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DOCTOR OF MEDICINE

Photoallergic contact dermatitis in Europe

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DOCTOR OF MEDICINE

# Photoallergic contact dermatitis in Europe

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## **4. A pilot irritancy study of organic ultraviolet absorbers**

This Chapter details the pilot study into assessing the maximum non-irritating concentration that can be used for each of the 19 organic UV absorbers to be tested in the EMCPPPTS.

### **4.1 Introduction**

#### **4.1.1 Background**

As outlined in Chapter 1, PPT provokes a type IV (delayed) allergic response seen when the agent under investigation comes in contact with the skin, producing varying degrees of an erythematous papulo-vesicular response. The morphology of this response can be graded using the ICDRG scale.[1] This 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 response. While clinicians experienced in reading photopatch tests may correctly identify an IR, less experienced clinicians can mistake these as allergic responses. Such “false positives” may result in the patient being incorrectly advised to avoid a photoallergen. If investigations are discontinued at that point, the patient may unknowingly continue to be exposed to the true causative agent.

#### **4.1.2 Factors influencing IRs**

An IR to a test agent can arise during any patch testing or PPT, but certain factors are known to increase the likelihood of an IR developing. Firstly, the agent under investigation must be tested in a suitable vehicle which is not likely to cause an IR in its own right. It is preferable if the agent is also soluble in that vehicle. Petrolatum (also known as WSP if purified) is the most common vehicle employed,

but others such as water may be used. Allergic reactions to petrolatum itself are very rare and it is generally accepted as a good vehicle as it also prevents oxidation of the agent, thus prolonging the shelf-life.[2,3] Secondly, the threshold for an IR can be lowered by concomitant dermatitis at the site of patch or photopatch 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/photoallergic reaction in susceptible patients, thereby avoiding “false negative” readings which 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 PPT, in addition to the above 3 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 a “false positive.” In PPT, a UVA dose of  $5 \text{ Jcm}^{-2}$  has generally been accepted as leading to fewer false positive phototoxic reactions than  $10 \text{ Jcm}^{-2}$ . [6] Furthermore, “false positives” during PPT can also be caused by the combination of suberythematous UV exposure plus a subclinical IR. [7]

#### **4.1.3 Determining optimum agent concentrations**

As outlined in Chapter 1, currently the two most common groups of agents leading to PACD are organic UV absorbers and topical NSAIDs. Unlike conventional patch testing, the optimum concentration of these two agent groups for PPT has not yet been determined. Such PPT series as that suggested by the British Photodermatology Group (BPG) in 1997 may include suggested concentrations for

testing but the experimental data to support these is lacking.[8] Current guidance from the European Commission on the maximum permissible concentration of the 25 organic UV absorbers which can be used in cosmetic products is given in Annex VII [9](see also Appendix 1). Of these 25, 13 can be used at a maximum concentration of 10% and one (drometrizole trisiloxane) at a maximum concentration of 15%. Consequently, when conducting PPT to organic UV absorbers, many dermatologists use 10% as a test concentration, although there remains no consensus on the topic.

It had been agreed that the EMCPPTS test series would include 19 organic UV absorbers listed in Annex VII. However, for the reasons outlined above, the maximum non-irritating concentration of these agents was not known and there was concern that multiple “false-positive” IR results could make determination of the true frequency of photoallergy in the EMCPPTS difficult.

#### **4.1.2 Objective**

The objective of this pilot study was to determine the frequency of IRs to three different concentrations (2%, 5% and 10%) of the 19 organic UV absorbers to be used in the EMCPPTS.

## 4.2 Methods

### 4.2.1 Participants

The 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 (ICH) Good Clinical Practice (GCP).[10] Healthy volunteer subjects were recruited via Drug Development Solutions (subsequently Chiltern Early Phase [Ltd]) based on the Ninewells Hospital campus in Dundee.

Inclusion criteria for subjects were as follows:

- Male or female, aged between 18-70 years
- Able to provide written informed consent and comply with the protocol and study procedures
- Of Fitzpatrick skin type 1-4

Exclusion criteria for subjects were as follows:

- Pregnancy or breastfeeding
- Known systemic disease or current immunosuppressive treatment
- Active skin disease on the back skin test site
- Tattoos on the back skin test site
- Exposure of the skin of the back to natural sunlight or UV radiation within the four weeks prior to testing, or during the testing period
- Application of potent topical steroids on the skin of the back within the five days prior to testing
- A known photodermatosis or history of reacting to a sunscreen

#### 4.2.2 PPT and test agents

The organic UV absorbers were prepared and supplied by Chemotechnique Diagnostics Ltd (Vellinge, Sweden). The 19 test agents and their chemical abstracts service (CAS) numbers are given in Table 4.1.

