

University of Dundee

DOCTOR OF MEDICINE

Photoallergic contact dermatitis in Europe

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DOCTOR OF MEDICINE

# Photoallergic contact dermatitis in Europe

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2012

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### **3. Chlorproethazine: A second photoallergen on the marketplace**

Following investigation of the veterinary NSAID carprofen in the Photobiology Unit in Dundee, there was a heightened awareness that current European regulatory mechanisms were not preventing all potential photoallergens from reaching the marketplace. Because of this awareness, there was a lowering of the threshold for investigating other existing agents of suspicion. This Chapter outlines the investigation of the phenothiazine chlorproethazine by means of human PPT and *in vitro* phototoxic studies.

#### **3.1 Introduction**

##### **3.1.1 Background**

In 2005, preliminary planning for the EMCPPTS was underway and potential collaborators across Europe had been contacted. During discussions regarding the possible composition of the test series to be used in the EMCPPTS, a potential collaborator working in France personally communicated to us that she had observed many sunlight-related adverse cutaneous reactions to an over-the-counter cream called Neuriplège<sup>®</sup>. As such, she queried the possibility of including this agent as part of the test series for the upcoming EMCPPTS.

##### **3.1.2 Neuriplège<sup>®</sup> cream**

Neuriplège<sup>®</sup> cream was available in France between 1963 and 2007 as a non-prescription medication which could be obtained over-the-counter. A tube of Neuriplège and its packaging is given in Figure 3.1.



Figure 3.1. A tube of Neuriplège cream.

This was donated by Dr Marie-Claude Marguery (Toulouse, France) and was used for further investigation.

The active ingredient of Neuriplège<sup>®</sup> was chlorproethazine (CPE), a derivative of the phenothiazine chlorpromazine (CPZ) and the structural similarity of the two molecules can be seen in Figure 3.2.

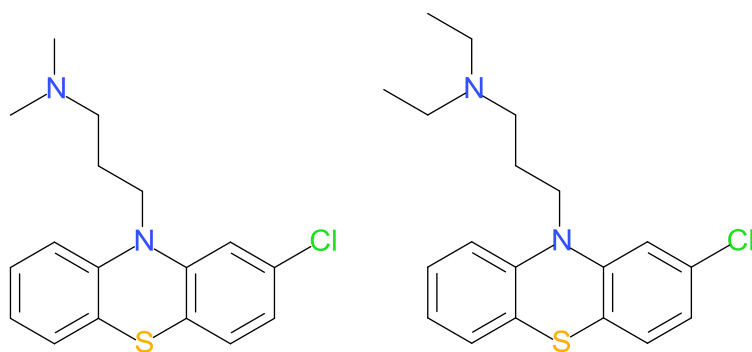


Figure 3.2. The molecular structure of chlorpromazine (left) and chlorproethazine (right).

Other ingredients included glycerin, aluminium stearate, lactic acid, benzyl alcohol and Balsam of Peru. It was marketed as an analgesic and muscle relaxant, on the basis that CPE was thought to interfere with the transmission of certain neurotransmitters.

The immediate phototoxic as well as delayed photoallergic properties of the related phenothiazines CPZ and promethazine have been previously demonstrated in photopatch test series.[1,2] A more detailed computer analysis of photopatch test reactions to 32 substances also highlighted CPZ and promethazine as causing “plateau” pattern reactions, thought to represent more prolonged phototoxic responses.[2] Neuriplège<sup>®</sup> cream itself and CPE have also been reported as causing ACD, PACD and phototoxic-like reactions. [3-5]

### 3.1.3 Objective

In 2005, because uncertainty existed as to the type of reaction pattern that CPE might lead to, were it to be included in the EMCPTS, the objective of this study was to investigate this agent further. This was performed by:

- 1) An assessment of photostability
- 2) An *in vitro* phototoxic study
- 3) A pilot PPT study of Neuriplège<sup>®</sup> cream
- 4) An extended PPT study of Neuriplège<sup>®</sup> cream and CPE

## **3.2 Materials and Methods**

### **3.2.1 Assessment of photostability**

A solution of CPE (10 µg/ml) in distilled water was prepared. Solutions in stirred quartz cuvettes were irradiated by a bank of two glass filtered Cosmedico 15500 100W tubes (emission spectrum centered around 365nm, Hospital Lamp Supplies, Leicester, UK). The irradiance of the filtered source was monitored with a UV meter (Waldmann, Schwenningen, Germany) calibrated to the source using a double-grating spectroradiometer (Bentham Instruments Ltd, Reading, UK) and adjusted to 1.77 mWcm<sup>-2</sup>. Sham-irradiated samples were covered with tinfoil. Absorbance measurements were made using a Hitachi model U-3010 spectrophotometer with baseline adjusted for distilled water between 190-900 nm.

### **3.2.2 Phototoxic *in vitro* studies**

Phototoxicity was assessed using a neutral red uptake assay, according to the Organisation for Economic Co-operation and Development (OECD) test guideline 432.[6] Cell culture chemicals were supplied by Sigma-Aldrich Co. Ltd (Dorset, UK) and sterile plastics were supplied by Greiner (Cambridge, UK). Firstly, HaCaT keratinocytes (donated by Professor Norbert Fusenig, DKFZ, Heidelberg, Germany) were seeded at a density of 2 x 10<sup>5</sup> cells/ml in Dulbecco's Modified Eagles Medium containing 5% foetal bovine serum and 1% non-essential amino acids. After an overnight incubation at 37°C/5% CO<sub>2</sub>, the growth media was removed and the cells were washed with phosphate buffered salt solution before being exposed to CPE freshly prepared in Earle's balanced salt solution (EBSS). The maximum administered dose of CPE was 100 µg/ml in the non-irradiated sample and 5 µg/ml in the irradiated sample (with a dilution factor of √2).

