

A double-blind, randomized assessment of the irritant potential of sunscreen chemical dilutions used in photopatch testing*

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Background: The maximum concentration of organic sunscreen filters in current usage that does not lead to irritant reactions when performing photopatch testing is not known. Such irritant reactions can be misinterpreted as positive photoallergic contact dermatitis reactions.

Objective: To determine the frequency of irritant reactions to 19 organic sunscreen filters in current use.

Patients/Methods: Ninety-four healthy volunteers were photopatch tested using the European consensus methodology to three different concentrations (2%, 5%, and 10%) of 19 organic sunscreen filters at the Photobiology Unit in Dundee, UK.

Results: Of the 94 subjects recruited, 80 were analysed after withdrawals and exclusions. Of the 19 organic sunscreen filters studied, only 2 compounds led to irritant reactions in $\geq 5\%$ subjects. Five per cent and 10% benzophenone-4 led to irritant reactions in four and six subjects, respectively. Five per cent methylene bis-benzotriazolyl tetramethylbutylphenol led to irritant reactions in six subjects, but unlike benzophenone-4, this was not in a dose-dependent fashion.

Conclusions: When performing photopatch testing according to the European consensus methodology with these 19 organic sunscreen filters, a 10% concentration is suitable for all filters, except benzophenone-4, which should be tested at a concentration of 2%.

Key words: irritant reaction; organic sunscreen; photoallergic contact dermatitis; photopatch test.
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Patch testing and photopatch testing are established methods for the investigation of patients suspected of having contact allergic dermatitis and photocontact allergic dermatitis (PACD), respectively. Both of these investigations provoke a type IV (delayed) allergic response seen when an allergen comes in contact with the skin, producing varying degrees of an erythematous papulovesi-

cular response. The morphology of this varying response has been incorporated into a scale for rating the intensity of allergic reactions by the International Contact Dermatitis Research Group (ICDRG) (1). This scoring system includes a grade of 'irritant reaction' (IR), which refers to an erythematous, often slightly oedematous, reaction that is not thought to be the result of a true type IV allergic contact dermatitis. While clinicians experienced in reading patch and photopatch tests may correctly identify an IR, less experienced clinicians can mistake these as allergic responses. Such

*The experiment was not registered with a national open database of clinical trials.

'false positives' may result in the patient being incorrectly advised to avoid an allergen while still being exposed to the true causative allergen.

An IR can arise to many patch test materials, but certain factors are known to increase the likelihood of an IR developing. First, the agent under investigation must be tested in a suitable vehicle that is not likely to cause an IR in its own right. It is preferable if the agent is also soluble in that vehicle. Petrolatum (pet.) is the most common vehicle employed, but others such as water may be used. Allergic reactions to pet. itself are very rare (2), and it is generally accepted as a good vehicle as it also prevents oxidation of the agent, thus prolonging the shelf-life (3). Second, the threshold for an IR can be lowered by concomitant dermatitis at the site of patch application or at a distant site (4). Finally, an IR can be caused by an inappropriately high test agent concentration, which can be exacerbated yet further if the quantity of agent per unit area of skin at this concentration is increased (5). In practice, this can be a delicate balance as the concentration used must also be high enough to trigger an allergic reaction in susceptible patients, thereby avoiding 'false-negative' readings that may lead to relevant allergens not being detected and subsequently avoided. In conventional patch testing, the optimum concentration of the many agents in use has been determined over several years by testing large numbers of patients and normal controls.

When one considers photopatch testing, in addition to the above three factors possibly causing an IR, irradiation of one of the test agent sets may lead to a phototoxic reaction, which can similarly be misidentified as false positive. In photopatch testing, an ultraviolet A (UVA) dose of 5 J/cm² has generally been accepted as leading to fewer false-positive phototoxic reactions than 10 J/cm² (6).