Test agent (INCI name)	CAS number
Butyl methoxydibenzoylmethane	70356-09-1
Homosalate	8045-71-4
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
Drometrizole trisiloxane	155633-54-8
Octocrylene	6197-30-4
Ethylhexyl salicylate	118-60-5
Ethylhexyl triazone	88122-99-0
Isoamyl- <i>p</i> -methoxycinnamate	71617-10-2
Terephthalylidene dicamphor sulfonic acid	90457-82-2
<i>Bis</i> -ethylhexyloxyphenol methoxyphenyl triazine	187393-00-6
Methylene <i>bis</i> -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

Table 4.1. The 19 organic UV absorbers used in the pilot irritancy study.

Also given are their CAS numbers.

All the test agents were prepared in petrolatum except terephthalylidene dicamphor sulfonic acid. This agent has a low pH, which necessitates the addition of a neutralizing agent to decrease irritation and it was therefore diluted in water. Each agent was prepared at three concentrations: 2%, 5% and 10%. All agents were stored between 4 and 7°C in a refrigerator.

A 5mm bar from a 5mL syringe (approx 20µl) of each agent in petrolatum was applied using a syringe to an 8mm diameter metal chamber (Finn Chamber<sup>®</sup>, Epitest Ltd Oy, Tuusula, Finland) mounted on hypoallergenic adhesive tape (Scanpor<sup>®</sup> tape, Actavis Norway AS, Norgesplaster, Vennessla, Norway). The terephthalylidene dicamphor sulfonic acid and water control were applied to a 7mm diameter filter paper disc (20 µL via a pipette) placed in an 8mm diameter metal chamber. Three controls were used: an empty metal chamber, water on a filter paper in a metal chamber and petrolatum in a metal chamber.

PPT was performed according to the European consensus methodology.[6] The agent photopatches were made up as duplicate sets and then applied to the left and right non-paravertebral skin of the upper back of subjects (0 hours). The layout of photopatch application is given in Figure 4.1. After 48 hours both sets of photopatches were removed and one set (either right or left) was covered with a UV-opaque material whilst the other was irradiated with 5 Jcm<sup>-2</sup> UVA (vertical bank of 10 Waldmann F15W/T8 tubes; peak emission at 352nm; 99.2% UVA and 0.8% UVB). For irradiation, the subject was placed 20cm from the source sitting with their back in a vertical position, parallel to the middle of the source.





Figure 4.1. The layout of photopatch application in the irritancy study.

A study subject at 0 hours is shown, illustrating the distribution of photopatches as duplicates on either side of back, and in upper/middle/lower areas.

### 4.2.3 Study design and statistical methods

Block-randomisation codes were computer-generated for each of the agents and each of the concentrations. Further block randomisation 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, Texas, USA]).

Readings of the test site were made by a blinded clinician pre-irradiation at 48 hours, immediately post-irradiation and at 72, 96 and 120 hours. Any positive reactions were photographed. All reactions were graded at all timepoints using both the ICDRG scale (given in Table 4.2) and an erythema scale (given in Table 4.3).

It was decided that it would be practicable to recruit about 80 subjects. With 81 subjects, there should be 90% power to detect if  $5\% \pm 4\%$  (that is 1% to 9%) of the wider adult Tayside population from whom our volunteers were drawn have IRs to a particular agent.[11]

If any of the agent concentrations were found to cause IRs in  $\geq 5\%$  of study sample subjects (i.e.  $\geq 4$  subjects), it was decided that they would not be suitable for PPT in the EMCPTS.

-	No reaction
?+	Doubtful reaction
+	Weak positive (erythema, infiltration, possibly papules)
++	Strong positive reaction (erythema, infiltration, papules, vesicles)
+++	Extreme positive reaction (intense erythema, infiltration, vesicles may coalesce to form a blister)
IR	Irritant reaction

Table 4.2. The ICDRG 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

Table 4.3. The erythema scale for grading photopatch test reactions.