The cells were incubated with the test compound for one hour then irradiated with 5 Jcm<sup>-2</sup> UVA, or not, using the same source used in the assessment of photostability. After irradiation, the EBSS was removed and replaced with drug-free complete media. The cells were returned to the incubator for 24 hours. After this time, viable cells were identified using a neutral red dye uptake method as previously described.[7] The concentration of drug required to reduce dye uptake by 50% (IC<sub>50</sub> value) was determined by non-linear regression (Graphpad Prism), and a phototoxic index (PI) was obtained.[8] Due to its known photoactive properties, CPZ dissolved in dimethyl sulfoxide, was used as the positive control.

### **3.2.3 Pilot PPT study**

The pilot PPT study was performed in two healthy volunteer subjects who had no history of exposure to Neuriplège<sup>®</sup> cream. Photopatches were applied to the skin of the inner forearm, rather than the conventional site of the upper mid back, but PPT was otherwise performed according to the European consensus methodology.[9] Approximately 20µl of Neuriplège<sup>®</sup> cream “as is” and a petrolatum control were applied 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). Duplicate sets were applied to the skin of the inner forearm for 24 hours. After 24 hours, both sets of patches were removed and one set 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 placed their forearm 20cm from the source, parallel to the middle of the source.



Readings of both sets were made pre-irradiation, immediately post-irradiation and 24 and 48 hours post-irradiation. Reactions were graded using a modified ICDRG scale as follows: no response (-), doubtful reaction (?+), weak (non-vesicular) reaction (+), strong (oedematous or vesicular) reaction (++), extreme reaction (+++), brown pigmentation (B), irritant reaction (IR) and no reading performed (NR).

### **3.2.4 Extended PPT study**

The Neuriplège<sup>®</sup> cream used in the pilot study was donated by the French collaborating dermatologist, but it was a further year until pure CPE was obtained and the extended PPT study was performed. For the extended PPT study, seven healthy volunteer subjects (6 males, 1 female; Fitzpatrick skin types I-IV) with no past history of photosensitivity or exposure to Neuriplège<sup>®</sup> cream were recruited, in addition to the two subjects who had previously been tested in the pilot study. The set of test agents and vehicles used were as follows:

- Neuriplège<sup>®</sup> cream “as is”
- 0.1% CPE in petrolatum
- 10% CPE in petrolatum
- 0.1% CPE in water
- 0.5% CPE in water
- petrolatum control
- water control

As with the pilot PPT study, approximately 20µl of each agent in petrolatum was applied to an 8mm diameter metal chamber mounted on hypoallergenic adhesive tape. For the agents in water, these were applied to a 7mm diameter filter paper disc (20 µL via a pipette) placed in an 8mm diameter metal chamber. Duplicate sets of

test agents were made up and applied vertically adjacent to each other on non-paravertebral skin of the back for 24 hours. After 24 hours, both sets were removed and one set (allocated at random by a non-blinded technician) was covered with a UV-opaque material whilst the other was irradiated with  $5 \text{ Jcm}^{-2}$  UVA with the same source used in the pilot PPT study. Readings were made at the same timepoints as in the pilot PPT study (plus some additional later times if strong reactions were seen) and graded using the same modified ICDRG scale.

Interestingly, in the extended PPT study, subject 2 experienced an uncomfortable “stinging” sensation during the process of irradiation with  $5 \text{ Jcm}^{-2}$  UVA, followed by a generalised erythematous flare in the irradiated set. Because the test site became unreadable, testing was abandoned and repeated one week later on a different area of the back using a reduced dose of  $2.5 \text{ Jcm}^{-2}$  UVA.

### 3.3 Results

#### 3.3.1 Assessment of photostability

An aqueous solution of CPE absorbed mainly in the UVB portion of the electromagnetic spectrum, with peaks of absorption extending into the UVA region. There was very little absorption of visible light. After irradiation with  $5 \text{ Jcm}^{-2}$  UVA there was a decrease in UVB absorption and a small increase in absorption at wavelengths longer than 400 nm, which confirms its photoinstability following such irradiation. In the dark at room temperature, CPE appeared to be spectrophotomerically stable for up to 44 hours (the last timepoint measured). The absorption spectrum of CPE in the dark and post-irradiation with  $5 \text{ Jcm}^{-2}$  is given in Figure 3.3.

