REVIEW ARTICLE

Drug Safety 2002; 25 (5): 345-372
0114-5916/02/0005-0345/$25.00/0

Drug-Induced Cutaneous Photosensitivity

Incidence, Mechanism, Prevention and Management

Douglas E. Moore

Faculty of Pharmacy, The University of Sydney, Sydney, New South Wales, Australia

Contents

Abstract

The interaction of sunlight with drug medication leads to photosensitivity responses in susceptible patients, and has the potential to increase the incidence of skin cancer. Adverse photosensitivity responses to drugs occur predominantly as a phototoxic reaction which is more immediate than photoallergy, and can be reversed by withdrawal or substitution of the drug. The bias and inaccuracy of the reporting procedure for these adverse reactions is a consequence of the difficulty in distinguishing between sunburn and a mild drug photosensitivity reaction, together with the patient being able to control the incidence by taking protective action. The drug classes that currently are eliciting a high level of

adverse photosensitivity are the diuretic, antibacterial and nonsteroidal anti-inflammatory drugs (NSAIDs). Photosensitising chemicals usually have a low molecular weight (200 to 500 Daltons) and are planar, tricyclic, or polycyclic configurations, often with heteroatoms in their structures enabling resonance stabilisation. All absorb ultraviolet (UV) and/or visible radiation, a characteristic that is essential for the chemical to be regarded as a photosensitiser. The photochemical and photobiological mechanisms underlying the adverse reactions caused by the more photoactive drugs are mainly free radical in nature, but reactive oxygen species are also involved. Drugs that contain chlorine substituents in their chemical structure, such as hydrochlorthiazide, furosemide and chlorpromazine, exhibit photochemical activity that is traced to the UV-induced dissociation of the chlorine substituent leading to free radical reactions with lipids, proteins and DNA. The photochemical mechanisms for the NSAIDs that contain the 2-aryl propionic acid group involve decarboxylation as the primary step, with subsequent free radical activity. In aerated systems, the reactive excited singlet form of oxygen is produced with high efficiency. This form of oxygen is highly reactive towards lipids and proteins. NSAIDs without the 2-arylpropionic acid group are also photoactive, but with differing mechanisms leading to a less severe biological outcome. In the antibacterial drug class, the tetracyclines, fluoroquinolones and sulfonamides are the most photoactive. Photocontact dermatitis due to topically applied agents interacting with sunlight has been reported for some sunscreen and cosmetic ingredients, as well as local anaesthetic and antiacne agents. Prevention of photosensitivity involves adequate protection from the sun with clothing and sunscreens. In concert with the preponderance of free radical mechanisms involving the photosensitising drugs, some recent studies suggest that diet supplementation with antioxidants may be beneficial in increasing the minimum erythemal UV radiation dose.

1. Solar Radiation and Human Skin

The incidence of skin cancers is doubling almost every decade in countries such as the USA and Australia, where there has been a steady movement of population to the sub-tropical regions of greater insolation. Basal and squamous cell carcinoma are found primarily on older individuals with lighter skin types. While these are easily treated by surgery and are rarely fatal, their cause is directly related to cumulative exposure to sunlight and sunburn incidents, particularly in the formative years.[1-3] Preventative measures are therefore straightforward – the use of protective clothing and sunscreens, and minimising exposure in the middle of the day. The increasing incidence is being addressed by public awareness campaigns with a major effort being directed towards children. Malignant melanoma is a far more deadly type of skin cancer whose occurrence is more complex, being attributed to sunlight exposure as but one factor.[4] Early detection of melanoma by regular examination is the key to reduction of the impact of this cancer.

In view of the relatively widespread occurrence of skin cancers, it is imperative that awareness be raised concerning the interaction of sunlight with drugs and other chemicals in or on human skin. The adverse skin effects that may ensue from the combination of sunlight and some medications are similar to sunburn, and, logically, must be considered as an additional factor contributing ultimately to the initiation of skin cancer. 'Photosensitivity' is

the broad term used to describe a skin eruption that is due to the combined effect of sunlight and a chemical.

1.1 The Sunburn Process

Solar radiation is that portion of the sun's emitted energy spectrum that reaches the surface of the Earth after passage through the atmosphere where the higher energy part is absorbed, principally by nitrogen, oxygen, carbon dioxide and ozone. The resulting average energy spectrum at the earth's surface is shown in figure 1, revealing the cut-off at a wavelength just below 300nm.[5] The cut-off wavelength and the light intensity at a particular location will vary with latitude and the season of the year. This is determined by the angle at which the sun's rays enter the atmosphere. A lower azimuthal angle increases the path-length through the attenuating components in the atmosphere, thereby modifying the extent of absorption.