## **4.3 Results**

### **4.3.1 Analysed population**

There were 94 subjects recruited over the duration of the study. Of these, ten subjects were withdrawn because the patches became detached within the 48 hour 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 at 48 hours. Of the 82, two subjects were excluded from further analysis as they had reactions thought to be spurious in nature. One of these subjects had grade “1” & “?+” reactions to all concentrations of all agents and controls in the covered set 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 set was not accidentally exposed to UVA radiation. The other subject had grade “0.5” & “?+” reactions to the 2% concentration of all agents (but not at the controls) in the irradiated set at 24 hours after irradiation. Therefore, the analysed population comprised 80 subjects. The baseline demographics of the both the recruited subjects and analysed subjects were not substantially different. These are given in Table 4.4.

Characteristic	Recruited subjects		Analysed subjects	
	Number	Percentage (%)	Number	Percentage (%)
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	3.2	2	2.5

Table 4.4. Baseline demographic data of recruited and analysed pilot irritancy study subjects.

#### 4.3.2 Number of reactions by ICDRG scale

Of the 80 subjects included for analysis, 21 were recorded as having a doubtful (“?+”) or weak positive (“+”) reaction at some time point using the ICDRG grading scale. An example of subject who displayed positive reactions in the upper panel of both irradiated and covered sets at 96 hours is given in Figure 4.2. Nine subjects had at least one “+” reaction (a further 4 of these also had at least one “?+” reaction at some timepoint). The remaining 12 subjects had at least one “?+” reaction at some timepoint.

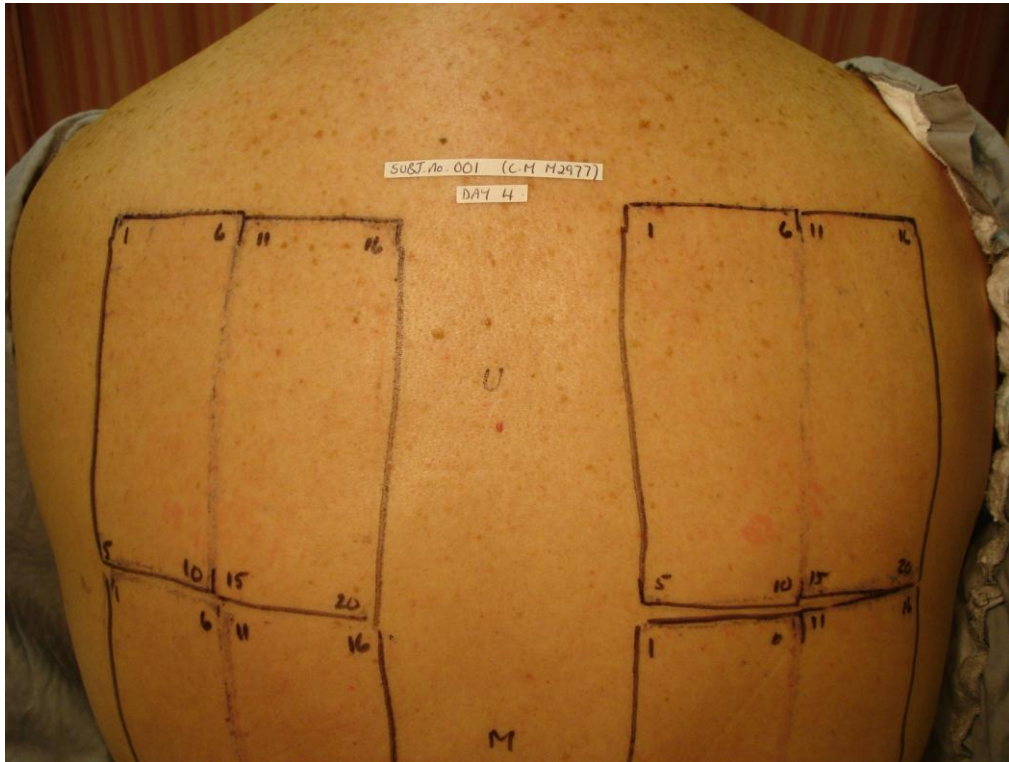


Figure 4.2. Pilot irritancy study positive reactions at 96 hours in a subject.

The positive reactions are visible as discrete circular areas of erythema at the position of agent 10, more noticeable on the right hand side, in the upper panel of both irradiated and covered sets.

With respect to concordance of the ICDRG reactions seen, seven of 21 subjects reacted to an agent or agents in the irradiated set only. The next largest group of subjects were the five who displayed only concordance (i.e. a reaction was seen in both irradiated and covered sets for an agent or agents at a timepoint) followed by four subjects who had both reactions at the irradiated set only plus concordant reactions. Three subjects had discordance of reactions (i.e. reactions were seen in the irradiated set only for one agent and the covered set only for another agent at a timepoint). One subject had concordance plus a covered set reaction only and one had a covered set reaction only to one agent.

