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DOCTOR OF MEDICINE

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Kerr, Alastair

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# Photoallergic contact dermatitis in Europe

Alastair Kerr

2012

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## **1. Introduction**

This introductory Chapter begins with a description of the process and clinical relevance of photoallergic contact dermatitis. There then follows a review of photoallergens of historical note and the concepts of persistent light reaction and systemic photoallergy. The middle part of the Chapter details photopatch testing, as well as the diverse methodologies which have been used for conducting this investigation and attempts to standardise these. The final part of the Chapter reviews the two largest groups of current photoallergens, organic UV absorbers and topical nonsteroidal anti-inflammatory drugs, along with relevant regulatory aspects in Europe.

### **1.1 Photoallergic contact dermatitis and historical aspects**

#### **1.1.1 Definition**

Photoallergic contact dermatitis (PACD) describes the delayed, type IV hypersensitivity reaction seen when an exogenous agent (the photoallergen) comes into contact with the skin in the presence of ultraviolet (UV) and/or visible light. In PACD, the photoallergen can only reach the skin via the topical route, and not by systemic means. PACD therefore presents clinically as a dermatitis which preferentially affects photo-exposed sites. Due to its immune aetiology, even exposure to small quantities of a photoallergen to which a patient is sensitised can lead to a florid dermatitis.

### 1.1.2 Differential diagnosis

PACD can closely resemble other pathological processes within the skin and differentiation on the basis of clinical appearance alone is not always possible. The differential diagnosis of PACD includes the following conditions:

- *Allergic contact dermatitis* (ACD) – Certain contact allergens, such as fragrances or sunscreens can cause dermatitis with a predominantly photo-exposed site distribution. Airborne contact allergens (e.g. powders, aerosolised particles and plant pollens) in particular may be implicated. The crucial difference between ACD and PACD is that true PACD reactions require the presence of UV and/or visible light for elicitation. Therefore, in PACD there may be greater involvement of photo-exposed sites with relative sparing of shadow sites such as within the scalp, beneath the chin and nose, behind the ears and on the upper eyelids.
- *Drug induced phototoxicity* – Whether this is due to systemic exposure to a drug or topical exposure to a drug or chemical, it can resemble PACD.[1] Phototoxicity is more common than PACD and in its “classical” form presents as a sunburn-like confluent erythema or lichenoid eruption. However, perhaps confusingly it can also have a dermatitic appearance. Phototoxicity is due to a direct, non-immune mechanism. Therefore, it will arise in any individual providing there is enough of the agent within the skin and sufficient subsequent UV and/or visible light radiation exposure of the appropriate wavelength. The clinical history is of key importance to determine the temporal relationship between commencing a potentially phototoxic medication and the onset of the eruption. Although in many cases this may be weeks, it can also be many months or years.

- *Chronic actinic dermatitis (CAD)* - This is a syndrome incorporating objective photosensitivity in the absence of exogenous agents, often with multiple contact allergies. It may arise on a background of chronic dermatitis (atopic or ACD) and can present as either a photo-exposed site dermatitis or may be entered into via an ACD presentation. In contrast to PACD, monochromator or solar simulator phototesting in CAD patients will show objective evidence of photosensitivity. Although PPT in CAD patients is not always positive, they often do have a tendency to develop PACD and ACD to agents such as sunscreen absorbers because they have to use them more frequently than the general population.[2,3]
- *Cutaneous lupus* – Cutaneous manifestations of systemic lupus erythematosus (SLE) as well as subacute cutaneous lupus (SCLE) can present as an erythematous and scaling eruption preferentially affecting photo-exposed skin. In such cases, there may be other systemic manifestations of lupus. Skin biopsy with direct immunofluorescence and peripheral blood autoimmune tests should aid differentiation from PACD.

### **1.1.3 Incidence**

The frequency of PACD reported in patients attending clinicians for the investigation of photosensitivity varies. Most retrospective and prospective studies cite figures of between 2 and 11% of such patients having relevant positive photopatch test reactions, although higher figures of 16%, 20% and 29% have been reported.[4-19] A prospective United Kingdom (UK) PPT study coordinated from Dundee found positive photopatch tests in 5.7% (66 of 1155) of subjects recruited.[20] The true incidence of PACD in the general population is not known,

but is likely to be significantly lower than these figures which are derived from a population of patients seeking medical attention for skin disorders.

PACD can affect any age of patient and due to the widespread nature of most photoallergens it can affect people in most geographical locations. Insufficient data has been reported to determine whether there is a difference in the incidence of PACD between the sexes. Certain reports have inferred that patients with idiopathic photodermatoses such as CAD and polymorphic light eruption (PLE) may develop PACD more frequently than the general population, [17,21] but this is not a universal finding across studies.[20]

#### **1.1.4 Historical photoallergens**

PACD to exogenous agents was first described over 60 years ago. One of the earliest reports of photoallergy was to the organic UV absorber *para*-aminobenzoic acid (PABA).[22]

##### **1.1.4.1 Antimicrobial agents**

The first period when a significant number of reports of PACD appeared in the medical literature was following the introduction of halogenated salicylanilides into soaps as antibacterial agents in the 1960s. The original outbreak reported was to the agent tetrachlorosalicylanilide (TCSA) among metalwork factory employees in England in 1960.[23] After the discovery of TCSA as the causative agent, manufacturers switched to the chemically related agent tribromosalicylanilide (TBSA). Unfortunately this also proved to be a photoallergen in its own right, as well as cross-reacting with TCSA.[24,25] Reports of PACD emerged to other antimicrobial agents over the next 15 years, including trichlorocarbanilide, hexachlorophene, bithionol, fenticlor, chlorhexidine and buclosamide.[26-33]

After the initial “epidemic,” TCSA was withdrawn from usage within soaps in the UK quickly.[24] In the United States of America (USA), regulatory authorities acted slightly later, with prohibitive regulations imposed on the use of bithionol in cosmetic products in 1968 and on other halogenated salicylanilides in 1975.[34] In Europe, directives prohibiting each agent’s use in cosmetics came into force in 1979 for TCSA and bithionol and in 1989 for bromide-containing salicylanilides.[35]

#### **1.1.4.2 Fragrances**

In the 1960s, there were sporadic reports in the literature of PACD due to men’s fragrances.[36,37] By the second half of the 1970s, the fragrance ingredient musk ambrette had been described as a notable cause of both ACD and PACD.[38,39] Musk ambrette was in widespread usage among cosmetic products at the time due to its high solubility in cosmetic vehicles and its low cost.[40] Further study confirmed it was indeed photoallergic and not phototoxic.[41] Although cross-reactions with other synthetic nitro-musk compounds were reported, these were thought to be rare.[40,42] As with certain antimicrobial agents, prohibitive legislation followed its confirmation as a photoallergen. In Europe it has been classed as a substance which must not form part of the composition of cosmetic products since 1997.[43] However, it appears to still be used to some extent in Asia, as it continues to be available for purchase for industrial use via the internet.

The synthetic fragrance 6-methylcoumarin has also been reported as leading to PACD.[11,15,44-46] It is not chemically related to musk ambrette but is similar to the furocoumarins (psoralens), which have known phototoxic properties. Manufacturers of sunscreens in the USA were asked to remove it from products in

1978.[47] It can still be used in oral hygiene products in Europe up to a concentration of 0.003%.[48]

#### **1.1.4.3 Veterinary products**

The veterinary antibiotic and growth-promoting food additive, quindoxin, was introduced to Europe in the early 1970s for piglets to reduce bacterial enteritis. However, within two years, reports of PACD in pig feed handlers began to emerge.[49,50] It was subsequently withdrawn from the market in 1973 when it was replaced by a derivative, olaquinox, but reports of PACD to this agent also began to emerge by the 1980s.[51,52] Both these compounds appeared to elicit PACD following direct contact with pig feeds containing the agents. Although olaquinox was removed from European countries in 1999, it may persist elsewhere.[53] Of interest, olaquinox is also unusual among photoallergens in that it does not lead to phototoxicity, even at high concentrations. As a rule, most agents which are able to elicit PACD can also lead to phototoxicity if the concentration of agent or dose of irradiation used is high enough.

#### **1.1.4.4 Medications**

The phenothiazine antipsychotic chlorpromazine (CPZ), more often thought of as a phototoxic agent, can also elicit true photoallergy.[54-56] PACD to CPZ was first seen in the carers of psychiatric patients, who crushed tablets for patients who had swallowing difficulties. It is likely that the introduction of a syrup formulation in the early 1970s (personal communication from Aventis Pharma Ltd) led to a clearance of this problem. Another phenothiazine, promethazine, has been reported as leading to PACD when used as a topical antipruritic.[57] Like CPZ, it can also cause phototoxicity.[58] Similarly, use of the early antihistamine diphenhydramine led to occasional reports of ACD and PACD.[59-61] Unusually, a case of PACD to



topical hydrocortisone has also been reported.[62] In this case, diagnosis was difficult, as the agent was being used to treat the photo-exposed site dermatitis.

#### **1.1.4.5 Inclusion of historical agents in PPT series**

Dermatologists working in the field of PACD and PPT have sometimes been guilty of responding slowly to the ever-changing landscape of photoallergens. As an example of this phenomenon, several different groups in separate countries continued to use PPT series after the early 1990s that still contained large numbers of agents that can be thought of as largely clinically irrelevant by that time.[5,7,8,63-69] This reluctance to remove numerous photoallergens of historical relevance led to large series, which took up much space on the back of patients. Additionally, younger dermatologists entering the field were not familiar with encountering these agents in the everyday environment, which likely contributed to confusion and under-usage of PPT as an investigation in certain circumstances.