Currently, common photoallergens that patients and consumers across Europe may come into contact with include topical non-steroidal anti-inflammatory drugs (NSAIDs) and also organic sunscreen filters. However, unlike conventional patch testing, the optimum concentration of these filters for photopatch testing has not yet been determined. Furthermore, the continual development of new filters coupled with abandonment of older ones has made the regular periodic updating of 'standard' series of sunscreens essential. Such series as that suggested by the British Photodermatology Group in 1997 (7) may include suggested concentrations for testing, but the experimental data to support these are lacking. Under European law, the maximum permissible concentration of most filters in cosmetic products

is 10% (8). Consequently, when conducting photopatch testing to UV filters, many dermatologists use 10% as a test concentration, although there remains no consensus on the topic. It was written in 1990 that 'the maximum non-irritating doses of putative antigens in a given vehicle have not been defined for sunscreen chemicals' (9). It is accurate to say that some 18 years later, this situation has not changed significantly.

In 2007, a group of European dermatologists met on behalf of the European Society for Photodermatology and the European Society of Contact Dermatitis. The purpose of the meeting was to set up a European multicentre photopatch test study to investigate the frequency of PACD to 19 current sunscreen filters and five topical NSAIDs. However, for the reasons outlined above, the maximum non-irritant concentration of sunscreen filters to use in this study is not known, and there was a concern that multiple false-positive IR results could make determination of the true frequency of photoallergy difficult. Therefore, the primary objective of this pilot study was to determine the frequency of IRs to three different concentrations (2%, 5%, and 10%) of the 19 UV filters to be used in this upcoming multicentre study.

Materials and Methods

Participants

This study was reviewed and approved by the Tayside Committee on Medical Research Ethics. It was conducted according to the principles of the Declaration of Helsinki and International Conference on Harmonisation Good Clinical Practice (10). Healthy male or female volunteers aged 18–70 years with Fitzpatrick skin type I–IV were recruited through Drug Development Solutions (now Chiltern Early Phase Ltd). Subjects were excluded if they had been exposed to sunlight or UV on their back within the 4 weeks prior to testing, had applied potent topical steroids on their back within the 5 days prior to testing, had a known photodermatosis, or had a known history of reacting to a sunscreen.

Photopatch testing and test series

The photopatch tests were performed according to the European consensus methodology (6). The 19 sunscreen agents (Table 1) were prepared by Chemotechnique Diagnostics, Vellinge, Sweden, in pet. except terephthalylidene dicamphor sulfonic acid. Terephthalylidene dicamphor sulfonic acid has a low pH, which needs the addition of a neutralizing agent to prevent IRs and was, therefore, diluted in water. Each agent was made up in three

Table 1. The 19 organic ultraviolet filter agents tested

International Nomenclature of Cosmetic Ingredients name	Chemical Abstracts Service number
Butyl methoxydibenzoylmethane	70356-09-1
Homosalate	118-56-9
4-Methylbenzylidene camphor	36861-47-9
Benzophenone-3	131-57-7
Ethylhexyl methoxycinnamate	5466-77-3
Phenylbenzimidazole sulfonic acid	27503-81-7
Benzophenone-4	4065-45-6
Octocrylene	6197-30-4
Ethylhexyl salicylate	6969-49-9
Ethylhexyl triazone	88122-99-0
Isoamyl- <i>p</i> -methoxycinnamate	71617-10-2
Drometrizole trisiloxane	155633-54-8
Terephthalylidene dicamphor sulfonic acid	90457-82-2
Bis-ethylhexyloxyphenol methoxyphenyl triazine	187393-00-6
Methylene bis-benzotriazolyl tetramethylbutylphenol	103597-45-1
Diethylamino hydroxybenzoyl hexyl benzoate	302776-68-7
Disodium phenyl dibenzimidazole tetrasulfonate	180898-37-7
Diethylhexyl butamido triazone	154702-15-5
Polysilicone-15	207574-74-1

concentrations (2%, 5%, and 10%). A 5 mm bar from a 5-ml syringe (approximately 20 µl) of each agent in pet. was applied using a syringe to an 8-mm diameter metal chamber (Finn Chamber[®]; Epitest Ltd Oy, Tuusula, Finland) mounted on hypoallergenic adhesive tape (Scanpor[®] tape; Actavis Norway AS, Norgesplaster, Vennesla, Norway). The terephthalylidene dicamphor sulfonic acid and water controls were applied to a filter paper disc placed in a metal chamber and saturated with the liquid. Three controls were used: an empty Finn Chamber, water on a filter paper in a Finn Chamber, and pet. in a Finn Chamber.