A number of changes occur in the skin as a result of exposure to the ultraviolet component of sunlight [ultraviolet radiation (UVR)]. These changes must be a manifestation of photochemical reactions following absorption of sunlight by the molecules in the skin, such as membrane proteins and lipids, and the proteins and nucleic acids of the dermal and epidermal cells. The only known beneficial effect of UVR on skin is the conversion of 7-dehydrocholesterol to vitamin D_3 in skin. Vitamin D_3 affects calcium absorption and calcification of bone, such that insufficient solar UVB exposure is reported to cause rickets in children.[6] Note that the amount of UVR required for this necessary photochemical reaction is quite small, and the deficiency is an issue only to populations in the most northerly latitudes in winter. There may well be other beneficial effects of the UV components of sunlight not yet proven or discovered, and some of these may be psychological. Humans have always sought the sun, for heat and clear vision, as well as for the sense of well-being that it brings.[5]

The observable changes to the sunlight-exposed skin are essentially detrimental, and include the following, listed in approximate chronological order of appearance, first for the case of a lengthy exposure:[7,8]

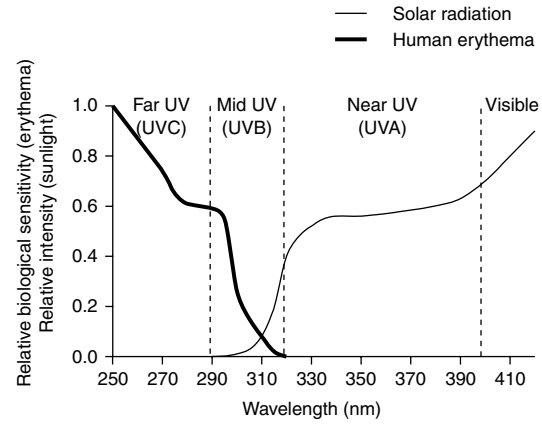

Fig. 1. Average sunlight intensity at the Earth's surface as a function of wavelength and the action spectrum for the induction of erythema in human skin (redrawn from data in Jagger[5]). **UV** = ultraviolet.

- immediate faint erythema (occurs during exposure – disappears quickly);
- delayed erythemal response (sunburn – at 2 to 4 hours, peaks at 14 to 20 hours and persists for 24 to 48 hours);
- histological definition at 24 to 30 hours: abnormal keratinisation, vacuolated cells;
- dead cells form a desquamating layer at 48 to 72 hours;
- desquamation (peeling) begins at 72 to 96 hours.

When the exposure is restricted to approximately the time taken for the first appearance of immediate faint erythema, i.e. the minimum erythema dose (MED), only a mild sunburn may be observed and peeling does not occur. Nonetheless, the following protective responses can be detected:

- thickening of the epidermis;
- darkening of existing pigment (immediate pigment darkening);
- new pigment formation (melanin formation – delayed tanning);

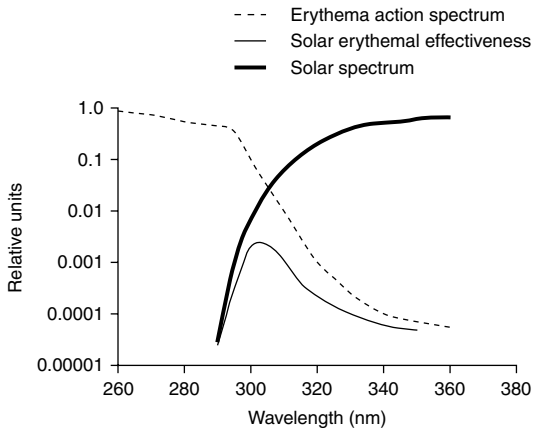

Fig. 2. Erythema effectiveness spectrum as a resultant of the overlap of the sunlight ultraviolet spectrum and the human erythema action spectrum (redrawn from data in Parrish et al.[7])

- proliferative and other changes in epidermal cells;
- suppression of T lymphocytes.

Even though the latter group of effects listed above are protective in nature, the accumulation of sunlight exposure over a number of years will lead to permanent damage, evident in the formation of:[9]

- actinic elastosis (premature skin aging);
- actinic keratosis, a precancerous condition; and
- squamous cell cancers, basal cell cancers, and probably some malignant melanomas.