#### **1.1.5 The Persistent Light Reactor**

The term “Persistent Light Reactor” (PLR) was first coined by Wilkinson in 1962 and referred to patients who had abnormal sensitivity to UV wavelengths and a persistent clinical reaction to light.[70] This abnormal photosensitivity continued to persist for many months or years, despite removal from ongoing exposure to soaps containing halogenated salicylanilides. Subsequently, Willis and Kligman conducted a series of experiments, and concluded that the abnormally sensitive responses of apparently normal skin to UVB and UVA wavelengths was most likely due to persistence of the photoallergen within the skin causing ongoing PACD.[71] They cited repeated application of salicylanilide soaps to most of the body as an explanation as to why many affected patients had generalized sensitivity.

Patients labelled as PLR to halogenated salicylanilides and fragrances continued to be reported.[72] However, the similarities of these patients with other photosensitive states led to the subsequent inclusion of PLR within the newly defined unifying syndrome of CAD.[73,74] CAD was described as a spectrum of chronic photosensitivity and therefore, not all patients with CAD needed to have been previously diagnosed (or suspected to have) with PACD. Where the literature seems weak is the clear evidence of PACD as demonstrated by a positive photopatch test, which is then followed by the development of unequivocal CAD. Over time, the concept of the PLR has largely fallen out of common usage.

#### **1.1.6 Mechanisms of PACD**

Although the exact mechanism of photoallergy is unknown, it is postulated that an exogenous low molecular weight compound (hapten) combines with a protein within the skin or circulation only in the presence of UV or visible light to create an antigenic conjugate.[44] This conjugate is then able to induce and elicit a delayed hypersensitivity response in the skin, leading to the clinical appearance of dermatitis. It is not known whether clinical photoallergens themselves act as haptens, or whether smaller metabolites of them are the haptens. It seems likely that both scenarios occur, given the diversity of the chemical structures different photoallergens exhibit. Much of the laboratory work in the area of photoallergy has used TCSA as a study molecule, given its apparent high potency seen clinically.

*In vitro* studies provided initial evidence that halogenated salicylanilides can bind to  $\gamma$ -globulin in the presence of daylight [75] and epidermal proteins without, and in the presence of UVA.[76] Work with human serum albumin (HSA) demonstrated that it first binds TCSA non-covalently without irradiation, before irradiation with UVA leads to a covalently bound TCSA anion/protein conjugate.[77] It is this

property that HSA exhibits for initial non-covalent binding which greatly increases the probability of subsequent covalent conjugate formation and indicates that not all proteins in the skin or circulation may be similarly capable of becoming carrier proteins with TCSA. In this covalent conjugation reaction, there was evidence that destruction of the amino acid histidine of the albumin occurs.[77] It was postulated that this destruction may be via photo-oxidative mechanisms, which could conceivably be extrapolated to the *in vivo* situation, given the oxygen-replete environment of the skin. Several other photoallergens have also been shown to be capable of forming conjugates with albumin after UV irradiation *in vitro*. [78-80]

The requirement of a complete hapten-protein photoconjugate to form for the subsequent sensitisation of lymphocytes to take place was implied by a guinea-pig macrophage migration-inhibition study.[81] Further evidence for the sensitising potential of such photoconjugates was seen when direct subcutaneous injection of an *in vitro* formed albumin-TCSA photoconjugate into naïve guinea pigs led to the elicitation of PACD.[82] The transfer of photosensitivity from sensitised animals, using peritoneal cells in guinea pigs and lymph node cells in mice and injecting them into naïve animals, has provided supportive evidence that PACD is a mononuclear cell-mediated type reaction.[31,83]

The presumed initial step in the induction of delayed type hypersensitivity is the uptake of a hapten applied to the skin by antigen-presenting cells within the epidermis, such as Langerhans' cells. Murine studies with the photoallergens TCSA and ketoprofen have lent support to this mechanism.[84,85] The next step of the induction model then proposes migration of such antigen-presenting cells via lymphatics to the local draining lymph nodes, where they stimulate proliferation of antigen-specific T-lymphocytes. Again, murine studies have provided supportive

evidence for the proliferation and specificity seen in such a step after exposure to TCSA plus UVA.[86,87] As regards the susceptibility of an individual to develop PACD and the magnitude of the response seen to any one agent, this appears to be influenced by their major histocompatibility complex (MHC) haplotype.[88]

In the years following the outbreak of PACD to TCSA, investigational studies on mechanisms of PACD were more numerous than in recent years. In that earlier period, an alternative to the protein-hapten conjugate theory postulated that UV was able to activate a pro-hapten to become an antigenic hapten, without the need for a carrier protein. This can be tested easily in the clinical setting, by pre-irradiation of an agent under investigation before application to the skin as a conventional patch test (i.e. no subsequent irradiation of the test site on the skin is required). One study from 2007 which used this method found no positive responses in three subjects known to have PACD to organic UV absorbers found in sunscreens.[89] The early experiments on the halogenated salicylanilides did provide some evidence for this as a possible mechanism, but the theory has largely fallen out of favour in the intervening years.[90]

### **1.1.7 Systemic photoallergy**

As defined above, PACD describes the reaction seen in the skin when an exogenous photoallergen reaches the skin via the topical route and not via a systemic route (which can be the case in phototoxicity). However, the concept of “photoallergy” occurring within the skin after exposure to a systemic agent has been reported in the literature.[91-96] In many cases, it appears that well known phototoxins are incorrectly cited as causing a dermatitis of photoallergic origin.[57,97] There has also been some confusion caused by the inappropriate use of PPT as an investigation in cases where adverse cutaneous reactions to systemic agents have

occurred.[96,98-100] PPT is specifically dependent upon the process of topical PACD and so any results seen when systemic agents are photopatch tested cannot be meaningfully interpreted.[101] The concept of systemic PACD seems a controversial area within the literature. As above, little in the way of logical evidence to support this concept has emerged and it appears that only topical drugs can cause PACD. If indeed agents can cause photoallergy by a systemic route, it seems to be a rare event relative to topical PACD.

## **1.2 Photopatch testing (PPT)**

### **1.2.1 Methodology**

Currently, the most appropriate and widely used method for investigating PACD in a subject is to perform PPT. In this process, agents under investigation are prepared in a vehicle (often petrolatum or water) and a small volume is placed within plastic or metal chambers, which have low chemical reactivity and are mounted on hypoallergenic adhesive tape. This combination of test agent, test chamber and adhesive tape is collectively referred to as a “photopatch.” After the preparation of one or more different photopatches as duplicate sets, they are then applied to the skin of the back of the subject under investigation. Ideally, the photopatches should not be placed on the paravertebral area 5cm either side of the midline, but should be placed lateral to this area on left and/or right sides.

After a variable period of time (conventionally 24 or 48 hours), the photopatches are removed. Any residual agent is carefully removed from the surface of the skin using a soft implement such as a cotton wool tip. At this point the entire test site where both sets were applied is often visually inspected and any reactions (including negative reactions) are recorded using a grading scale. After inspection and grading, the area which was beneath one of the duplicate sets of photopatches is covered with a material that does not allow the transmission of any UV or visible light. This UV-opaque material is also used to cover all other exposed skin on the back, neck, head and upper limbs of the subject, except for the area which was beneath the other set of photopatches. The exposed test area is then irradiated with a defined dose of UV (or visible light). The UV-opaque protective material is then removed from the subject. At variable timepoints after irradiation, usually multiples

of 24 hours, the entire test site, including both irradiated and covered sets are visually inspected and any reactions recorded with the grading scale.

Photographs illustrating the different steps involved in PPT are given in Figure 1.1.



The photopatches are prepared as duplicate sets.



The photopatches are applied to the skin of the back for 24 or 48 hours.

Figure 1.1. The process of conducting PPT.(continued on following page)



The photopatches are removed after 24 or 48 hours. Both sets are visually inspected for any reactions and a pen is used to mark the borders of the test sets.



One of the test sets, as well as the rest of the subject's back, neck and head are covered with a UV-opaque material.



The exposed test set is irradiated with a dose of UVA

Figure 1.1 (continued). The process of conducting PPT.



### **1.2.2 PPT in photosensitive subjects**

On certain occasions, when a patient requires investigation for possible PACD, they may be objectively photosensitive due to another condition e.g. CAD or drug-induced phototoxicity. Despite this background photosensitivity, it may still be possible to perform PPT if it is carefully conducted. The essential additional step required is to perform minimal erythema dose (MED) testing prior to irradiation of the photopatch test site. For MED testing, a small area of the back skin which is not in close proximity to the PPT site is exposed to a series of incremental doses of UV radiation. Some groups advocate performing MED testing for UVB alone,[63] UVA alone,[102,103] and both UVA and UVB.[19,104,105] The most logical option would appear to be performing an MED to the wavelength that is to be used for irradiation.

When an MED has been performed in photosensitive subjects, the method of using the value obtained to determine the best dose with which to irradiate the test site is again not standardised. Using a standard figure such as 50% or 66 % of the MED has been suggested [19,105] but it is probably best to assess such subjects on an individual basis, using the MED to decide on the dose used.[102] However, it is also the case that in some subjects, their photosensitivity is such that it is not safe to perform any irradiation because a large area of painful confluent erythema would likely arise over the test site. This situation, where positive photoallergic responses cannot be evaluated due to confluent erythema across the test site was often termed a “masked” test in previous literature reports from the USA.

### **1.2.3 Divergent PPT methodologies**

Because the process of PPT involves several separate steps, each of which can be varied, there has historically been a lack of standardisation of methodologies

employed between different clinicians and different centres. As an example, some centres have advocated applying the irradiated and covered sets of allergens for different durations.[10] This automatically creates variation between the two sets in each subject which could be easily avoided. The PPT methodology reported by seven different study groups between the years 1982 and 2007, showing the range of different variables that has been employed over that time is given in Table 1.1.