#### **4.3.3 Number of reactions by erythema scale**

As regards the erythema scale, 19 subjects were recorded as having at least one reaction at some time point. Of these, 2 subjects had a grade 2 erythema at at least one timepoint (both also had at least one grade 1 erythema at some timepoint). 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 timepoint.

#### **4.3.4 Agreement between ICDRG and erythema scales**

There were 2 subjects who were recorded as having a weak positive reaction using the ICDRG scale, but who had no concomitant erythema score recorded. One of the subjects had a “+” reaction to 10 % benzophenone-4 in the irradiated set at 96 hours and the other subject had a “+” reaction to 5% methylene *bis*-benzotriazolyl tetramethylbutylphenol in the irradiated set at 48 hours (immediately post-irradiation). Apart from these two reactions, all other positive reactions were recorded as being graded by ICDRG and erythema scales.

#### **4.3.5 Number of doubtful and weak positive ICDRG graded reactions by set and time**

The total number of doubtful and weak positive ICDRG graded reactions seen at some time point was 39 in the irradiated set (27 “?+” and 12 “+” reactions) and 28 in the covered set (22 “?+” and 6 “+” reactions). The timing and grade of these reactions are given in Figure 4.3. It can be seen that there was only one reaction recorded prior to irradiation at 48 hours. There are several reactions seen immediately post-irradiation, with the peak occurring at 72 hours, before declining thereafter.

#### **4.3.6 Number of doubtful and weak positive ICDRG graded reactions by UV absorber**

The number of ICDRG reactions (“?+” and “+” combined) recorded for the 19 organic UV absorbers and three controls is given in Figure 4.4. It can be seen that eight UV absorbers did not lead to any reactions at any time points. Of the 11 agents that did cause reactions at some time point, only two absorbers caused reactions in four or more subjects: 5% benzophenone-4 (4 subjects); 10% benzophenone-4 (6 subjects); and 5% methylene *bis*-benzotriazolyl tetramethylbutylphenol (6 subjects). However, only benzophenone-4 exhibited a dose-response pattern, with increasing concentrations leading to increasing numbers of reactions. The peak of reactions observed for 5% methylene *bis*-benzotriazolyl tetramethylbutylphenol could not be explained in this manner, as there were only two reactions seen at the 2% concentration and one reaction seen at the 10% concentration.