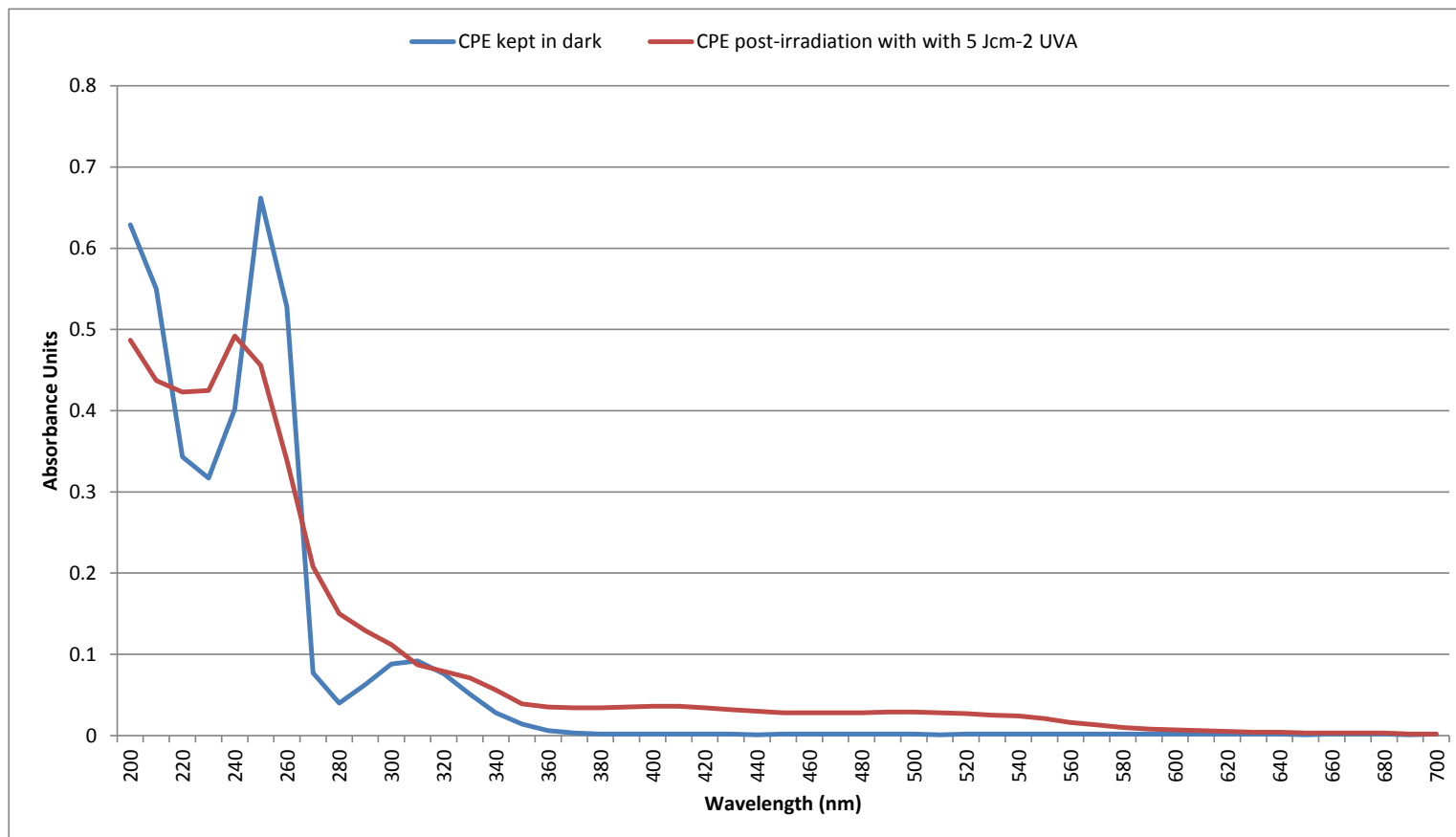


Figure 3.3. Absorption spectrum of CPE in the dark and post-irradiation with 5 Jcm<sup>-2</sup>.

### 3.3.2 Phototoxic *in vitro* studies

A one hour incubation with CPE was approximately 13-fold (PI = 12.7) more toxic to HaCaT keratinocytes in the presence of 5 Jcm<sup>-2</sup> filtered UVA light compared with incubation with the drug alone, as given in Table 3.1.

Compound		IC <sub>50</sub> (µg/ml)	95% Confidence Interval
CPE	+ UVA	0.9	0.8 - 1.0
	- UVA	11.9	11.3 - 12.6
CPZ	+UVA	0.3	0.1 - 0.5
	- UVA	22.9	11.5 - 46.1

Table 3.1. Results of the *in vitro* neutral red uptake phototoxicity assay.

This gives IC<sub>50</sub> values for HaCaT keratinocytes incubated with CPE and CPZ with and without UVA irradiation.

### 3.3.3 Pilot PPT study

In the pilot PPT study, subject 1 had negative reactions to both Neuriplège<sup>®</sup> cream “as is” and petrolatum in both the irradiated and covered sets at all timepoints. However, subject 2 had a “+” reaction to Neuriplège<sup>®</sup> cream “as is” at 24 and 48 hours post-irradiation in the covered set and “++” reactions at the same time points in the irradiated set. The reactions seen at 24 hours post-irradiation are given in Figure 3.4. These reactions had persisted at 96 hours post-irradiation and this “plateau” pattern was considered to be consistent with a prolonged phototoxic response.