		Reported study [Reference number]
Length of agent application (hours)	24	[10,19,63,104]
	48	[2,10,19,68,103]
Irradiation wavelengths used	UVA alone	[2,10,19,68,103,104]
	UVA and UVB	[63]
Dosage of UVA used ( $\text{Jcm}^{-2}$ )	5	[2,103,104]
	8	[19]
	10	[10,19,68]
	13	[63]
Post-irradiation timepoints used for recording reactions (hours)	0	[10,68,103,104]
	24	[10,63,68,103]
	48	[2,10,19,63,68,103,104]
	72	[10,103]
	168	[19]

Table 1.1. Different PPT methodologies reported between the years 1982 and 2007. The methodology reported from seven different study groups shows the range of different variables employed. Each of the seven groups cited were based in one of the following countries: UK[2]; Germany/Austria/Switzerland[10]; USA[19]; Spain[68]; France[63]; Italy[103]; Sweden[104].

#### **1.2.4 Wavelengths for irradiation**

Presently, the most commonly used sources for irradiation are those that produce predominantly UVA wavelengths i.e. between 315 and 400nm. However, this was not always the case, and has been arrived at by experimentation. In the original investigation of halogenated salicylanilides, “black light” which has wavelengths between 300-400nm (centred around 350nm) was used for 30 minutes at a distance of 25cm as the irradiation source.[30] A different group then reported that irradiation of a test site with both UVB and UVA sources led to more reactions than UVA alone, and speculated that this was due to UVB-mediated cutaneous damage.[106] Using triplicate sets of photopatches (UVB-irradiated, UVA-irradiated and covered) has also been previously reported,[107,108] with French investigators varying this slightly to employ polychromatic (UVB, UVA and visible wavelengths) light instead of UVB alone.[53,63,109] However, one group found that irradiation with UVB did not pick up any reactions that were not found by UVA irradiation alone and suggested that the use of UVA as the sole source of radiation seemed justified.[110]

Ideally, in order to choose the most appropriate wavelengths with which to irradiate a photopatch test site, one needs to know the wavelengths which are required for the photoallergic reaction to occur in the skin. The range of wavelengths between which the reaction will occur for an individual agent is termed its “action spectrum.” The action spectrum has been defined for certain halogenated salicylanilides [29,111] and musk ambrette [41,112] but unfortunately has not yet been clearly defined for most photoallergens of current relevance. A reasonably straightforward way to determine the action spectrum is for an agent is by performing PPT using a monochromator for irradiation. By employing such a

method, members of the Photobiology Unit in Dundee have shown that the action spectrum for eliciting PACD is within UVA wavelengths for the organic UV absorber benzophenone-3 and the topical nonsteroidal anti-inflammatory drug (NSAID) etofenamate.[113,114]

The action spectrum of an agent is dependent upon the absorption spectrum of that agent. The absorption spectrum represents the fraction of incident radiation that the molecule absorbs over a range of wavelengths and can be easily measured *in vitro* using a spectrophotometer. Interestingly, previous studies have shown that many photosensitisers exhibit maximum *in vitro* absorption spectra below 315nm, yet also have some absorption within the UVA range.[27,40,46,52,77,111,112] It is logical to think that the action spectrum for a molecule should be closely linked to its absorption spectra. However, the *in vitro* absorption spectrum obtained can be easily altered by changing other test variables such as the pH of the solution. Because of this, the *in vitro* spectrum may not as closely reflect the *in vivo* spectrum of an agent in the skin, where there are numerous other variables e.g. interaction with proteins.[61]

One theory proposed to explain why the action spectra for most agents lie in the UVA range is that photohaptten-protein interactions occur below the epidermis. At this depth, UVB wavelengths are attenuated to such a degree that the action spectrum is shifted towards longer UVA wavelengths which penetrate to the dermis.[112] There are occasional reports of photosensitisers which appear to have absorbance and action spectra only in the UVB wavelengths.[61,115] However, with wavelengths shorter than 315nm, the dose required to elicit PACD is often higher than the minimal erythema threshold, making the interpretation of responses difficult.[29,102]

### **1.2.5 Dose for irradiation**

As can be seen from Table 1.1, there has been variation in the doses of UVA used between centres over time. There has been a gradual move in Europe towards using  $5 \text{ Jcm}^{-2}$  as the standard and doses well below this may be adequate to elicit positive photopatch test reactions.[42,116-118] Higher doses such as  $10 \text{ Jcm}^{-2}$  are more time-consuming to deliver and more importantly lead to a greater risk of producing phototoxic reactions, which could be misinterpreted as positive PACD reactions.[10,56,116]

### **1.2.6 Timing of photopatch application and readings**

There has been less variation between centres in the duration that photopatches are applied for and, by extension, the timepoints that are chosen for recording the results of PPT. This is because the division of the working week into days naturally lends itself towards photopatches being applied for multiples of 24 hours and also clinicians performing readings at 24 hour intervals. The main division that has existed has been between photobiology units and contact dermatitis units. Contact units which also perform PPT traditionally apply photopatches for 48 hours and perform readings another 48 hours after that. Photobiology units often only apply photopatches for 24 hours, as they undertake additional investigations which require reading at 24 hour intervals.

There has been little formal study of the influence of adopting different time periods have on the results of PPT. A recent study from Sweden using the topical NSAID ketoprofen found that applying the agent for one hour picked up almost the same number of cases of PACD as a 24 hour application.[119] Previously, the Leeds group has looked into two separate aspects. In one study, the group found that no late positive PACD reactions were seen when readings were performed at 5

days post-irradiation that were not present at 2 days post-irradiation.[110] In a later study, the group reported that more PACD reactions were detected by using a period of 48 hours application than with 24 hours, although this was a retrospective review.[120] Overall, given the difficulty in altering the set-up within a unit, it seems likely that it will continue to be more practical for units to choose to apply patches for either 24 *or* 48 hours, a fact recognised in the UK guidelines on PPT methodology from 1997.[102]

### **1.2.7 Recording results**

When recording the results of reactions in the test site, various grading scales have been adopted by different centres, although these do bear similarity to one another.[19,104] However, with the increasing need to compare results between centres, the scale employed by the International Contact Dermatitis Research Group (ICDRG) has gained fairly widespread acceptance.[121] In addition to denoting when positive reactions occur, clinicians usually attempt to determine their relevance with respect to the problem that the patient presented with. The COADEX system is one such system that has been employed.[122] This classifies positive reactions as follows: C – current relevance; O – old/past relevance; A – an active sensitisation reaction; D – unknown relevance; E – history of exposure but not resulting in dermatitis; X – cross-reaction with another test agent.

### **1.2.8 Interpretation of results**

The correct interpretation of PPT results is not always straightforward and requires experience. Because there are duplicate sets of agents (irradiated and covered) there are several potential combinations of reactions that may occur. The system outlined by Bryden *et al* in 2006 is practical and identifies four main patterns of

immunologically-mediated reactions possible for a single agent.[20] These are listed below:

- *PACD* – a positive reaction (of any ICDRG grade) is seen in the irradiated set only. The same agent in the covered set is negative.
- *ACD* – a positive reaction (of any ICDRG grade) is seen in the irradiated set and a reaction of equal grade is seen at the same agent in the covered set.
- *Photoaugmentation of ACD* – a positive reaction is seen in the covered set and a positive reaction which is at least one ICDRG grade higher is seen at the same agent in the irradiated set.
- *Photoinhibition of ACD* – a positive reaction is seen in the covered set and a positive reaction which is at least one ICDRG grade lower is seen at the same agent in the irradiated set.

In addition to these four patterns, phototoxic responses, Irritant Reactions and negative responses can occur during PPT. One of the most common findings in the literature is that reactions which would be defined as photoaugmentation of ACD using the system above were instead reported as ACD plus PACD.[7,8,123-125]

The sensitive mechanisms underlying PPT reactions have been explored by some groups. It has been shown that both photoaugmentation and photoinhibition of ACD and irritancy can result from adjusting certain variables when performing PPT, which could lead to misinterpretation.[126] In a separate study, a group looked at the effect on decreasing the concentration of the agent and changing the UVA dose used. They found that previously positive PPT PACD reactions were more sensitive than ACD reactions to small reductions in concentration, often being abolished.[127] They also found that doses of UVA below  $5 \text{ Jcm}^{-2}$  caused loss of PACD reactions, but conversely, increasing the dose beyond  $5 \text{ Jcm}^{-2}$  did not lead to

augmentation of ACD or PACD reactions.[127] Due to the complex human pathophysiology underlying PPT, it is not always a precise and predictable process, and negative results can occur in a subject who gives a history strongly suggestive of PACD.

### **1.2.9 Standardisation**

With such a wide range of different methodologies being employed by different groups, the comparison of study findings between publications has been difficult. It is because of this issue, that early attempts at standardising the methodology of PPT arose.[10,68,102,104] These attempts laid the foundation for the most recent European consensus methodology, which was published under the auspices of the European Society of Contact Dermatitis (ESCD) and the European Society for Photodermatology (ESPD) in 2004.[128] Among variables, agreement was reached that photopatches should be applied for either 24 or 48 hours followed by irradiation with  $5 \text{ Jcm}^{-2}$  of UVA and readings should be made at 24, 48 and if possible, 72 hours post-irradiation. In recent years, the European consensus methodology has been adopted by an increasing number of investigators and over time, this should enable more meaningful comparison of results between centres.



### **1.3 Current Photoallergens**

As outlined earlier in this Chapter, there are many photoallergens which are now of historical interest and diminishing relevance. However, these have been replaced by newer photoallergens which are present in the everyday environment. Currently, the two largest groups of agents leading to PACD are organic UV absorbers used in sunscreens and topical NSAIDs used for pain relief.