The patches were made up as duplicate sets and then applied to the left and right non-paravertebral skin of the upper back of subjects. After 2 days, the patches were removed, and a set on one side of the back was covered with an UV-opaque material, while the other was irradiated with 5 J/cm² UVA (vertical bank of 10 Waldmann F15W/T8 tubes; peak emission at 352 nm; 99.2% UVA and 0.8% UVB). For irradiation, the subject was placed 20 cm from the source sitting with their back in a vertical position, parallel to the middle of the source.

Study design and statistical methods

Block randomization codes were computer generated for each of the agents and each of the concentrations. Further block randomization codes

were generated for the application of the concentrations (2%, 5%, and 10%) to the upper, middle, or lower back and the side of the back (left or right) to be irradiated [using the 'ralloc' command by P. Ryan, implemented in STATA 10 (StataCorp, College Station, TX, USA)]. Readings of both sites were made by a blinded clinician pre-irradiation (D2, 0 hr), immediately post-irradiation, and at D1, D2, and D3, respectively, post-irradiation. Any positive reactions were photographed. All reactions were graded using both the ICDRG scale (1) (Table 2) and an erythema scale (Table 3).

It was decided that it would be practicable to recruit about 80 subjects. With 81 subjects, we should have 90% power to detect if $5 \pm 4\%$ (i.e. 1–9%) of the wider adult Tayside population from whom our volunteers were drawn have IRs to a particular agent (calculated with OPENEPI, version 2; <http://www.openepi.com/SampleSize/SSPropor.htm>, 2007). If any of the filter concentrations were found to cause IRs in $\geq 5\%$ of study sample subjects (i.e. four or more subjects), it was decided that they would not be suitable for photopatch testing in future studies, including the upcoming European multicentre study.

Results

There were 94 subjects recruited over the duration of the study. Of these, 10 subjects were withdrawn because the patches became detached within the 2-day application period. Two further subjects were excluded from analysis because they failed to attend for any readings after patch application. Therefore, 82 subjects had at least one assessment on D3. Of the 82, 2 subjects were excluded from further analysis as they had reactions thought to be spurious in nature. One of these subjects had grade '1' and '+/–' reactions to all concentrations of all agents and controls in the covered site immediately post-irradiation. It was thought this may have been the result of removal of the adhesive tape, or possibly an unexpected effect of the process of irradiation nearby, as the covered site was not accidentally exposed to UVA radiation. The

Table 2. The International Contact Dermatitis Research Group scale for grading photopatch test reactions

–	No reaction
+/–	Doubtful reaction (in these cases, the reaction was only scored using the erythema score)
+	Weak positive (erythema, infiltration, and possibly papules)
++	Strong positive reaction (erythema, infiltration, papules, and vesicles)
+++	Extreme positive reaction (intense erythema, infiltration, and vesicles may coalesce to form a blister)

Table 3. The erythema scale for grading photopatch test reactions

0	Negative, no response
0.5	Equivocal reaction, barely perceptible erythema with no clearly defined border
1	Mild but definite erythema with a clearly defined border
2	Moderate clearly defined erythema
3	Strong erythema

other subject had grade '0.5' and '+/–' reactions to the 2% concentration of all agents (but not at the controls) in the irradiated site 1 day after irradiation. Therefore, the analysed population comprised 80 subjects. The baseline demographics of both the recruited subjects and the analysed subjects are summarized in Table 4.

Number of reactions by scale

Of the 80 subjects, 21 were recorded as having a doubtful (+/–) or weak positive (+) reaction at some time-point using the ICDRG grading scale. Nine had at least one + reaction (a further four of these also had at least one +/– reaction at some time-point). The remaining 12 subjects had at least one +/– reaction at some time-point.

With respect to concordance of the ICDRG reactions seen, 7 of 21 subjects reacted to a filter or filters at the irradiation site only. The next largest group of subjects were the five who displayed only concordance (i.e. a reaction was seen at both irradiation and covered sites for a filter or filters), followed by four subjects who had a combination of reactions plus concordant reactions at the irradiation site only. Three subjects had discordance of reactions (i.e. reactions were seen at the irradiation site only for one filter and at the covered site only for another filter). One subject had concordance and a covered site reaction only, and one had a covered site reaction only to one filter.