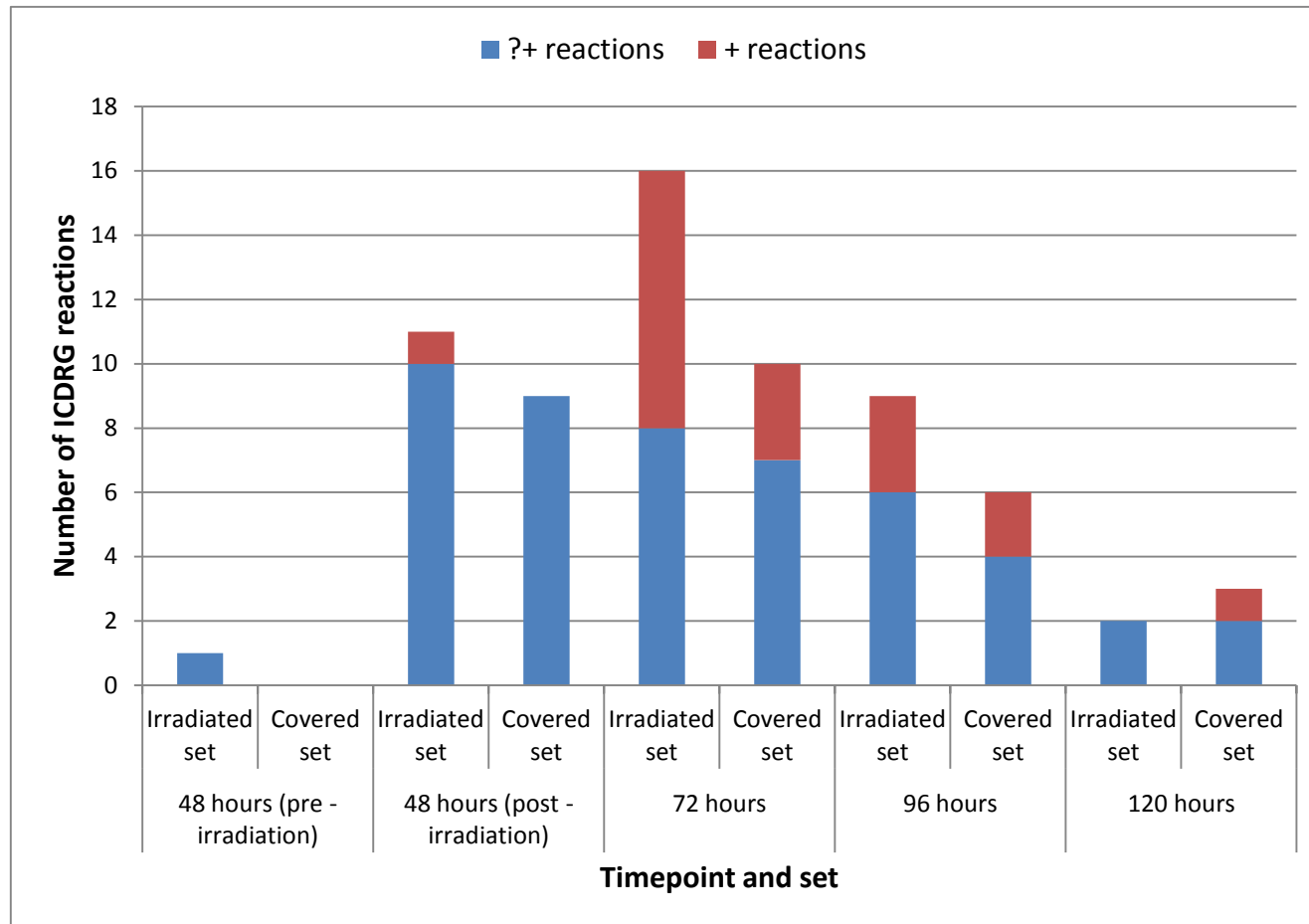


Figure 4.3. The number of doubtful and weak positive ICDRG graded reactions by set and time.