#### **1.3.1 Organic UV absorbers**

The organic UV absorbers are used within sunscreens to protect the skin against the harmful effects of UV radiation and are currently the largest group of agents which commonly cause PACD. They are chemical molecules whose main mode of action is to absorb damaging shorter UV wavelengths (between approximately 250nm-350nm) through their conjugated aromatic ring structures. These absorbed wavelengths have a relatively high energy and consequently cause the sunscreen molecule to be raised to an excited state. The molecule then spontaneously returns to the ground state, emitting longer UV, visible and infra-red wavelengths (380-800nm) which have lower energy and less detrimental effects on the skin. There are many organic UV absorbers used in sunscreens, which can be classified into families, according to their chemical structure. Each individual agent absorbs, and therefore protects the skin against, a different range of UV wavelengths. It is by combining different quantities of different UV absorbers into a sunscreen that manufacturers can create a sunscreen with the protective qualities desired.

##### **1.3.1.1 History of development**

In the early years of sunscreen manufacturing from the 1920s onwards, products were marketed as a fashion accessory to promote the development of a “tan” among Caucasian consumers. This was accomplished by incorporating absorbers which

protected against the erythema (sunburning) UVB wavelengths, but not against the melanogenic (tanning) UVA wavelengths. As an example, the earliest manufactured sunscreen in the USA in 1928 contained absorbers from two classes (salicylates and cinnamates), both of which are protective against UVB wavelengths.[129] Over time, a grading system which allowed consumers to determine the amount of protection a sunscreen would provide against sunburn evolved, the sun protection factor (SPF) system. The SPF can be defined as “the ratio of the least amount of UV energy required to produce a minimal erythema on sunscreen protected skin to the amount of energy required to produce the same erythema on unprotected skin.” [130] Between the 1930s and the 1990s, SPF values were generally less than ten and most sunscreens continued to contain predominantly UVB absorbers. However, in the 1990s, the importance of UVA wavelengths in contributing to damage within the skin was recognised and accordingly, UVA absorbers began to be incorporated into most sunscreens.[131] At the same time as this broadening of the protective spectrum led to higher numbers of absorbers being used in each sunscreen, a parallel increase in SPF in this period meant that the concentration of some of the absorbers used also increased.

#### **1.3.1.2 Regulation of sunscreens in Europe**

In Europe, sunscreens are treated as cosmetics by regulatory authorities. Currently, each organic UV absorber which is permitted for use in cosmetic products by the European Commission is listed within its database, under Directive Annex VII which can be viewed online [132](see also Appendix 1). This also provides information on the maximum authorised concentration which can be used. These concentrations vary between different absorbers and are in place to help limit adverse effects and encouragingly, a chemical analysis of 75 sunscreen products in

Denmark in 2001 found that all tested were compliant with Annex VII regarding concentrations.[133]

### **1.3.1.3 Agent classes and reports of PACD and ACD**

As outlined above, over time sunscreen manufacturers have responded to market trends by increasing the number and concentration of absorbers used within sunscreens. At the same time, sunscreen consumers have become increasingly aware about the potential dangers of over-exposure to the sun and the need to use sunscreens. It is the combination of these trends that has contributed to an increase in the incidence of PACD to organic UV absorbers.[9] The following sections summarise the main classes of UV absorber used over time in Europe, and review the literature regarding reports of PACD to each notable agent. Although there is a focus on PACD, the phenomenon of concomitant ACD occurring during PPT studies is frequent and so reports of this are also highlighted for most agents. Unfortunately, the nomenclature of agents has become complicated over time, due to the adoption of several synonyms by industry and regulatory bodies. The multiple synonyms for the 19 organic UV absorbers used in the European multicentre photopatch test study (EMCPPTS) are given in Table 1.2. In this thesis, agents are referred to by their International Nomenclature of Cosmetic Ingredients (INCI) name unless stated otherwise.

<b>International Nomenclature of Cosmetic Ingredients (INCI) name</b>	<b>Other names</b>	<b>United states adopted name (USAN)</b>	<b>Proprietary / trade names (all registered trademarks)</b>
Ethylhexyl salicylate	Octyl salicylate	octisalate	Escalol 587, Eusolex OS, Neo Heliopan OS,
Homosalate	Homomenthyl salicylate	homosalate	Eusolex HMS, Neo Heliopan HMS
Octocrylene	Octocrilene	octocrylene	Escalol 597, Eusolex OCR, Neo Heliopan 303, Parsol 340, Uvinul 539 T
Ethylhexyl-methoxycinnamate	Octyl methoxycinnamate	octinoxate	Escalol 557, Eusolex 2292, NeoHeliopan AV, Parsol MCX, Tinosorb OMC, Uvinul MC 80
Isoamyl- <i>p</i> -methoxycinnamate		amiloxate	Neo Heliopan E1000
Benzophenone-3		oxybenzone	Escalol 567, Eusolex 4360, Neo Heliopan BB, Tinosorb B3, Uvinul M40
Benzophenone-4		sulisobenzone	Escalol 577, Uvinul MS 40
Butyl methoxydibenzoylmethane		avobenzone	Escalol 517, Eusolex 9020, NeoHeliopan 357, Parsol 1789
4-Methylbenzylidene camphor		enzacamene	Eusolex 6300, Neo Heliopan MBC, Parsol 5000, Uvinul MBC 95
Phenylbenzimidazole sulfonic acid		ensulizole	Eusolex 232, Neo Heliopan Hydro
Polysilicone-15			Parsol SLX
Ethylhexyl triazone	Octyl triazone		Uvinul T150
Diethylhexyl butamido triazone		iscotrizinol	Uvasorb HEB
Terephthalylidene dicamphor sulfonic acid		ecamsule	Mexoryl SX
Diethylamino hydroxybenzoyl hexyl benzoate			Uvinul A Plus
Disodium phenyl dibenzimidazole tetrasulfonate		bisdisulizole disodium	Neo Heliopan AP
<i>Bis</i> -ethylhexyloxyphenol methoxyphenyl triazine		bemotrizinol	Escalol S, Tinosorb S
Methylene <i>bis</i> -benzotriazolyl tetramethylbutylphenol	MBBT	bisotrizole	Tinosorb M
Drometrizole trisiloxane			Mexoryl XL, silatrizole

Table 1.2. Synonyms of the 19 organic UV absorbers used in the EMCPPPTS.

***“Older” organic UV absorbers***

The agents described below have been in use for many years in Europe, and some were among the absorbers first used by commercial manufacturers. Although some of these agents subsequently fell out of usage, most continue to be used in Europe. In comparison with the “newer” agents described later in this Chapter, they tend to be smaller molecules with a lower molecular weight.

### *Salicylates*

The salicylates were some of the earliest organic absorbers incorporated into sunscreens, having been used for greater than 50 years.[134-136] They absorb UVB wavelengths between 290-315nm, but are often classed as weak, requiring high concentrations to increase the SPF of a sunscreen.[129] They do not penetrate the stratum corneum of the epidermis but homosalate and ethylhexyl salicylate are insoluble in water, meaning that they are used in “water resistant” sunscreens.[137] Currently, these are also the only two salicylates listed in Annex VII.[132] Their molecular structure is given in Figure 1.2. Among the salicylate class, benzyl salicylate also has UV absorbing properties but is not listed in Annex VII. It was the UV absorber used in the first widely used commercial sunscreen, an Ambre Solaire<sup>®</sup> product, in 1935.[135] Presently, it is often incorporated within sunscreens as a fragrance ingredient, but will also have the beneficial effect of increasing the SPF.[138] The salicylates are generally acknowledged as safe absorbers with limited reports of PACD [5,14] and ACD. [134,139,140]

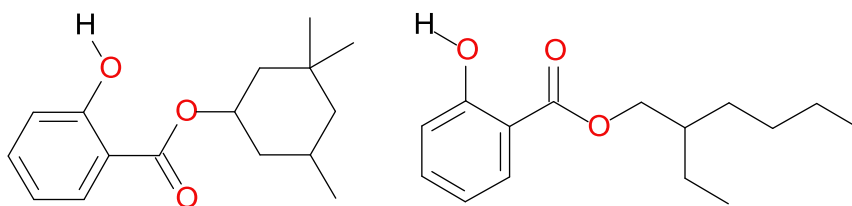


Figure 1.2. The molecular structure of homosalate (left) and ethylhexyl salicylate (right).

### *Cinnamates*

Certain cinnamate molecules are used as UV absorbers within sunscreens, whilst others are frequently used as fragrances and flavourings. Ethylhexyl methoxycinnamate absorbs predominantly UVB wavelengths between 270-328nm

and was the most commonly used UVB absorber in Europe from the 1980s until the middle of the 2000s.[133,138,141] It is insoluble in water, but unfortunately when combined with the widely used UVA absorber butyl methoxydibenzoylmethane, the resulting photolability can decrease the product SPF, thereby limiting its usefulness.[137] This may be one reason that its use appears to be decreasing among sunscreen manufacturers.

Currently, there are two cinnamates, ethylhexyl methoxycinnamate and isoamyl-*p*-methoxycinnamate listed in Annex VII.[132] Their molecular structure is given in Figure 1.3. Interestingly, a 2005 UK survey of sunscreen products found another cinnamate, ethyl methoxycinnamate, which has not been listed in Annex VII, as a constituent of some products.[138] The cinnamate UV absorbers have the potential to cross-react to other cinnamon-related agents e.g. Balsam of Peru, cinnamic acid, cinnamic aldehyde and cinnamon oils.[142] However, a study found no positive photopatch tests to ethylhexyl methoxycinnamate and isoamyl-*p*-methoxycinnamate in 18 subjects with previous patch test positives to cinnamon compounds.[143] Given their previous very high levels of usage, reports of PACD [13,144-149] and ACD [142,150,151] to the cinnamates are relatively rare.

