative of true photoallergy, a phototoxic response (likely to be of no clinical relevance), or summation of a subclinical chemical irritant and ultraviolet erythemal reaction. As with patch testing, strongly positive allergic reactions can be distinguished easily from minor non-specific irritant/phototoxic reactions, but difficulty in interpretation may occur with weaker allergic reactions. A positive reaction at the non-irradiated site with a stronger reaction at the irradiated site may indicate combined contact and photocontact allergy, 22 but the clinical significance is not known. Any erythema developing on skin exposed to the radiation alone is a strong indication of generalized UVA photosensitivity.

**Testing in patients with generalized photosensitivity**

Photopatch testing is difficult in patients with generalized photosensitivity, and may be impossible in those with extreme UVA sensitivity. The UVA dose should be chosen on the basis of the MED: 50% of the UVA MED is

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**Table 1. Three protocols for photopatch testing.** Phototest signifies investigation of the patient using an irradiation monochromator or similar ultraviolet source to determine the ultraviolet A (UVA) minimal erythema dose.

<table>
<thead>
<tr>
<th></th>
<th>Day 0</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
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<tbody>
<tr>
<td>(1)</td>
<td>Phototest</td>
<td>Read phototest results</td>
<td>Apply allergens</td>
<td>Remove patches and irradiate allergens</td>
<td>Read results</td>
</tr>
<tr>
<td>(2)</td>
<td>Apply allergens</td>
<td>Remove patches, read results and irradiate allergens</td>
<td>Read results</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(3)</td>
<td>Apply allergens</td>
<td>Phototest</td>
<td>Read phototest results</td>
<td>Remove patches, read results and irradiate allergens</td>
<td>Read results</td>
</tr>
</tbody>
</table>

often recommended but may still result in phototoxic reactions of uncertain relevance. Some specialist units find it helpful to use a series of UVA doses, ranging from 10 to 50% of the UVA MED. Conventional phototesting is therefore required to determine MEDs prior to photopatch testing. The skin region used for testing should preferably be clinically clear. It is common practice to cease topical application of corticosteroids for 1 week prior to testing. The effect of immunosuppressive drugs such as azathioprine on the photocontact reaction is not known.

### Allergens

In several countries, standard series of allergens for photopatch testing have evolved. However, many of the substances routinely tested seem to be of little current clinical relevance. Once identified, significant photoallergens tend to be excluded from future products. Potential photoallergens can be grouped as: sunscreen chemicals; antibacterial agents; fragrances; and a number of miscellaneous chemicals.

(i) **Sunscreen chemicals**

Ultraviolet absorbers in sunscreens are now the commonest cause of positive photopatch tests. Within this group, changing formulation has resulted in agents such as the benzophenones largely taking over from para-aminobenzoic acid (PABA) and its derivatives as the commonest photoallergens.

*Para aminobenzoic acid and its esters.* Frequent contact and photocontact allergy has led to reduction in the use of PABA, although it is still widely available and may be found in cosmetic products. PABA esters, particularly octyl dimethyl PABA (Padimate O, Escalol 507), are still used and may cause photocontact allergy.

*Cinnamates.* Cinnamate derivatives are also used widely in sunscreens. 2-ethoxyethyl-4-methoxycinnamate (Cinoxate, Givtan F) caused photosensitivity but is not used in the U.K. Photoallergy is rare with the most widely used cinnamate, 2-ethylhexyl-4-methoxycinnamate (Parsol MCX).

*Benzophenones.* These agents mainly absorb in the UVA region, and are found in many ‘PABA-free’ sunscreens. Photocontact allergy has been reported with 2-hydroxy-4-methoxybenzophenone (Oxybenzone) and 2-hydroxy-4-methoxy-benzophenone (Mexenone).

### Dibenzoylmethanes

These UVA absorbing chemicals are used widely in continental Europe. Photocontact allergy is infrequent but has been reported with 4-tert-butyl-4-methoxy dibenzoylmethane (Parsol 1789), 4-isopropyl dibenzoylmethane (Eusolex 8020), another photosensitizer, has been withdrawn.

### Camphor derivatives

There are few reports of reactions to the camphor derivatives. Contact allergy to methylbenzylidene camphor (present in Eusolex 8021) has been documented, but not photocontact allergy.

(ii) **Antibacterial agents**

Antibacterial agents such as TCSA, other halogenated salicylanilides, and chlorinated phenol compounds (bithionol and fentichlor) were found to be potent photoallergens when added to soaps and other products in the 1960s and 1970s. Following reports of contact and photocontact dermatitis, use of these compounds ceased or diminished to the point where they are no longer relevant allergens, at least in Europe.

(iii) **Fragrance ingredients**

Musk ambrette, was one of the commonest identified causes of photoallergic contact dermatitis in the late 1970s when it was used in relatively high concentration in perfume products. It is no longer added to topical preparations available in Europe, but may still be present in perfumes manufactured before around 1994, or in products purchased elsewhere, particularly from Asia.

6-Methyl coumarin is a synthetic fragrance and potent photoallergen but is no longer used as a fragrance component. Phototoxic reactions may occur with balsam of Peru, but do not indicate photoallergy.