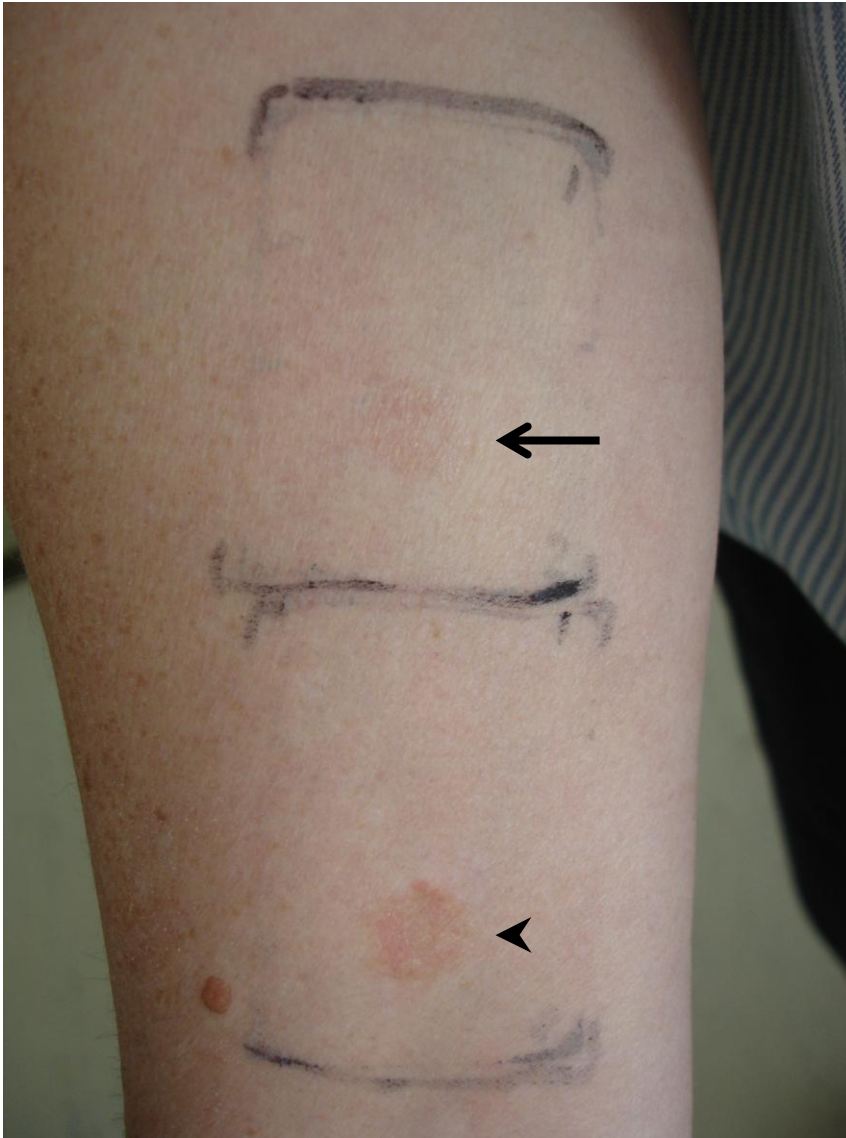


Figure 3.4. Neuriplège<sup>®</sup> pilot PPT readings at 24 hours post-irradiation in subject 2. A dose of 5 Jcm<sup>-2</sup> UVA has been used. The ICDRG grade “+” reaction to Neuriplège<sup>®</sup> cream “as is” can be seen in the covered set (arrow) and a “++” grade reaction to Neuriplège<sup>®</sup> cream “as is” can be seen in the irradiated set (arrowhead).

### 3.3.4 Extended PPT study

In the extended PPT study no positive reactions to any agent in either set were recorded after removal of the photopatches (at 24 hours) but before irradiation of the irradiated set. No positive reactions were seen in the petrolatum or water controls in either irradiated or covered sets of any subjects at any timepoint. The only agent leading to reactions in the covered set was Neuriplège<sup>®</sup> cream “as is,” which led to reactions graded “?IR,” “++” and “?+” in subjects 2, 7 and 8 respectively at 48 hours post-irradiation.

The strongest reactions in the irradiated set were seen with Neuriplège<sup>®</sup> cream “as is” and 10% CPE in petrolatum, which are summarised in Table 3.2. It can be seen from this table that the strongest reaction was seen in subject 2 (the second pilot study patient) who developed a “+++” grade “crescendo” pattern reaction to the Neuriplège<sup>®</sup> cream “as is” at 48 hours post-irradiation, which was evolving by 24 hours and persisted to 9 days. This was despite a reduced dose of 2.5 Jcm<sup>-2</sup> UVA being used for irradiation. This reaction was significantly stronger and of a different morphology than the prolonged “plateau” phototoxic reaction observed in this subject in the pilot study one year earlier. The reaction was consistent with a photoallergic response, as were the non-extreme “++” vesicular reactions seen to all dilutions of CPE in both vehicles. The reactions seen in the irradiated set at 48 hours post-irradiation are given in Figure 3.5.

In subject 1 (who had not developed any reactions in the pilot study), a “++” grade reaction to Neuriplège<sup>®</sup> cream “as is” had developed by 48 hours post-irradiation, which persisted to 5 days post-irradiation. The reactions seen at 48 hours post-irradiation are given in Figure 3.6. As with subject 2, the morphology was consistent with a photoallergic response.