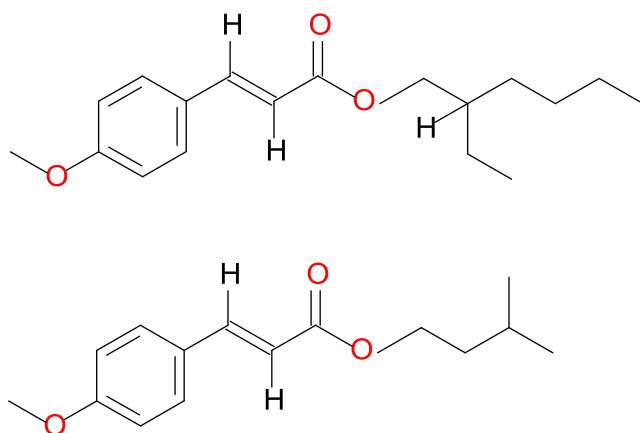


Figure 1.3. The molecular structure of ethylhexyl methoxycinnamate (top) and isoamyl-*p*-methoxycinnamate (bottom).

### *Octocrylene*

Octocrylene is an agent that absorbs UVB and some UVA wavelengths between 290-360nm.[137] It is often grouped with the cinnamates, as it has structural similarities.[152] Its molecular structure is given in Figure 1.4. Octocrylene loses its efficacy when exposed to water, but is effective at stabilising the UVA absorber butyl methoxydibenzoylmethane. As a result, its usage within sunscreens has been increasing over recent years.[136,138] Although it is relatively new among established agents, reports of PACD [153,154] and ACD [155,156] to octocrylene have arisen.

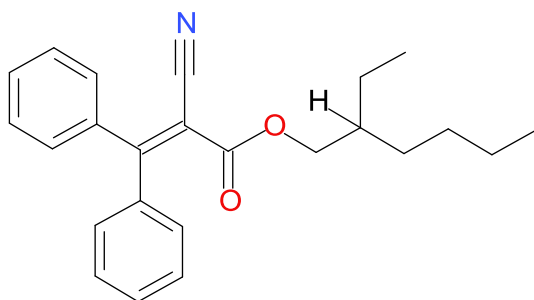


Figure 1.4. The molecular structure of octocrylene.

### *Phenylbenzimidazole sulfonic acid*

Phenylbenzimidazole sulfonic acid is a miscellaneous agent which absorbs UVB wavelengths and has been used since the 1930s.[135] Its molecular structure is given in Figure 1.5. There are reports of both PACD [157,158] and ACD [159] to this agent although they appear to be relatively uncommon.

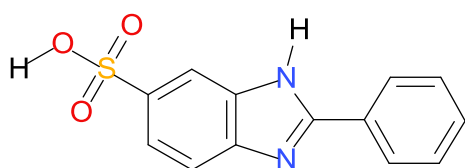


Figure 1.5. The molecular structure of phenylbenzimidazole sulfonic acid.



### ***Para-aminobenzoic acid (PABA)***

PABA and its esters were some of the earliest UVB absorbers, widely used in sunscreens from the 1940s onwards.[135] PABA has a peak absorption wavelength of 283nm and can penetrate into the stratum corneum where it binds tightly to keratinocytes via hydrogen bonds. This made it attractive for inclusion in “water-resistant” preparations.[129,137] It requires an alcohol vehicle for use in sunscreens, which can lead to a “stinging” sensation and yellow staining of clothing.[141,152] These reasons contributed to a decline in its usage by sunscreen manufacturers, but its removal from Annex VII in Europe was due to concerns following the accumulation of reports of PACD [15,160] and ACD.[161,162] Its molecular structure is given in Figure 1.6. During the years where it was frequently used in sunscreens, it was the absorber most commonly reported as causing ACD and PACD.[21] In this period, certain *in vitro* studies hinted at the carcinogenic potential of PABA, although later photogenotoxicity studies did not clarify that this was the case.[163]

Esters of PABA were used increasingly in the 1970s and 1980s due to their greater compatibility with other cosmetic vehicles and a decreased propensity for staining.[141,152] Despite initial hopes that they would cause fewer allergic reactions due to a decreased ability to penetrate the stratum corneum, PACD [5,164,165] and ACD [142,161,166] to the PABA esters were also commonly reported. There are still two esters, ethylhexyl dimethyl PABA and PEG-25 PABA, listed in Annex VII but these seem to be infrequently used by manufacturers.[132] The molecular structure of ethylhexyldimethyl PABA is given in Figure 1.6. PABA and its esters can also lead to cross-reactions with a large range of related “*para-*

amino” compounds on patch testing including *para*-phenylenediamine, sulphanilamide, Disperse Orange 3 and *para*-aminoazobenzene.[164]

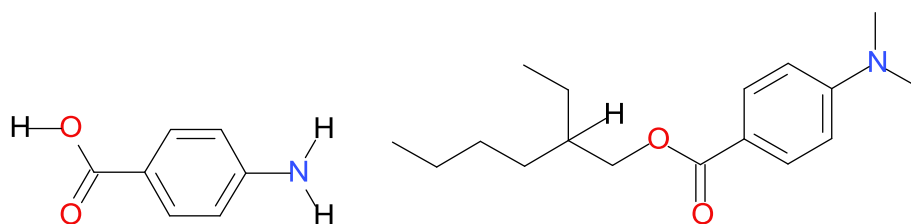


Figure 1.6. The molecular structure of PABA (left) and ethylhexyldimethyl PABA (right).

### ***Benzophenones***

The benzophenones are predominantly UVB absorbers, but are sometimes classed as “broad spectrum” because they also absorb into UVA wavelengths. They have been incorporated in sunscreens since the 1960s.[135,167] The most commonly used agent in this class is benzophenone-3 which absorbs from 270-350nm.[137] Its molecular structure is given in Figure 1.7. During its long history of use, many reports of PACD [113,145,146,168-175] and ACD [123,124,161,172,176-178] to benzophenone-3 have emerged. In addition to delayed type hypersensitivity reactions, it has also been reported as causing immediate hypersensitivity in the form of contact urticaria, photocontact urticaria and anaphylaxis.[113,176,179,180] There have been concerns about the potential endocrine and carcinogenic effects of benzophenone-3, as it can be taken up systemically after topical application.[181] However, a review of *in vitro*, *in vivo* and human studies suggested that topical use does not lead to significant hormonal disruption in humans.[182] Benzophenone-3 remains in Annex VII, but because of the allergenic and systemic findings, European sunscreens incorporating it must be labelled with the wording “contains

oxybenzone” (the adopted name in the USA).[132] Sunscreen manufacturers have moved away from using benzophenone-3 in recent years, as more effective dedicated UVA absorbers have been developed.[129]

Another agent in the benzophenone class is benzophenone-4, which is also listed in Annex VII.[132] However, it is not used in most products marketed as sunscreens, being more commonly found within other cosmetics to lessen the photodegradation of all ingredients inside translucent or transparent packaging.[167] Its molecular structure is given in Figure 1.7. It has been reported as causing PACD [5,8,11] and ACD.[159,183,184] Benzophenone-10 is another agent in the class which was previously used in sunscreens, but has now been removed from Annex VII. Reports of PACD [13,18,124,185] and ACD [123,186] to benzophenone-10 arose during the period it was used. As with benzophenone-4, it may still be used in some non-sunscreen cosmetic products.

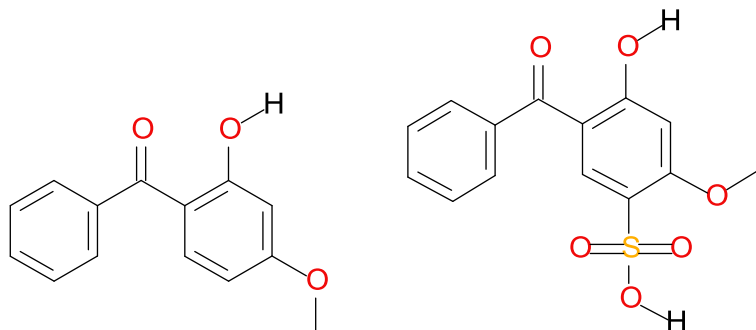


Figure 1.7. The molecular structure of benzophenone-3 (left) and benzophenone-4 (right).

### *Camphor derivatives*

The camphor derivatives are UVB absorbers and currently five are listed under Annex VII.[132] These are as follows: 4-methylbenzylidene camphor, 3-benzylidene camphor, camphor benzalkonium methosulfate, benzylidene camphor sulfonic acid and polyacrylamidomethyl benzylidene camphor. A sunscreen survey in Europe in 1983 found that this class of absorber was the second most commonly used after the cinnamates.[141] Presently, only 4-methylbenzylidene camphor appears to be used commonly by manufacturers of sunscreens.[138] Its molecular structure is given in Figure 1.8. There have been reports of PACD [146] and ACD [125,149,150,187-189] to this agent.

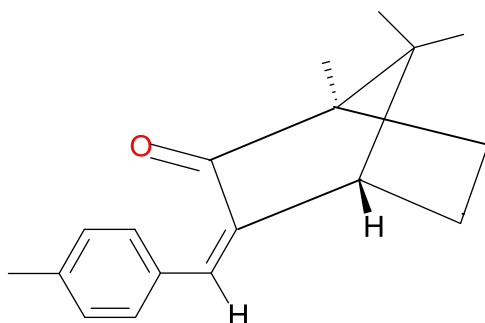


Figure 1.8. The molecular structure of 4-methylbenzylidene camphor.

### *Dibenzoylmethanes*

The dibenzoylmethanes were the first dedicated UVA absorbers used in sunscreens and were introduced in Europe in 1979.[129] The only agent within this class listed in Annex VII is butyl methoxydibenzoylmethane, which absorbs almost exclusively UVA between 310-400nm. Its molecular structure is given in Figure 1.9. It is not only the most widely used UVA absorber, but also the most widely used absorber overall in Europe.[133,138] However, it is intrinsically photo-unstable and requires the addition of other absorbers such as octocrylene and/or non-UV absorbing

stabilisers within sunscreen formulations.[190] Although theoretically problematic, in practice it can be combined with inorganic sunscreen filters such as titanium dioxide.[137] When successfully achieved, this combination allows the concentration of both agents to be lowered. There are reports of both PACD [146-148,154,191-193] and ACD [192,194] to butyl methoxydibenzoylmethane.