As regards the erythema scale, 19 subjects were recorded as having at least one reaction at some time-point. Of these, two subjects had a grade 2

erythema at at least one time-point (both also had at least one grade 1 erythema at some time-point). A further 12 subjects had at least one grade 1 erythema at some time-point (4 of these subjects also had at least one grade 0.5 erythema at some time-point). Five subjects were reported as having at least one grade 0.5 erythema at some time-point. There were two subjects who were recorded as having a weak positive reaction using the ICDRG scale with no concomitant erythema score [a + to 10% benzophenone-4 in the irradiated site at D4 and a + to 5% methylene bis-benzotriazolyl tetramethylbutylphenol in the irradiated site at D2 (post-irradiation)].

Number of doubtful and weak positive ICDRG-graded reactions by site and time

The total number of doubtful and weak positive ICDRG-graded reactions seen at some time-point was 39 at the irradiation site (27 +/– and 12 + reactions) and 28 at the covered site (22 +/– and 6 + reactions). The timing and grade of these reactions are given in Fig. 1. It can be seen that there was only one reaction recorded prior to irradiation on D2. There are several reactions seen immediately post-irradiation, with a peak at D3 (1 day after irradiation) before steadily declining.

Number of doubtful and weak positive ICDRG-graded reactions by sunscreen filter

The number of ICDRG reactions recorded for the 19 sunscreen filters and controls is given in Fig. 2. It can be seen that eight filters did not produce any reactions at any time-points. Of the 11 that did cause reactions at some time-point, only 2 filters caused reactions in four or more subjects; 5% benzophenone-4 (four subjects), 10% benzophenone-4 (six subjects), and 5% methylene bis-benzotriazolyl tetramethylbutylphenol (six subjects). However, only benzophenone-4 exhibited a dose–response pattern, with increasing concentrations leading to increasing numbers of reactions. The peak of reactions seen at 5% methylene bis-benzotriazolyl tetramethylbutylphenol could not be explained in this manner as there were only two reactions at the 2% concentration and one reaction at the 10% concentration. These results support using all 19 filters at a 10% concentration when conducting photopatch testing, except benzophenone-4 that should be used at a concentration of 2%.

Discussion

The primary objective of this pilot study was to determine the frequency of irritant responses to

Table 4. Baseline demographic data of the recruited and analysed subjects

Characteristics	Recruited subjects	Analysed subjects
	n (%)	n (%)
Total number	94	80
Mean age (years)	32.9	33.2
Age range (years)	18–61	18–61
Females	53 (56.4)	44 (55)
Males	41 (43.6)	36 (45)
Skin type I	5 (5.3)	3 (3.8)
Skin type II	42 (44.7)	37 (46.3)
Skin type III	44 (46.8)	38 (47.5)
Skin type IV	3 (3.21)	2 (2.5)

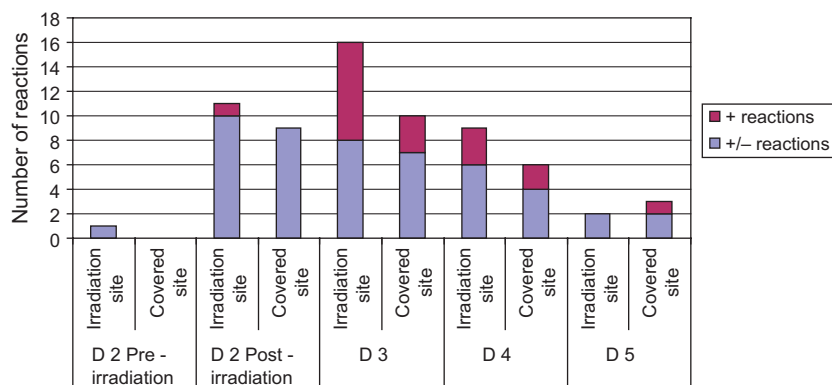


Fig. 1. The number of doubtful (+/-) and weak positive (+) reactions using the International Contact Dermatitis Research Group scale by day and irradiation site.

three different concentrations of 19 organic sunscreen filters when used to conduct photopatch testing according to the European consensus methodology (6). To our knowledge, this is the only study to date undertaken to attempt to address the issue of the maximum non-irritating concentration of organic UV filters. Of the 19 filters studied, only benzophenone-4 caused positive reactions in $\geq 5\%$ of subjects in a dose-dependent manner. We would therefore advise clinicians not to use a concentration of benzophenone-4 greater than 2% in pet. when performing photopatch testing according to this methodology.