Subject	Immediately post-irradiation				24 hours post-irradiation				48 hours post-irradiation				Further readings (days post-irradiation)			
	Neuriplège <sup>®</sup>		10% CPE in petrolatum		Neuriplège <sup>®</sup>		10% CPE in petrolatum		Neuriplège <sup>®</sup>		10% CPE in petrolatum		Neuriplège <sup>®</sup>		10% CPE in petrolatum	
	C	I	C	I	C	I	C	I	C	I	C	I	C	I	C	I
1 *	-	+	-	-	-	+	-	-	-	++	-	-	- (5 days)	++ (5 days)	- (5 days)	?+B (5 days)
2 * ¶	-	+B	-	+	-	+++	-	++	?IR	+++	-	++	- (9 days)	+++ (9 days)	- (9 days)	++ (9 days)
3	-	-	-	-	-	-	-	-	-	++	-	?+	- (7 days)	+ (7 days)	- (7 days)	- (7 days)
4	-	-	-	+	-	-	-	+	-	-	-	+	NR	NR	NR	NR
5	-	?+	-	+	-	+	-	+	-	++	-	+	- (5 days)	++ (5 days)	- (5 days)	++ (5 days)
6	-	+	-	-	-	++	-	+	-	++	-	+	NR	NR	NR	NR
7	-	+	-	+	-	++	-	+	++	++	-	+	- (6 days)	+ (6 days)	- (6 days)	+ (6 days)
8	-	++B	-	++	-	?+	-	?+	?+	+	-	+	- (3 days)	++ (3 days)	- (3 days)	IR (3 days)
9	-	-	-	+	-	-	-	+	-	-	-	?+	NR	NR	NR	NR

Table 3.2. Extended study results of PPT to Neuriplège<sup>®</sup> cream “as is” and 10% CPE in petrolatum.

(C = Covered set; I = Irradiated set)

(\* Subjects 1 and 2 were enrolled in the pilot study, where they developed phototoxic reactions to Neuriplège<sup>®</sup> cream “as is”)

(¶ Subject 2 received a reduced UVA irradiation dose of 2.5 Jcm<sup>-2</sup>)



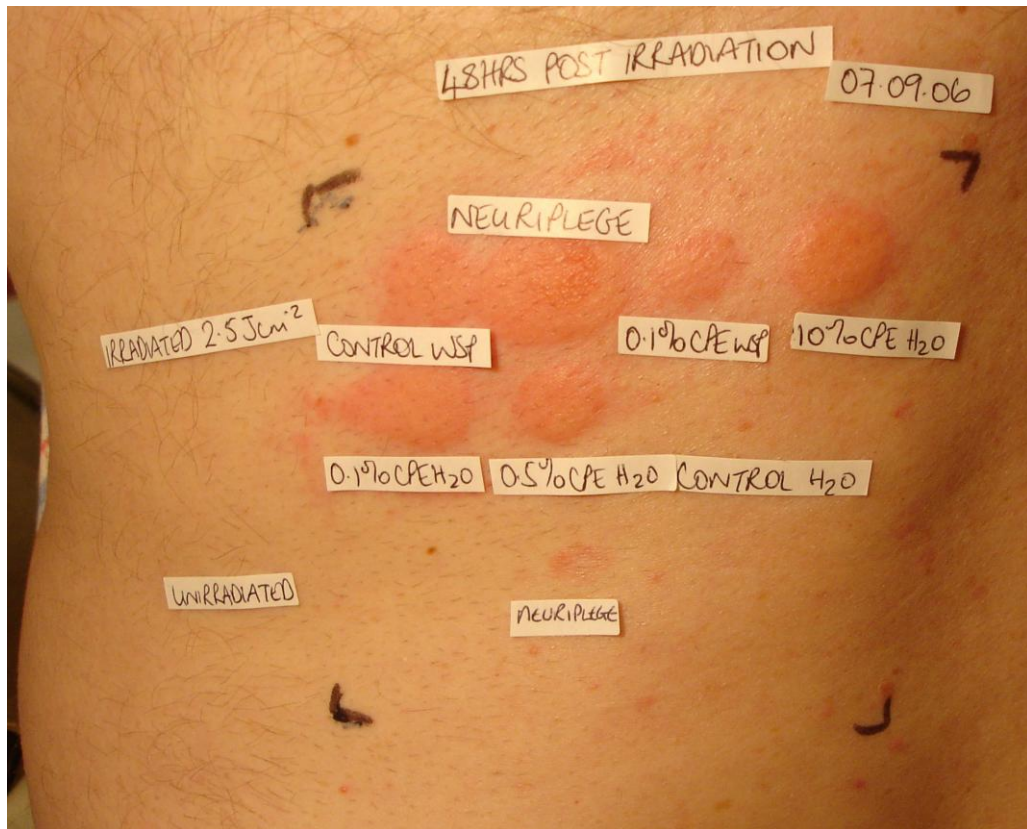


Figure 3.5. Extended PPT readings at 48 hours post-irradiation in subject 2.

A dose of  $2.5 \text{ Jcm}^{-2}$  UVA has been used. Several oedematous, vesicular “crescendo” morphology reactions, consistent with PACD to Neuriplège<sup>®</sup> cream “as is” and the different dilutions/vehicles of CPE can be seen in the irradiated set. (The reaction visible at the petrolatum [WSP] position in the irradiated set was thought to be due to contamination from the adjacent Neuriplège<sup>®</sup> cream “as is” chamber occurring during the 24 hours of photopatch application.)