A second absorber from this class, isopropyl dibenzoylmethane was used in Europe between 1979 and 1993.[105] However, it was voluntarily removed from the marketplace by manufacturers in 1993 after the accumulation of reports of photoallergy.[152,195] There were several reports of PACD [192,193] and ACD [125,150,187,189,192,194,196] to isopropyl dibenzoylmethane during the years it was used within sunscreens. It is likely that some of the earlier reports of PACD and ACD to butyl methoxydibenzoylmethane represented cross-reactions from prior exposure to the isopropyl molecule. However, the ongoing emergence of occasional reports citing PACD to butyl methoxydibenzoylmethane in the years after the withdrawal of the isopropyl molecule, demonstrate that it can be photoallergenic in its own right.[148] Recent laboratory work using murine assays suggests that photoallergy to the dibenzoylmethanes may be due to arylglyoxal photodegradation products.[197]

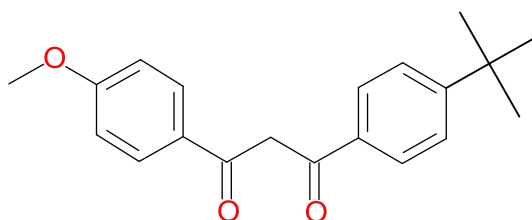


Figure 1.9. The molecular structure of butyl methoxydibenzoylmethane.

### ***“Newer” organic UV absorbers***

As outlined previously, there have been market trends influencing manufacturers to increase the SPF and broaden the UV protective spectrum of sunscreens over time. These targets also have to be achieved whilst decreasing the total number of UV absorbers used in products, thereby lessening the likelihood of adverse effects occurring. This task has been achieved by the development of new absorbers, some of which can protect against both UVB and UVA wavelengths. These “newer” agents have considerably higher molecular weights (often >500 Daltons) than the “older” agents, which should mean they are less able to penetrate into the skin and elicit PACD and ACD. Virtually all common contact allergens have a molecular weight of less than 500 Daltons and this figure has been proposed as a lower limit by some for any new sunscreen absorbers developed.[198]

The development principle of the “newer” absorbers was to extend or multiply existing chemical chromophores or graft the chromophore onto a polymer backbone.[198] In comparison to some “older” agents, they are more photostable. These “newer” agents are discussed in the following sections. They gained approval for use in Europe between the years 1993 and 2003 and are listed within Annex VII.[132] The INCI name has been given, but given the length of some of these, the commonly used proprietary name has also been given following this in brackets.

**UVB absorbers**

**Ethylhexyl triazone (Uvinul T150<sup>®</sup>)** This is a “triple chromophore” which trebles the PABA chromophore by linking it to a triazine ring. Its peak absorption is at 314 nm.[198] When it was included in the test series for the UK multicentre PPT study, two subjects developed PACD responses and three developed ACD responses.[20,199] Its molecular structure is given in Figure 1.10.

**Diethylhexyl butamido triazone (Uvasorb HEB<sup>®</sup>)** This is a “triple chromophore,” sometimes regarded as an “improved version” of ethylhexyl triazone due to its increased solubility. Its peak absorption is at 312 nm.[198] No reports of PACD or ACD to this agent have yet emerged. Its molecular structure is given in Figure 1.10.

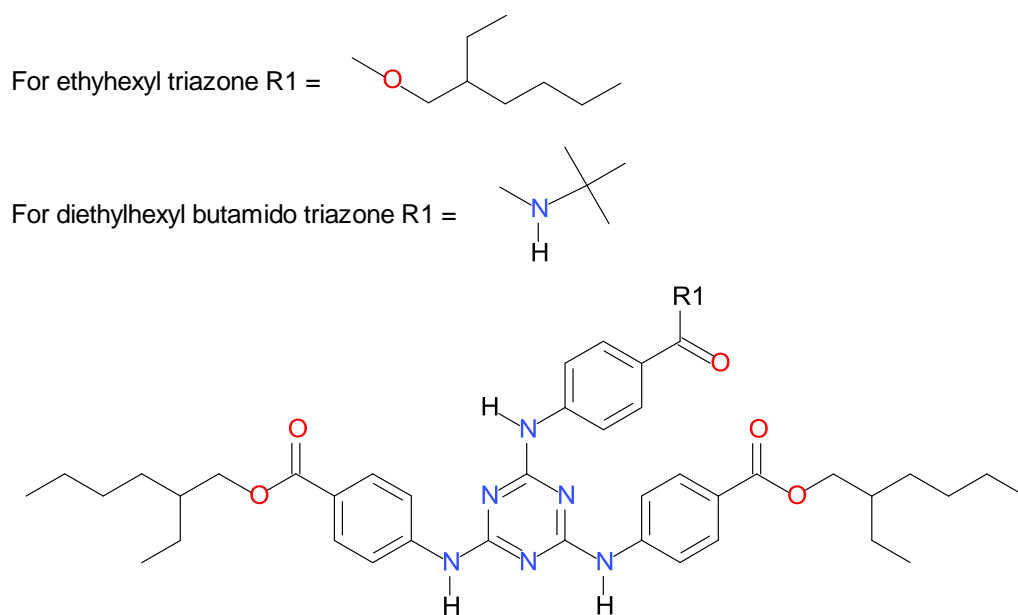


Figure 1.10. The molecular structure of ethylhexyl triazone and diethylhexyl butamido triazone.

**Polysilicone-15 (Parsol SLX<sup>®</sup>)** This has a “polymer backbone” containing silicon and oxygen, with chromophores in the side chains. Its molecular structure is given in Figure 1.11. Its peak absorption is at 312 nm. It has a very high molecular mass (approximately 6,000 Daltons) which practically inhibits any skin penetration.[198] No reports of PACD or ACD to this agent have yet emerged.

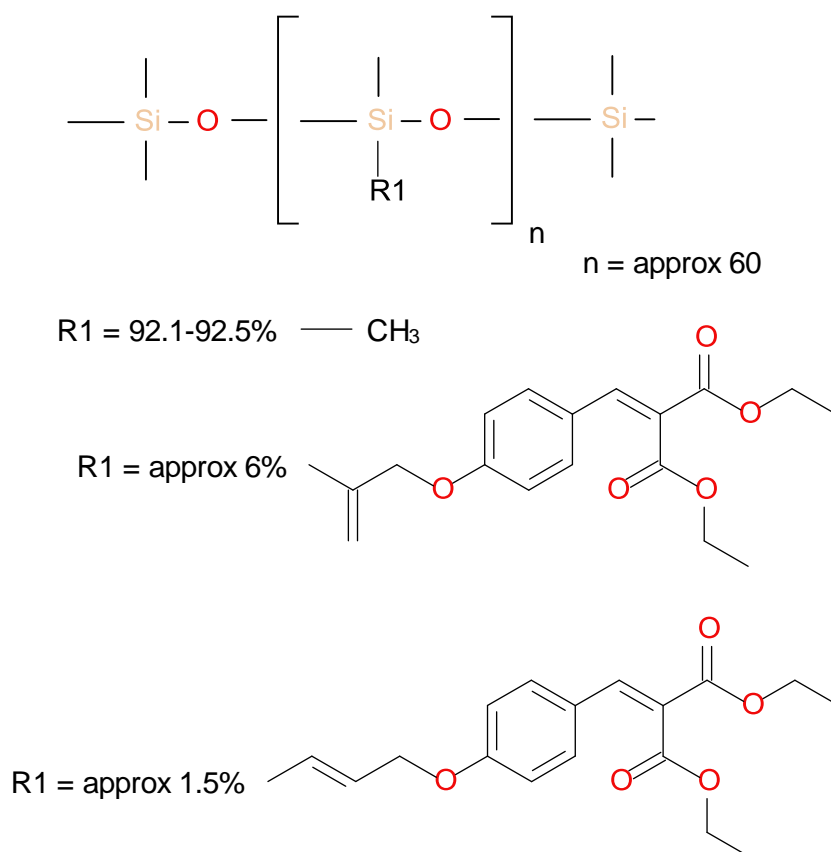


Figure 1.11. The molecular structure of polysilicone-15.



### *UVA absorbers*

***Terephthalylidene dicamphor sulfonic acid (Mexoryl SX<sup>®</sup>)*** This is an “extended chromophore,” which is water soluble, making it less useful for “water resistant” sunscreens. Its molecular structure is given in Figure 1.12. Its peak absorption is at 345 nm. It was developed and patented by the company L’Oreal Ltd, which has published many studies demonstrating its usefulness as a UVA absorber.[198,200] No reports of PACD or ACD to this agent have yet emerged.

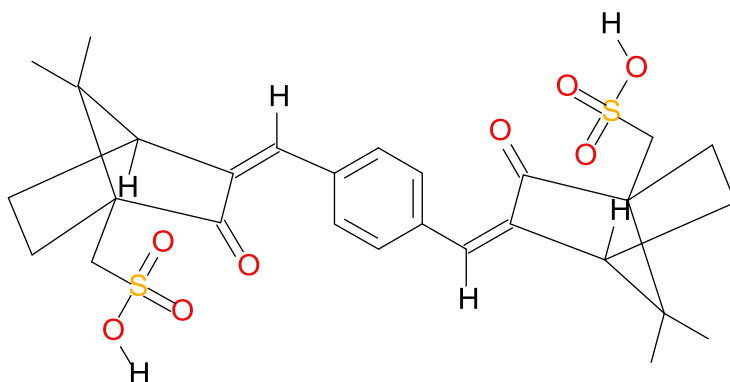


Figure 1.12. The molecular structure of terephthalylidene dicamphor sulfonic acid.

***Diethylamino hydroxybenzoyl hexyl benzoate (Uvinul A Plus<sup>®</sup>)*** This is an “extended chromophore” based on the benzophenone structure. Its molecular structure is given in Figure 1.13. It has a peak absorption at 354nm and good photostability.[198] No reports of PACD or ACD to this agent have yet emerged.