Because of the use of healthy volunteers and focus on irritancy, direct comparison of our results with previous studies is difficult. One previous retrospective review of patch testing in 553 patients showed 13 (2.3%) reactions to 10% benzophenone-4. The authors stated that these reactions were invariably negative 2 days after patch removal and positive on D4, supporting a contact allergic mechanism rather than an IR (11). In our study, methylene bis-benzotriazolyl tetramethyl-

butylphenol also led to a number of reactions, most notably at 5% concentration, yet it is not known why it failed to demonstrate a dose-response pattern. In one previous photopatch report, a patient developed reactions to 2% methylene bis-benzotriazolyl tetramethylbutylphenol on D2 and D4 in both the irradiated and the unirradiated sites, which was interpreted as contact allergy (12). The authors tested the same agent in 20 control subjects with negative results. In our study, only 2 of 80 subjects had reactions to 2% methylene bis-benzotriazolyl tetramethylbutylphenol, and although the frequency of IR does appear low, it should be considered when photopatch testing with this filter.

One limitation of this study is the relatively small population tested (80 subjects) that may be important, given that interindividual variation in the propensity to develop IRs has been previously demonstrated (13). Such variation means that as well as the reactions highlighted, it is possible that IRs could still occur at any concentration of any of the agents tested here. Another limitation of

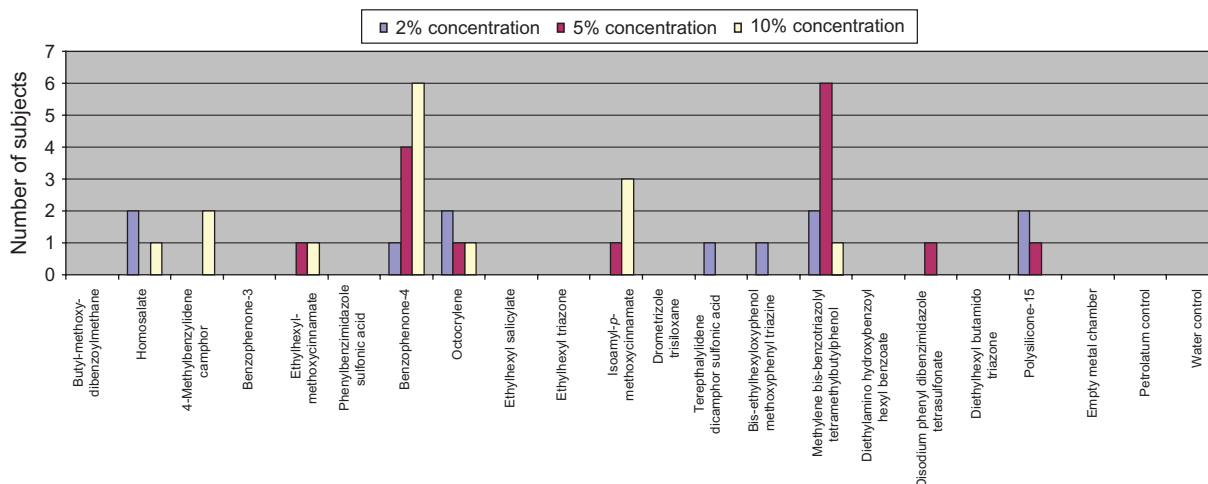


Fig. 2. The number of subjects with International Contact Dermatitis Research Group reactions graded as doubtful (+/-) or weakly positive (+) to the 19 ultraviolet filters and 3 controls.