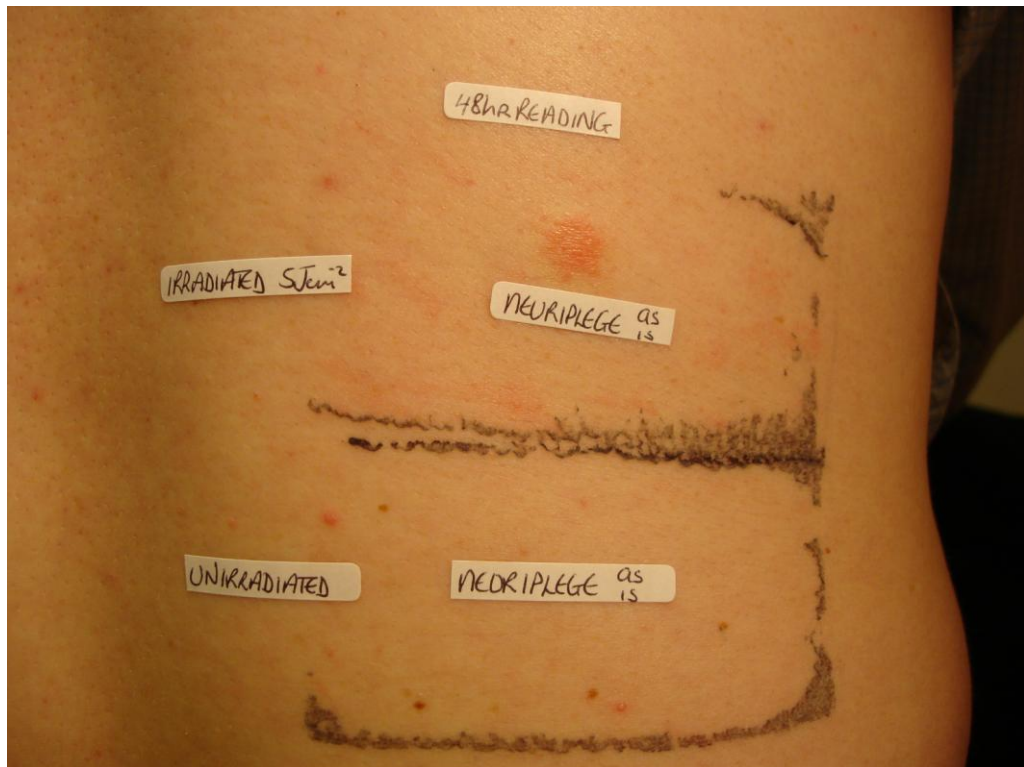


Figure 3.6. Extended PPT readings at 48 hours post-irradiation in subject 1.

A dose of  $5 \text{ Jcm}^{-2}$  UVA has been used. The ICDRG grade “++” reaction with a photoallergic morphology can be seen to Neuriplège<sup>®</sup> cream “as is” in the irradiated (upper) set.

It can be seen from Table 3.2 that five of the seven subjects (subjects 3, 5, 6, 7 & 8) not previously exposed to Neuriplège<sup>®</sup> cream “as is” had reactions of grade “+” or “++” at 48 hours post-irradiation. The morphology of these reactions was the same as the phototoxic response seen on the arm of subject 2 in the pilot study, with uniform erythema confined to the area underlying the metal chamber. The reactions seen at 48 hours post-irradiation in subject 7 are given in Figure 3.7.

Again, later readings showed these reactions were prolonged in a “plateau” phototoxic pattern in two subjects (subjects 5 & 8). Similar prolonged reactions were seen in a further two subjects (subjects 3 & 7), but due to later readings at 7 and 6 days respectively, it was the resolving phase of these which was recorded.