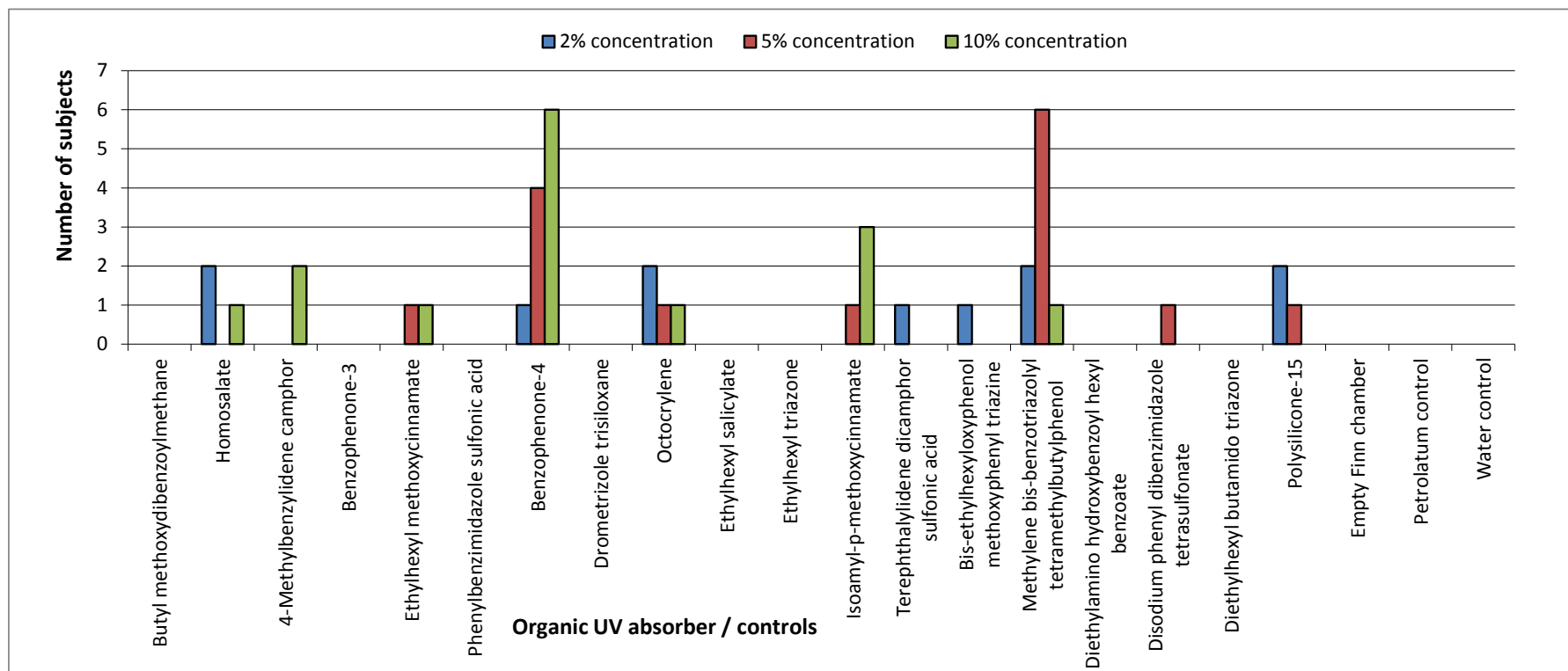


Figure 4.4. The number of subjects with ICDRG reactions graded as doubtful (“?+”) or weakly positive (“+”) to the 19 organic UV absorbers and 3 controls at any timepoint.

#### 4.4 Discussion

The objective of this pilot study was to determine the frequency of IRs to three different concentrations of 19 organic UV absorbers when used to conduct PPT according to the European consensus methodology.[6] It is the first study which has been conducted and reported in the scientific literature which has attempted to determine the maximum non-irritating concentration of organic UV absorbers. Of the 19 agents studied, only benzophenone-4 led to positive reactions in  $\geq 5\%$  of subjects in a dose-dependent manner.

##### 4.4.1 Comparison with previous studies

Due to the use of healthy volunteers and focus on irritancy, direct comparison of the 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 at 48 hours (at patch removal) and positive at 96 hours, supporting a contact allergic mechanism rather than an IR.[12]

In the present study, methylene *bis*-benzotriazolyl tetramethylbutylphenol also led to a number of reactions, most notably at the 5% concentration, but it is not clear why it failed to demonstrate a dose-response pattern. Methylene *bis*-benzotriazolyl tetramethylbutylphenol is the organic UV absorber in the product marketed as Tinosorb M<sup>®</sup> (which was the stable formulation tested in the present study). However, Tinosorb M<sup>®</sup> also contains the surfactant decyl glucoside. One previous report, cited ACD at 48 and 96 hours in a subject who was photopatch tested to 2% methylene *bis*-benzotriazolyl tetramethylbutylphenol.[13] Although the authors tested the same agent in 20 control subjects with negative results, they did not test decyl glucoside alone. More recently, a further report of ACD to Tinosorb M<sup>®</sup> has

emerged in a subject who was then also found to have ACD to decyl glucoside.[14] The results of the present study suggest that positive reactions to Tinosorb M<sup>®</sup> may occur during PPT and the possibility of decyl glucoside contributing to such reactions may need to be considered.

#### **4.4.2 Limitations of the study**

One limitation of the study is the relatively small population tested (80 subjects) which may be important, given that inter-individual variation in the propensity to develop IRs has been previously demonstrated.[15] 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 the study was the use of healthy volunteers who had no active dermatoses, history of photodermatoses or history of reacting to sunscreens. The majority of subjects (59 of 80) had no reactions at all which will be reassuring to sunscreen manufacturers, clinicians and consumers. However, it is likely that in the setting of performing PPT in patients who present to a clinician with a photo-exposed site skin problem, the number of IRs seen may be higher. A previous Swedish study investigated 35 patients who had complained of reactions to commercial sunscreen products. Although three patients did have PACD on PPT, the majority of the reactions were attributed to irritant effects from the sunscreen absorbers and excipients.[16] A longitudinal study in Australia studied the reactions to two UV absorbers (ethylhexyl 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 absorbers. This further highlights the importance of IRs in numerical terms when conducting patch and photopatch testing to UV absorbers and sunscreen excipients.[17]

#### **4.4.3 IRs and PPT**

IRs to sunscreen products have been described for many years.[18] Manufacturers of sunscreens must often combine multiple UV absorbers to increase the spectrum of protection, as well as increasing the SPF. In this process concentrations of absorbers are usually kept below the maximal permissible level.[19] However, this study demonstrates that IRs under PPT 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 PPT to the individual absorbers and excipients in the product. It can be helpful to separate out potential allergens/photoallergens in this way, as inhibitory and augmentary interactions between the constituents can occur. However, for reasons stated previously, such testing can also be misleading if the absorber concentration is too low to elicit a positive ACD or PACD reaction or if it is too high, leading to an IR.