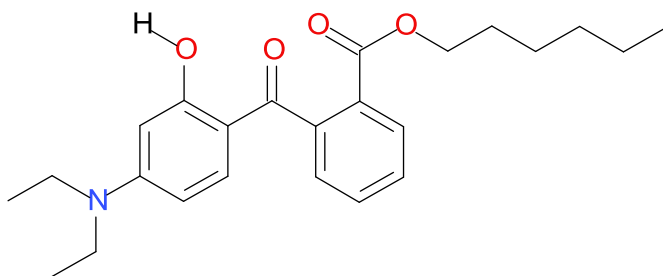


Figure 1.13. The molecular structure of diethylamino hydroxybenzoyl hexyl benzoate.

***Disodium phenyl dibenzimidazole tetrasulfonate (Neo Heliopan AP<sup>®</sup>)*** This is an “extended chromophore” based on phenylbenzimidazole sulfonic acid. Its molecular structure is given in Figure 1.14. Its has a peak absorption at 334 nm and is water soluble.[198] Although classical PACD and ACD to this agent have not been reported, a case of contact urticaria has emerged.[201]

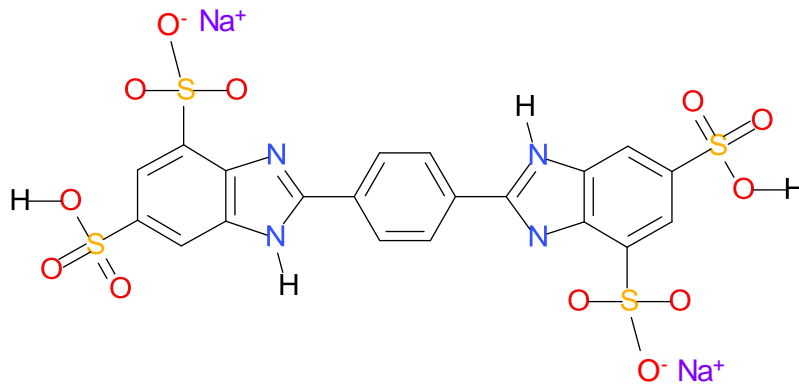


Figure 1.14. The molecular structure of disodium phenyl dibenzimidazole tetrasulfonate.

### *UVB and UVA absorbers*

***Drometrizole trisiloxane (Mexoryl XL<sup>®</sup>)*** This is an “extended molecule” which is oil-soluble and has absorption peaks at 303nm and 341nm. Its molecular structure is given in Figure 1.15. It was developed and patented by the company L’Oreal Ltd and has been used in Europe since 1998.[198] The combination of Mexoryl XL<sup>®</sup> and Mexoryl SX<sup>®</sup> works synergistically to increase the UVA protection within products.[190] A report of ACD to drometrizole trisiloxane has emerged.[202]

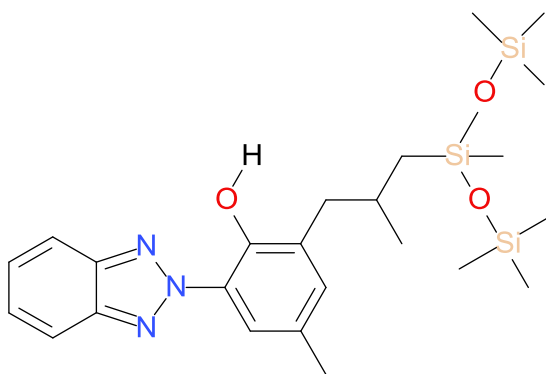


Figure 1.15. The molecular structure of drometrizole trisiloxane.

**Methylene bis-benzotriazolyl tetramethylbutylphenol (Tinosorb M<sup>®</sup>)** This is a “double chromophore” which has absorption peaks at 305nm and 360nm. Its molecular structure is given in Figure 1.16. Researchers at the company Ciba Ltd increased the solubility of the molecule by creating it as microfine organic particles, of size <200nm. These are stabilised in a 50% aqueous dispersion by adding the surfactant decyl glucoside (7.5%), the thickener xanthan gum (0.2%) and propylene glycol (0.4%). The particles also act in sunscreens by UV scattering.[198] There have been reports of PACD [203] and ACD [204] to methylene bis-benzotriazolyl tetramethylbutylphenol, as well as ACD to decyl glucoside.[205,206]

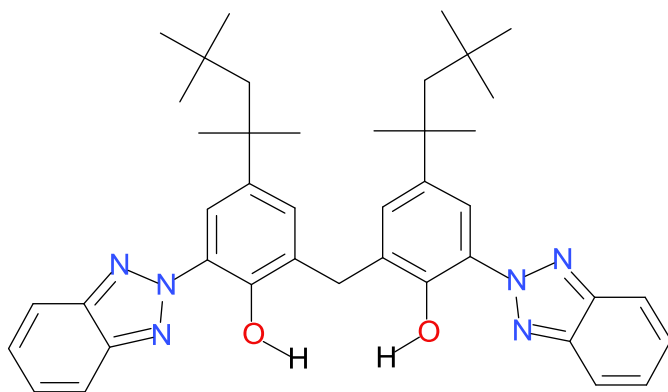


Figure 1.16. The molecular structure of methylene bis-benzotriazolyl tetramethylbutylphenol.

***Bis-ethylhexyloxyphenol methoxyphenyl triazine (Tinosorb S<sup>®</sup>)*** This is an “extended chromophore” which is oil soluble and has absorption peaks at 310nm and 343nm. Its molecular structure is given in Figure 1.17. It is a very effective broad spectrum absorber that has high compatibility with other cosmetic molecules and is inherently photostable.[198] No reports of PACD or ACD to this agent have yet emerged.

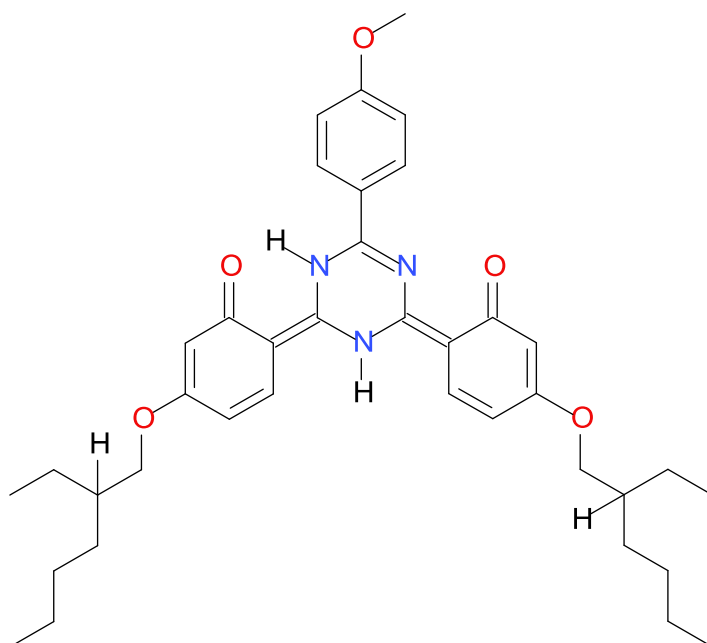


Figure 1.17. The molecular structure of *bis*-ethylhexyloxyphenol methoxyphenyl triazine.

A summary of the reports of PACD and ACD to all the organic UV absorbers discussed above is given in Table 1.3. It can be seen that within the “older” agents, some appear to accrue more reports than others. Although it was not possible to obtain every report of PACD or ACD published over time, the numbers cited *may* suggest there are differing levels of allergenic potential between molecules. It can also be seen that in comparison to the “older” agents, relatively few reports have emerged to the “newer” agents. This is likely to be partly due to the shorter time that they have been used within sunscreens as there is often a “lag phase” between the release of an agent onto the marketplace and the emergence of such reports. However, if the number of reports stays low over time, this may signal that they do indeed have a reduced potential for leading to PACD and ACD.

It should be noted that many of the case reports and studies reviewed here also highlight the importance of testing a subjects own sunscreen “as is” if they present with a history suggestive of possible PACD.[113,123,124,145,147,168,174,193] Such testing is frequently positive and if a clinician can then obtain the individual ingredients, it may be possible to determine which of these (including other non-UV absorbing ingredients, such as preservatives, fragrances and stabilizers) is the culprit photoallergen.[21,157,167,207]

Class of compound	UV absorber (INCI name)	UVA or UVB absorber?	Reports of PACD [Reference number]	Reports of ACD [Reference number]
PABA	* PABA	UVB	[15,160]	[161,162]
PABA ester	Ethylhexyl dimethyl PABA	UVB	[5]	[142,161]
Salicylates	Ethylhexyl salicylate	UVB	[5]	[139,140]
	Homosalate	UVB	[14]	[134]
Cinnamates	Octocrylene	UVB (+UVA)	[153,154]	[155,156]
	Ethylhexyl methoxycinnamate	UVB	[13,144-148]	[142,150]
	Isoamyl- <i>p</i> -methoxycinnamate	UVB	[148,149]	[151]
Benzophenones	Benzophenone-3	UVB (+ UVA)	[113,145,146,168-175]	[123,124,161,172,176-178]
	Benzophenone-4	UVB (+ UVA)	[5,8,11]	[159,183,184]
	* Benzophenone-10	UVB (+ UVA)	[13,18,124,185]	[123,186]
Dibenzoylmethanes	* Isopropyl dibenzoylmethane	UVA	[192,193]	[125,150,187,189,192,194,196]
	Butyl methoxydibenzoylmethane	UVA	[146-148,154,191-193]	[192,194]
Camphor derivatives	4-Methylbenzylidene camphor	UVB	[146]	[125,149,150,187-189]
Miscellaneous	Phenylbenzimidazole sulfonic acid	UVB	[157,158]	[159]
New (polymer backbone)	Polysilicone-15	UVB	NR	NR
New (triple chromophore)	Ethylhexyl triazone	UVB	[20,199]	[20]
	Diethylhexyl butamido triazone	UVB	NR	NR
New (extended chromophore)	Terephthalylidene dicamphor sulfonic acid	UVA	NR	NR
	Diethylamino hydroxybenzoyl hexyl benzoate	UVA	NR	NR
	Disodium phenyl dibenzimidazole tetrasulfonate	UVA	NR	NR
	<i>Bis</i> -ethylhexyloxyphenol methoxyphenyl triazine	UVB + UVA	NR	NR
New (double chromophore)	Methylene <i>bis</i> -benzotriazolyl tetramethylbutylphenol	UVB + UVA	[203]	[204]
New (extended molecule)	Drometrizole trisiloxane	UVB + UVA	NR	[202]

Table 1.3. Reports of PACD and ACD to organic UV absorbers.