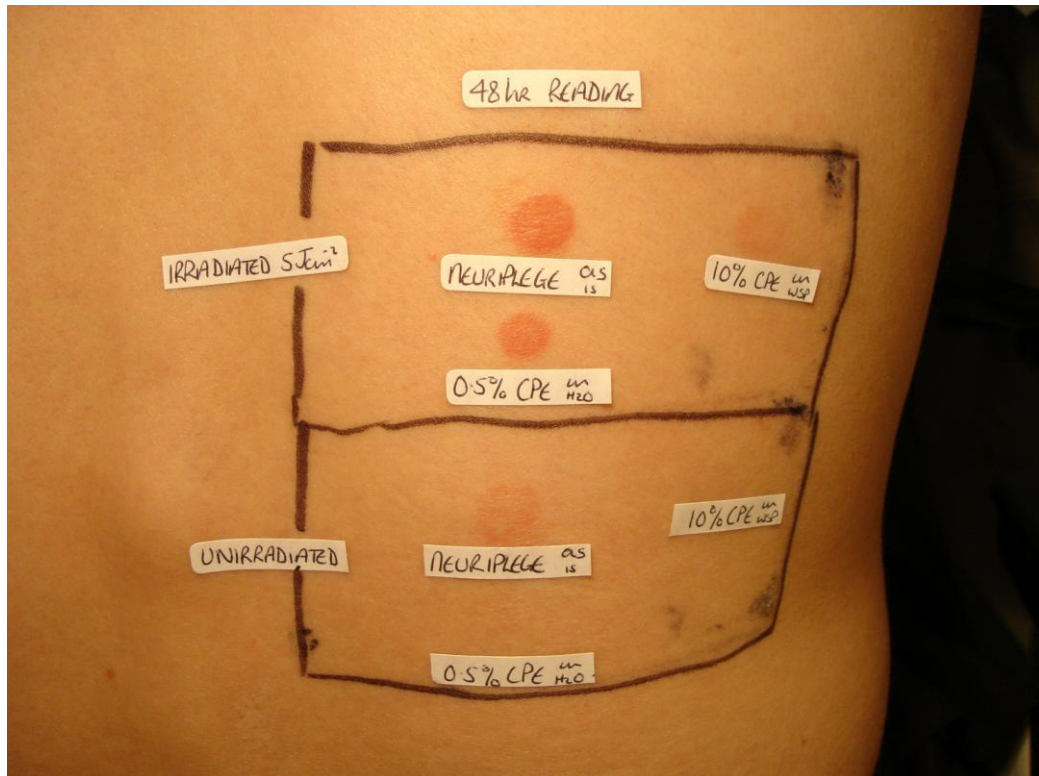


Figure 3.7. Extended PPT readings at 48 hours post-irradiation in subject 7.

A dose of  $5 \text{ Jcm}^{-2}$  UVA has been used. Flat, uniform erythema limited to the area under the test chamber consistent with a phototoxic response to Neuriplège<sup>®</sup> cream “as is” and 0.5% CPE in water can be seen in the irradiated (upper) set.

It can be seen from Table 3.2 that the reactions seen with 10% CPE in petrolatum were similar but usually less pronounced than those to Neuriplège<sup>®</sup> cream “as is.” Exceptions to this trend were seen in subjects 4 & 9, who developed “+” and “?+” reactions respectively at 48 hours post-irradiation to 10% CPE in petrolatum but no reactions to Neuriplège<sup>®</sup> cream “as is.” One possible explanation is that there was inhibition of the UVA-induced phototoxic response by one or more of the other Neuriplège<sup>®</sup> cream excipients.

The reactions recorded to CPE tested at other concentrations and in other vehicles (0.1% CPE in petrolatum, 0.1% CPE in water and 0.5% CPE in water) *in the irradiated set only* are given in Table 3.3. In general, less positive reactions are seen with 0.1% CPE in petrolatum and water than with 0.5% CPE in water across all timepoints. The larger number of positive reactions observed with the 0.5% CPE concentration were more concordant with the positive reactions produced by Neuriplège<sup>®</sup> cream “as is” and the 10% CPE in petrolatum.

In subject 5, the “++” grade reactions seen at 5 days post-irradiation in the irradiated set to both Neuriplège<sup>®</sup> cream “as is” and 10% CPE in petrolatum apparently persisted until 16 days post-irradiation (there were no readings performed between 5 and 16 days post-irradiation). However, this subject had also developed a “++” grade reaction to Neuriplège<sup>®</sup> cream “as is” and a “+” grade reaction to 10% CPE in petrolatum in the covered set. This was thought to represent an active ACD sensitisation event, which had appeared in the 11 days between readings. Because of this phenomenon coupled with the severe PACD responses seen in subject 2, it was decided to discontinue testing any further subjects in the extended PPT study to limit further sensitisation events.

Subject	Immediately post-irradiation			24 hours post-irradiation			48 hours post-irradiation			Further readings (days post-irradiation)		
	0.1% CPE in petrolatum	0.1% CPE in water	0.5% CPE in water	0.1% CPE in petrolatum	0.1% CPE in water	0.5% CPE in water	0.1% CPE in petrolatum	0.1% CPE in water	0.5% CPE in water	0.1% CPE in petrolatum	0.1% CPE in water	0.5% CPE in water
1 *	-	-	-	-	-	-	-	-	-	- (5 days)	- (5 days)	- (5 days)
2 * ¶	-	-	-	?+	+	+	++	++	++	NR	NR	NR
3	-	-	-	-	-	+	-	?+	+	- (7 days)	- (7 days)	+(7 days)
4	-	-	+	-	-	+	-	-	+	NR	NR	NR
5	-	-	-	-	-	-	-	-	-	- (5 days)	- (5 days)	- (5 days)
6	-	-	+	-	-	+	-	-	+	NR	NR	NR
7	-	-	+	-	-	++	-	-	++	- (6 days)	- (6 days)	+(6 days)
8	-	++	++B	-	++	++	-	++	++	- (3 days)	+(3 days)	++(3 days)
9	-	+	-	-	+	-	-	+	-	NR	NR	NR

Table 3.3. Extended study results for PPT to 0.1% CPE in pet, 0.1% CPE in water and 0.5% CPE in water from the irradiated sets only.

(all corresponding covered set reactions were negative)

(\* Subjects 1 and 2 were enrolled in the pilot study, where they developed phototoxic reactions to Neuriplège® cream “as is”)

(¶ Subject 2 received a reduced UVA irradiation dose of 2.5 Jcm<sup>-2</sup>)

### 3.4 Discussion

The photobiological investigations of CPE found in Neuriplège<sup>®</sup> cream demonstrate that it can elicit both topical phototoxic and photoallergic reactions in healthy volunteers. This is not an unexpected finding, given that the closely related phenothiazine CPZ is also known to possess both phototoxic and photoallergic properties. The phototoxic properties of CPE in the presence of UVA radiation were demonstrated *in vitro* using cultured keratinocytes. Its photoinstability after UVA irradiation, seen spectrophotomerically, may be one mechanism leading to such phototoxicity. In healthy human volunteers, the pilot PPT study confirmed the topical phototoxic potential of CPE *in vivo* which was emphasised in five further naïve subjects in the extended PPT study. The prolonged “plateau” pattern of phototoxic reactions seen was consistent with previously reported PPT studies which included the related phenothiazines CPZ and promethazine in their test series.[2]