our study was the use of healthy volunteers who had no active dermatoses or history of reacting to sunscreens. The majority of these (59 of 80) had no reactions at all, which will be reassuring to sunscreen manufacturers and consumers alike. However, it is likely that in the setting of photopatch testing patients who present to a dermatologist with a photo-exposed site skin problem, the number of IRs seen may be higher. One previous Swedish study investigated 35 patients who had complained of reactions to commercial sunscreen products. Although three patients did have photoallergy on photopatch testing, the majority of the reactions were attributed to irritant effects from the sunscreen filters and excipients (14). A longitudinal study in Australia studied the reactions to two UV filters (octyl methoxycinnamate and butyl methoxydibenzoylmethane) in a sunscreen preparation. Among the 90 of 603 patients who had an inflammatory reaction to the sunscreen after daily use, the majority were deemed to have had an IR. Furthermore, a number of IRs were seen on patch and photopatch testing to the sunscreen, and no subjects had positive patch or photopatch reactions to the two filters. This further highlights the importance of irritant responses in numerical terms when one is patch and photopatch tested to UV filters and sunscreen excipients (15).

IRs to sunscreen products have been known about for many years (16). Manufacturers of sunscreens often combine multiple filters to increase the spectrum of protection as well as increasing the sun protection factor. Concentrations of filters are usually kept below the maximal allowed concentration, but as this study demonstrates, IRs under patch test conditions are still possible at these concentrations. When patients present with a history of reacting to a sunscreen, a common practice is to test the patient to their sunscreen product 'as is', and if a positive reaction is seen, attempt to perform further photopatch testing to the individual filters and excipients in the product. It can be helpful to separate out potential allergens in this way as inhibitory and augmentary interactions between the constituents can occur. However, for reasons stated earlier, such testing can also be misleading if the filter concentration is too low to elicit a positive reaction or if it is too high, leading to an IR.

One difficulty of conducting this study was attempting to detect true irritant responses. We chose to employ two clinical scales to detect any possibly relevant reactions because this was a pilot study for a larger clinical study in which the ICDRG grading scale will be used. The ICDRG scale is based primarily on true allergic reactions causing a papular and/or vesicular response, so we

thought that the use of both the ICDRG and the erythema scales in the present study might increase the sensitivity for detecting possible IRs. The scales were considered to be compatible as only two reactions graded with the ICDRG scale were not concomitantly graded with the erythema scale.

Some investigators have employed various bioengineering methods for attempting to quantify IRs (17). Differences in cytokine profiles between IR and true allergic responses have been demonstrated (18), but many features that were thought previously unique to the allergic response have also been seen in the IR, meaning that an actual distinction between the two could be argued as conceptual rather than actual (19). In practice, clinicians will continue to rely on a combination of morphology, time-course, and knowledge of allergens to differentiate between an IR and a true allergic reaction.

When conducting photopatch testing, the process of irradiation was seen to be an important variable in its own right, which had a bearing on the number of positive reactions seen. The peak seen at 1 day post-irradiation in the irradiated site (which included 8 + reactions) that then settled would be consistent with a phototoxic aetiology rather than true photoallergy. Although it is known that 10 J/cm² UVA leads to more phototoxic reactions than 5 J/cm² (20), a clinically relevant number of phototoxic reactions will also occur at 5 J/cm². For the purposes of analysing results from the planned multicentre study, similar 'decrecendo' patterns will need careful interpretation as possible phototoxic reactions. Interestingly, irradiation also appears to be important in determining the number of reactions at the covered site. There were no reactions recorded at this site pre-irradiation, yet 9 reactions were seen immediately post-irradiation, peaking at 10 reactions at 1 day post-irradiation. Although there were more reactions in total seen in the irradiated than in the covered site, the pattern of covered site reactions implies that irradiating the back may cause a 'general excitability' of the skin, which must also be taken into account when conducting and interpreting photopatch tests.

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Author Contributions

The idea of the study was conceived by A. C. K. and J. F. The study protocol was devised by A. C. K., R. S. D., and J. F. Readings of photopatch test reactions

were made by A. C. K. and J. F. Comments on this design and preparation of test materials in appropriate vehicles and at appropriate concentrations were done by B. N., A. M. E., and M. K. Contribution to the study design and recruitment of volunteer subjects were done by B. S. All authors contributed to the drafting of the paper. A. C. K. and J. F. have direct access to the original data and vouch for the accuracy and completeness of this report.

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