(iv) **Miscellaneous compounds**

Chlorpromazine can induce photoallergic contact dermatitis, for example in health-care workers, but the frequent occurrence of positive photopatch results without clinical relevance indicates non-specific phototoxicity. Likewise promethazine (used at one time as an antipruritic agent) frequently causes a phototoxic response on testing.

Compositae, lichens and various wood mixes may...
cause airborne contact dermatitis and thus mimic photosensitivity. Positive patch tests to compositae are commonly found in patients with chronic actinic der-
mimic photosensitivity. Positive patch tests to compositae are commonly found in patients with chronic actinic der-
matitis,5,39 but there is no convincing evidence that any of these compounds are significant photoallergens.

In Table 2 a number of other chemicals are listed which have been reported as infrequent or isolated causes of photoallergy.

A standard series of allergens for routine photopatch testing

Many of the agents tested routinely in some countries are no longer significantly relevant photoallergens, at least in the U.K. Some, for example TCSA, are now merely of historical interest. Others, for example chlorpromazine, frequently produce positive test results, but these are usually without clinical significance. An allergen might be incorporated in a standard series if it is widely used or appears, from published data, to be a relatively common cause of photoallergy. On this basis, the workshop participants recommend that six compounds (five sunscreen chemicals and musk ambrette), all readily available from suppliers of patch-test allergens, should form a standard photocontact series (Table 3). The concentrations quoted are those that are available commercially in a patch-test formulation; little or no information exists as to the optimal concentration for detection of photoallergy. Other allergens listed in Table 2 could be added to the standard series when appropriate, including any product used by the patient that may be of relevance.

Periodic review will be required of the allergens included in a standard photopatch series, in order to reflect the agents that are in current commercial use. Photopatch testing is still an evolving technique and further research is required into all of its components.

References


Table 2. Agents reported to cause photocontact allergic dermatitis

<table>
<thead>
<tr>
<th>Sunscreen chemicals</th>
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<tbody>
<tr>
<td>Para-aminobenzoic acid (PABA)</td>
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<tr>
<td>Amyl dimethyl PABA (Padimate A, Escalol 506)</td>
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<tr>
<td>Octyl dimethyl PABA (Padimate O, Eusolex 6007, Escalol 507)</td>
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<tr>
<td>2-ethoxyethyl-p-methoxycinnamate (Cinnoxate, Givtan F) (withdrawn)</td>
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<tr>
<td>2-ethylhexyl-p-methoxycinnamate (Parsol MCX)</td>
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<tr>
<td>2-hydroxy-4-methoxybenzophenone (Oxybenzone, Benzophenone 3, Eusolex 4360)</td>
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<tr>
<td>2-hydroxy-4-methoxybenzophenone (Mexenone, Benzophenone 10)</td>
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<tr>
<td>4-isopropyl dibenzoylmethane (Eusolex 8020, withdrawn)</td>
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<tr>
<td>4-tert-butyl-4-methoxy dibenzoylmethane (Parsol 1789)</td>
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<tr>
<td>Fragrance ingredients</td>
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<tr>
<td>Musk ambrette</td>
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<td>6-methyl coumarin</td>
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<tr>
<td>Sandalwood oil</td>
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<tr>
<td>Antibacterial agents (only of historical relevance in the U.K.)</td>
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<tr>
<td>Bithionol</td>
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<td>Baclosamide</td>
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<td>Hexachlorophene</td>
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<tr>
<td>Fenticon</td>
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<tr>
<td>Tetrachlorsalicylanilide (TCSA) and other halogenated salicylanilides</td>
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<tr>
<td>Miscellaneous compounds</td>
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<tr>
<td>Patient’s own product</td>
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<tr>
<td>Benzocaine</td>
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<tr>
<td>Chlorhexidine</td>
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<tr>
<td>Chlorpromazine</td>
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<tr>
<td>Diphenhydramine</td>
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<td>Hexamidine</td>
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<tr>
<td>Hydrocortisone</td>
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<td>Promethazine</td>
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<td>Thiourea</td>
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Table 3. Suggested standard series of photocontact allergens. The concentrations quoted are those that are available commercially as patch-test formulations

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<tr>
<td>Para-aminobenzoic acid (PABA) (5%; 10%)</td>
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<tr>
<td>Octyl dimethyl PABA (Padimate O, Eusolex 6007, Escalol 507) (2%; 10%)</td>
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<tr>
<td>2-ethylhexyl-p-methoxycinnamate (Parsol MCX) (2%; 10%)</td>
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<tr>
<td>2-hydroxy-4-methoxybenzophenone (Oxybenzone, Benzophenone 3, Eusolex 4360) (2%; 10%)</td>
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<tr>
<td>4-tert-butyl-4-methoxy dibenzoylmethane (Parsol 1789) (2%; 10%)</td>
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<tr>
<td>Musk ambrette (1%; 5%)</td>
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<tr>
<td>Patient’s own product (diluted as appropriate)</td>
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</tbody>
</table>
29 Davies MG, Hawk JLM, Rycroft RJG. Acute photosensitivity from the sunscreen 2-ethylhexyl-p-methoxycinnamate. *Contact Dermatitis* 1982; 8: 190–2.
31 Buckley DA, O’Sullivan D, Murphy GM. Contact and photocontact allergy to dibenzoylmethanes and contact allergy to methylbenzy- lidene camphor. *Contact Dermatitis* 1993; 29: 47.
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