The photoallergic potential of Neuriplège cream was confirmed when the two subjects from the pilot PPT were re-exposed one year later in the extended PPT study. The extreme “+++” grade reaction seen in subject 2 suggests that CPE may be a potent photoallergen. The allergenic potential of CPE was further highlighted by the apparent active sensitisation of subject 5, evident in the covered set 17 days after agent application. At this stage, after nine subjects had been recruited, it was decided to discontinue the extended PPT study to limit the possibility of sensitising further individuals.

The extended PPT study also provided some additional information about the possible optimum dose of UVA to use for irradiation when performing PPT with CPE. Although the European consensus PPT methodology advises 5 Jcm<sup>-2</sup> UVA is

appropriate for the irradiation of most agents in most individuals, the use of 2.5 Jcm<sup>-2</sup> in subject 2 confirms that a flexible and pragmatic approach to altering the dose when required can minimise uncomfortable adverse events.[9] The smaller dose was sufficient to elicit PACD and it seems likely that, in keeping with previous observations of CPZ, those already sensitised to CPE may require a dose of UVA which is sufficient to elicit PACD, yet not so high as to lead to phototoxicity.[10] The study also suggests that, putting the other variable of concentration aside, topical phototoxic responses to CPE can be produced with a dose of 5 Jcm<sup>-2</sup> UVA. However, the small numbers of subjects tested mean it is not possible to determine the optimum dose of UVA that should be used and further work in this area would be required to resolve this.

As well as determining the optimum UVA dose to use when PPT with CPE, the task of determining the optimum vehicle and concentration of CPE to use remains. It is always advisable to test a patient's own agents "as is," but sometimes this can lead to severe reactions. The results of the extended PPT study suggest that performing PPT with a 0.1% concentration of CPE (in either petrolatum or water) may not be adequate to detect clinically relevant reactions to Neuriplège<sup>®</sup> cream and/or CPE. Indeed, as with many other photoallergens, further PPT in larger numbers of healthy volunteers over time would be required to determine the optimum concentration and vehicle. The results from this study could serve as a starting point for further investigation, given that other data for this agent in the literature is sparse. However, a decision to proceed with any such future study would have to be carefully considered given the potential for sensitising subjects and seems unlikely given its current marketing status, discussed below.



In comparison to 10% CPE in petrolatum, Neuriplège<sup>®</sup> cream “as is” produced both stronger phototoxic and PACD responses, in a roughly consistent fashion. However, the inconsistency that can be observed when conducting PPT was also highlighted by some reactions. For example, two of the seven naïve individuals tested in the extended PPT study (subjects 7 & 8), developed “++” and “?+” grade reactions at 48 hours post-irradiation to the Neuriplège<sup>®</sup> cream “as is” in the covered set. Such covered set reactions were not seen in the other five naïve subjects. Similarly, subject 9 developed positive responses to 0.1% CPE in water and 10% CPE in petrolatum, but negative responses to all other dilutions. Clinicians performing PPT need to bear in mind that it is not always a precise science and experience in assessing observed reactions is of utmost importance.

Neuriplège<sup>®</sup> cream had been available on the marketplace for many years before the 2002 European guideline on photosafety testing of pharmaceutical products outlined in Chapter 1 was adopted. The guidance states that “Photoallergy testing should be performed according to the state of the art.” This study, and the study of carprofen in Chapter 2, can be used as persuasive evidence that PPT in humans is a “state of the art” method for detecting other potential photoallergens in future. Although PPT in humans could potentially sensitise test subjects, which some may consider unethical, it seems likely this would be preferable to the current state of testing, which can allow the sensitisation of many more people by the release of a potent sensitiser onto the market.

Authorisation to market Neuriplège<sup>®</sup> cream was withdrawn by the French regulatory body (agence française de sécurité sanitaire des produits de santé [afssaps]) in February 2007.[11] This followed two national pharmacovigilance surveys which highlighted serious photosensitivity and contact dermatitis cutaneous

reactions. The results of this study provide supportive evidence that CPE is a potent phototoxin and photoallergen and the decision to remove it from the French marketplace was correct. As regards its inclusion in the set of test agents for the EMCPPPTS, this was not deemed appropriate. This was because it had been withdrawn from the marketplace in France and also because of its ability to cause phototoxic responses when performing PPT which could be incorrectly interpreted as photoallergic responses. It has therefore joined the long list of agents discussed in Chapter 1 which are now largely of historical interest and relevance. Although it was not deemed appropriate to include it in either of the two European PPT series (see Chapter 8), the methodology described in this Chapter could be used to investigate any sporadic cases of suspected CPE photoallergy that arise.

The initial investigation of CPE was prompted by the question of its inclusion in the EMCPPPTS series. Although this was not found to be appropriate, other preparatory work was still required prior to the start of subject recruitment for the EMCPPPTS. In particular, the issue of determining the maximum non-irritating concentration for PPT of the 19 organic UV absorbers had to be addressed. This pilot study is detailed in the following Chapter.

### 3.5 References

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