(\* = no longer in Annex VII; NR = No report found)

### 1.3.2 Topical NSAIDs

The second largest group of current photoallergens are the topical NSAIDs. Although NSAIDs are administered most commonly via systemic routes, over recent years there has been an increase in the number of topical preparations available and usage of these by individuals. As a result, topical NSAIDs have increasingly come to the attention of dermatologists as a growing cause of PACD.[44] Within Europe, the popularity and usage of topical NSAIDs seems particularly high in the Mediterranean region.[208-210] Preparations are usually in the form of gels which are semi-solid thickened aqueous solutions containing high molecular weight polymers. The gels dry after application, leaving a film of the active ingredient on the surface of the skin. In other instances, NSAIDs are incorporated into adhesive dressings. Both these topical preparations have the proposed advantage of improving symptoms at the local site of application without any associated potential systemic adverse effects, a mechanism supported by some observations.[211]

Like the phenothiazine medications, NSAIDs can elicit phototoxicity, when administered either systemically or topically.[212] However, they can also cause topical PACD and ACD, as illustrated by the references given in Table 1.4. Like organic UV absorbers, NSAIDs can be further sub-divided into different classes. The arylpropionic acid derivatives have been reported as the group responsible for the largest number of ACD and PACD reactions.[208,213] Systemic forms of several agents in this class have been previously removed from the human marketplace for various reasons, often including photosensitivity.[214] Such agents include suprofen and benoxaprofen as well as carprofen, an agent which is discussed in greater detail in Chapter 2.



Class of compound	Topical NSAID	Reports of PACD [Reference number]	Reports of ACD [Reference number]
Arylpropionic acid derivatives	Ketoprofen	[64,68,103,173,213,215-219]	[213,220]
	Ibuprofen	[64,68]	[213,221]
	Tiaprofenic acid*	[103,213,222,223]	[222]
Other NSAIDs	Diclofenac	[103,224]	[213,225-227]
	Etofenamate	[64,68,209]	[209,213,228,229]
	Piroxicam	[64,68,103,213]	[213]
	Indomethacin	[68]	[226,227,230]
	Benzydamine	[68,231,232]	[213,233]

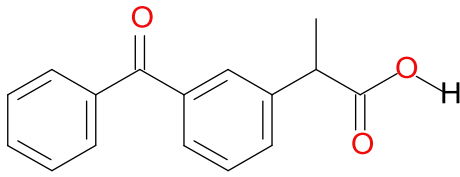
Table 1.4. Reports of PACD and ACD to topical NSAIDs.

(\* Tiaprofenic acid is not available in topical form in Europe[210])

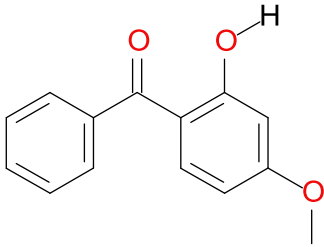
As with organic sunscreens, there appears to be a “hierarchy” of photoallergic potency among NSAIDs, with some agents leading to more reactions than others. Of the agents available within Europe, there has been a gradual accumulation of evidence that ketoprofen may be particularly potent. A large retrospective study from Spain demonstrated that despite being a less commonly sold NSAID, ketoprofen caused by far the greatest number of PACD reactions.[234] Even small quantities of ketoprofen on items of clothing worn again several months after an initial exposure, or contact with a dance partner who has used ketoprofen can be sufficient to elicit PACD.[235,236] As noted earlier in this Chapter, a one hour application of ketoprofen during PPT appears to be sufficient to elicit PACD, which may also be a result of its potency.[119]

When performing PPT, cross reactions between NSAIDs from different classes are not usually found.[208,209,228] However, cross-reactions have been reported between ketoprofen and chemically-related benzophenone moiety-containing

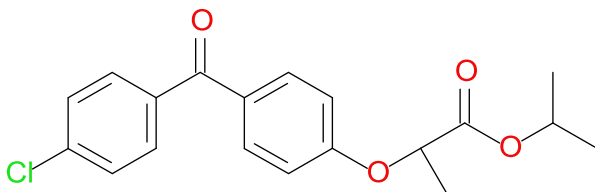
molecules, including the sunscreen benzophenone-3 and the lipid-lowering agent fenofibrate.[68,173,216,218,237] The chemical structural similarity of these molecules can be seen in Figure 1.18. The thiophene-phenylketone structure of the tiaprofenic acid molecule, also seen in Figure 1.18, is similar to the benzophenone moiety and may explain why cross-reactions between this agent and ketoprofen are also commonly reported. [173,208,238] However, cross reactions do not usually occur between these two benzophenone-like arylpropionic acid derivatives and other less structurally similar arylpropionic acid derivatives such as naproxen or ibuprofen.[218,238] Furthermore, cross reactions between ketoprofen and certain fragrance substances, notably the cinnamic derivatives, have also been reported.[210,215,218,239]



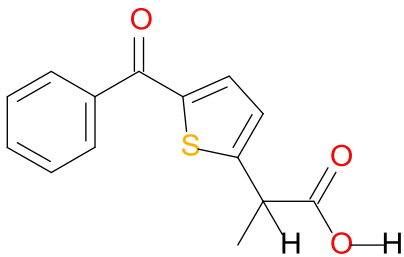
ketoprofen



benzophenone-3



fenofibrate



tiaprofenic acid

Figure 1.18. The molecular structure of ketoprofen, benzophenone-3, fenofibrate and tiaprofenic acid.

### 1.3.3 Photosafety testing of potential photoallergens

When cosmetics and drugs are to be sold on the marketplace, it is clearly important to know in advance whether a molecule could be a potential photoallergen or not. Previously, regulatory authorities have sought to have clinically relevant predictive information available prior to approval of an agent. To obtain this information, various laboratory animal study techniques have been employed, including the guinea pig maximisation test, which was originally developed for investigating ACD in the late 1960s.[240] It was subsequently adapted for photoallergy by several groups. [241,242] In the 1980s, other animal tests such as the murine localised lymph node assay (LLNA) and the murine ear swelling model were introduced and again, adaptations for photoallergy were made.[243-246] However, both these animal tests were acknowledged as unable to sensitively and specifically detect all agents that could lead to PACD in humans.

Currently, the European Medicines Agency (EMA) is the body charged with the regulation of pharmaceutical products across Europe, and provides guidance to industry on the issue of photosafety. The current guideline on requirements for photosafety testing of pre-market and marketed pharmaceutical products came into operation in Europe in December 2002.[247] It advises testing for those chemicals that absorb light between the wavelengths of 290-700 nm and which are topically applied or reach the skin or eyes following systemic exposure. For phototoxicity, the 3T3 Neutral Red Uptake (NRU) *in vitro* test has been validated and officially accepted by European Union (EU) member states. However, photoallergy testing is usually performed using the various guinea pig and murine models noted above, none of which have similar validation. The 2002 guidance states that “Photoallergy testing should be performed according to the state of the art.”[247]

Shortcomings in the 2002 guidelines were recognised and a concept paper was released in 2008 suggesting revisions. However, these revisions were not pursued because the International Conference on Harmonisation subsequently announced it had begun the process of producing a guideline on photosafety testing (S10), and it is likely this would be adopted by EU member states.[248] This guideline may be finalised by June 2013. In the interim, a “Question and Answer” document was adopted by EMA in March 2011.[249] In this document, although there was ongoing ambiguity about the most useful tests for both phototoxicity and photoallergy, it does allow the possibility for testing to be performed in humans for either process if deemed appropriate. It seems this may become a greater possibility, given that the European Commission plans to ban the marketing of cosmetic products that have been tested in animals by 2013.[250] Overall, the present guidance appears to be lacking in clarity and the possibility of photoallergens entering the marketplace seems tangible.

## 1.4 Summary

In summary, PACD has been defined and although probably uncommon, its precise incidence in Europe is not known. Several photoallergens of historical interest have been described, but their relevance in current practice and inclusion within PPT series is now doubtful. The reticence of some clinicians to remove these historical agents from test series has also likely contributed to confusion about the place of PPT as an investigation. The mechanisms behind PACD have been discussed, as have the controversial concepts of the persistent light reactor and systemic photoallergy.

The procedure of PPT and the variables involved have been described. It has been a divergence of methodologies and lack of standardisation between centres that have also contributed to the under-use of PPT as an investigation. The wider adoption of the European consensus methodology should enable meaningful comparison of results between centres and an increase in the appropriate use of PPT.

The two largest groups of current photoallergens, the organic UV absorbers and topical NSAIDs were reviewed. Among the agents in both groups, there does appear to be a hierarchy of photoallergenic potential. The regulation of these agents was also explored and the guidance on photosafety testing for pharmaceutical agents in particular was found to be lacking in clarity.

The following two Chapters describe the investigation of two suspected photoallergens, carprofen and chlorproethazine. The findings serve to highlight the shortcomings of the current regulatory system in Europe in preventing some pharmaceutical photoallergens from reaching the marketplace.

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