#### **4.4.4 Determining IRs**

One inherent difficulty in conducting this study was attempting to detect true IRs. Therefore, two clinical scales (the ICDRG and erythematous scales) were concomitantly employed to detect any possibly relevant reactions. As stated, the present study was a pilot study for the EMCPTTS in which the ICDRG grading scale alone will be used. The ICDRG scale is based primarily on true allergic reactions causing a papular and/or vesicular response, so it was hypothesised that

the use of both the ICDRG and erythema scales in the present study might increase the sensitivity for detecting possible IRs. The finding that only two reactions graded with the ICDRG scale were not concomitantly graded with the erythema scale suggests that it would be unlikely that many IRs in the EMCPPPTS would be missed by employing the ICDRG scale alone.

Some investigators have employed various bioengineering methods for attempting to quantify IRs.[20] Differences in cytokine profiles between IRs and true allergic responses have been demonstrated but many features that were thought previously unique to the allergic response have also be seen in the IR, meaning that an actual distinction between the two could be argued as conceptual rather than actual.[21,22] As in other studies, the decision as to whether any ICDRG grade “?+” or “+” reactions seen in the EMCPPPTS are designated as IRs will depend upon the experience of the individual clinicians interpreting them.

#### **4.4.5 The effect of UVA irradiation**

When conducting PPT, 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 of ICDRG reactions seen at 72 hours in the irradiated set (which included 8 “+” reactions), which subsequently settled could be consistent with a phototoxic aetiology rather than true PACD. Although it is known that  $10 \text{ Jcm}^{-2}$  UVA leads to more phototoxic reactions than  $5 \text{ Jcm}^{-2}$ , a clinically relevant number of phototoxic reactions could also occur at  $5 \text{ Jcm}^{-2}$ . [23] Another possible aetiology of such responses is the combination of suberythema UVA exposure combined with subclinical irritancy and/or allergy, which has been previously reported to occur.[7] Interestingly, irradiation also appears to be important in determining the number of reactions in the covered set. There were no ICDRG reactions recorded in

this set pre-irradiation, yet nine reactions were seen immediately post-irradiation, peaking at 10 reactions at 72 hours. Although there were more reactions in total seen in the irradiated than the covered set, the pattern of covered set 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.

#### **4.4.6 Implications for the EMCPPPTS**

This pilot study suggests that, with respect to the potential to lead to IRs, all 19 organic UV absorbers could be photopatch tested at a concentration of 10% in the EMCPPPTS, apart from benzophenone-4, which should be tested at a concentration of 2%.

Of note is the fact that of these 19 agents, only 13 can be used at a concentration of 10% in cosmetics products according to Annex VII guidance (see also Appendix 1). These 13 agents will be tested in the EMCPPPTS at a 10% concentration. However, the remaining six agents are only permitted at lower maximum concentrations of between 4% and 8%. Given that few IRs were demonstrated to these agents, five of these six will also be tested at a concentration of 10%. This should have the advantage of increasing the sensitivity of PPT for detecting PACD and ACD reactions to a higher level than if their maximum permitted concentrations were used. These agents are as follows: phenylbenzimidazole sulfonic acid, butyl methoxydibenzoylmethane, ethylhexyl triazone, ethylhexyl salicylate and 4-methylbenzylidene camphor. The remaining agent, benzophenone-4, is permitted at a maximum concentration of 5%, and so the test concentration of 2% to be used in the EMCPPPTS is below its maximum authorized concentration. This does raise the possibility that the resulting decreased sensitivity may lead to some PACD and

ACD reactions being missed. However, on balance, this seems preferable to causing a larger number of IRs among subjects.

The issue of determining the maximum non-irritating concentration for conducting PPT with the 19 organic UV absorbers to be used in the EMCPPTS has been addressed in this pilot study. However, the separate and difficult issue of interpreting the results obtained in the EMCPPTS with respect to possible subject population exposure patterns to organic UV absorbers remains. An attempt to find a surrogate for such exposure patterns is addressed in the following Chapter, which outlines a UK sunscreen survey.



#### 4.5 References

- 1 Wahlberg JE. Patchtesting. In: *Textbook of contact dermatitis* (Rycroft R, Menne T, Frosch P et al., eds), 3<sup>rd</sup> edn. Berlin: Springer-Verlag. 2001; 939-68.
- 2 Dooms-Goossens A, Degreef H. Contact allergy to petrolatums. Sensitizing capacity of different brands of yellow and white petrolatums. *Contact Dermatitis* 1983; **9**: 175-85.
- 3 Beck M, Wilkinson S. Contact Dermatitis: Allergic. In: *Rook's Textbook of Dermatology* (Burns T, Breathnach S, Cox N et al., eds), Seventh edn., Vol. 1. Oxford: Blackwell Science. 2004; 20.99.
- 4 Bjornberg A. "Status eczematicus". In: *Skin reactions to primary irritants in patients with hand eczema. An investigation with matched controls*. Gothenburg: Oscar Isacson's Tryckeri AB. 1968; p117-27.
- 5 Frosch PJ, Kligman AM, Frosch PJ *et al.* The Duhring chamber. An improved technique for epicutaneous testing of irritant and allergic reactions. *Contact Dermatitis* 1979; **5**: 73-81.
- 6 Bruynzeel DP, Ferguson J, Andersen K *et al.* Photopatch testing: a consensus methodology for Europe. *J Eur Acad Dermatol & Venereol* 2004; **18**: 679-82.
- 7 Beattie PE, Traynor NJ, Woods JA *et al.* Can a positive photopatch test be elicited by subclinical irritancy or allergy plus suberythematous UV exposure? *Contact Dermatitis* 2004; **51**: 235-40.
- 8 Anonymous. Photopatch testing-methods and indications. British Photodermatology Group. *Br J Dermatol* 1997; **136**: 371-76.
- 9 European Commission, Enterprise and Industry, Cosmetic Ingredients and Substances. Annex VII - List of permitted UV filters which cosmetic products may contain. Accessed on 16/01/2012 at: [http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.results&annex\\_v1=VII&search](http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.results&annex_v1=VII&search)
- 10 ICH Harmonised Tripartite Guideline. Guideline for Good Clinical Practice E6 (R1). Accessed on 03/02/2012 at: [http://www.ich.org/fileadmin/Public\\_Web\\_Site/ICH\\_Products/Guidelines/Efficacy/E6\\_R1/Step4/E6\\_R1\\_Guideline.pdf](http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1_Guideline.pdf).
- 11 Open Epi - Open Source Statistics for Public Health: Sample size for a proportion or descriptive study (Authors Kevin M. Sullivan, Andrew G. Dean and Roger A. Mir). Accessed on 03/02/2012 at: <http://www.openepi.com/SampleSize/SSPropor.htm>.
- 12 Hughes TM, Stone NM. Benzophenone 4: an emerging allergen in cosmetics and toiletries? *Contact Dermatitis* 2007; **56**: 153-56.

- 13 Gonzalez-Perez R, Trebol I, Garcia-Rio I *et al.* Allergic contact dermatitis from methylene-bis-benzotriazolyl tetramethylbutylphenol (Tinosorb M). *Contact Dermatitis* 2007; **56**: 121.
- 14 Andrade P, Goncalo M, Figueiredo A. Allergic contact dermatitis to decyl glucoside in Tinosorb M. *Contact Dermatitis* 2010; **62**: 119-20.
- 15 Basketter DA, Griffiths HA, Wang XM *et al.* Individual, ethnic and seasonal variability in irritant susceptibility of skin: the implications for a predictive human patch test. *Contact Dermatitis* 1996; **35**: 208-13.
- 16 Fischer T, Bergstrom K. Evaluation of customers' complaints about sunscreen cosmetics sold by the Swedish pharmaceutical company. *Contact Dermatitis* 1991; **25**: 319-22.
- 17 Foley P, Nixon R, Marks R *et al.* The frequency of reactions to sunscreens: results of a longitudinal population-based study on the regular use of sunscreens in Australia. *Br J Dermatol* 1993; **128**: 512-18.
- 18 Adams RM, Maibach HI. A five-year study of cosmetic reactions. *J Am Acad Dermatol* 1985; **13**: 1062-69.
- 19 Rastogi SC. UV filters in sunscreen products - A survey. *Contact Dermatitis* 2002; **46 (6)**: 348-51.
- 20 Agner T, Serup J. Skin reactions to irritants assessed by non-invasive bioengineering methods. *Contact Dermatitis* 1989; **20**: 352-59.
- 21 Gerberick GF, Rheins LA, Ryan CA *et al.* Increases in human epidermal DR+CD1+, DR+CD1-CD36+, and DR-CD3+ cells in allergic versus irritant patch test responses. *J Invest Dermatol* 1994; **103**: 524-29.
- 22 Rietschel RL. Mechanisms in irritant contact dermatitis. *Clinics in Dermatol* 1997; **15**: 557-59.
- 23 Berne B, Ros AM. 7 years experience of photopatch testing with sunscreen allergens in Sweden. *Contact Dermatitis* 1998; **38**: 61-64.