The changes in the skin as a result of sunlight-induced reactions can be viewed by histological examination.[8] The biological markers include the increase in melanin and a decrease in the number of Langerhans cells, which are macrophage-like cells of the epidermis. There is also an increase in the activity of the inducible enzyme ornithine decarboxylase, which is the rate-limiting enzyme in the polyamine biosynthetic pathway. Its up- or down-regulation is rapidly reflected in an alteration in the ornithine-putrescine ratio (turnover time of 10 to 20 minutes), making it a marker for the carcinogenic properties of UVR.[10]

The action spectrum for the induction of erythema in human skin – determined with the use of artificial UV sources – shows that the greatest effect occurs with wavelengths less than 300nm (figure 1). Since the solar spectrum only begins at about 300nm, there is only a very small overlap between the two crucial components (as shown in figure 1). The resultant of the overlap, shown in an expanded form in figure 2, is called the 'solar erythemal effectiveness spectrum'.[7] From this overlap, the maximum interaction between sunlight and human skin occurs for the wavelength range of 300 to 308nm (depending on the season). The consequence is the division of UVR into three distinct regions – UVA (or near-UV) covers the range 400 to 320nm; UVB (the sunburn region) is defined as 320 to 280nm; UVC (or far-UV) is the 280 to 200nm region only accessible with artificial radiation sources (such as germicidal lamps). The effect of depletion of the ozone layer in the upper atmosphere would be manifest as an increase of intensity in the shorter wavelength side of the sunburn region, leading to a larger overlap area and more sunburn response. The depletion or 'ozone hole' is occurring mainly in the Antarctic region, and as yet is not a major issue in the temperate and sub-tropical zones.[11,12]

The depth of penetration of UVR into human skin is determined by the presence of absorbing molecules in the outer layers. Light in the red region of the visible spectrum (750nm) has the greatest penetration, reaching well into the subcutis layer, while at 300nm, only 10% of the incident UVR passes through the epidermis of Caucasian skin.[8] The epidermis contains living cells, so that proteins and nucleic acids are exposed to small amounts of UVR. While the absorption spectra of these biomolecules are recorded as being maximal at 280 and 260nm, respectively, there is residual absorption through the UVB region whereby the photochemical activation can occur leading to the initiation of the sunburn process.

1.2 Photochemical Initiation of Chemical Change in the Skin

A photon corresponding to the ultraviolet wavelength 300nm has energy of about 400 kJ/mol, which is of comparable magnitude to the bonding energy of organic compounds. The fact that a molecule absorbs radiation in the ultraviolet or visible region of the electromagnetic spectrum means that it is absorbing energy that is sufficient to break a bond in the molecule. Thus the property of absorption is a first indication that the molecule *may* be capable of participating in a photochemical process leading to its own decomposition or that of other components of the formulation. The statement is a qualified one because there are a number of processes that may occur following absorption of UV or visible light, some of which lead to no net change to the absorbing molecule or the system. The photochemical reaction must follow the basic law of photochemical absorption, established by Grotthus and Draper in 1818, that no photochemical (or subsequent photobiological) reaction can occur unless electromagnetic radiation is absorbed. The absorption spectrum of a compound is therefore an immediate way of determining the wavelength range to which the molecule may be sensitive.

In addition to the naturally occurring skin cell constituents, other chemical substances with UVR-absorbing properties may be present in or on the skin, with the potential to initiate photochemical processes. Examples of photoactive substances encountered topically are coal tar ingredients, such as anthracene, and the psoralens, which are plant natural products. Fifty years ago, it was a common practice to treat certain skin eruptions topically with such compounds in association with exposure to sunlight.[7] Nowadays, the approach has been modified to involve systemic administration, specifically of methoxsalen (8-methoxypsoralen), followed by UVA. However, the treatment must be carefully monitored, as numerous cases of skin cancer have been associated with this so-called PUVA regimen. Photocarcinogenicity is due to the formation of mutagenic psoralen-DNA adducts by a photosensitised interaction in which the psoralen is the absorbing species.[7] In PUVA the photosensitivity response is a desired effect, so long as it is not taken too far. With other drug substances, photosensitivity is an adverse response.

1.3 Adverse Photosensitivity Responses

The World Health Organization definition of an adverse drug reaction (ADR) has been in use for about 30 years, describing an ADR as 'a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function'. Because of some debate over the vagueness of the word 'noxious' a modified definition has been proposed recently.[13] Thus, an ADR is 'an appreciably harmful or unpleasant reaction related to the use of a medicinal product, such that hazard is predicted with future administration, thereby warranting specific treatment, alteration of the dosage regimen, or withdrawal of the product'.

The adverse cutaneous photosensitivity reaction, arising from a combination of the administration of certain drugs and sunlight exposure, falls clearly within this definition. The patient's response is manifest through the biochemical changes occurring in the tissue subsequent to an exogenous substance absorbing sunlight as the first step. The process is termed 'photosensitisation' and the initiator is the 'photosensitiser', a term that may embrace a wide range of compounds. It is a process that is additional to that which initiates the so-called normal pathological response to sunlight, i.e. sunburn. The photosensitiser may originate in the natural environment (e.g. from plants, coal tar, etc.) or from contact with cosmetics, insecticides, paints, sunscreens, etc. The ingestion of food and drugs represents the principal pathway of systemic introduction of photosensitisers to animals and humans. There are, in addition, several disease conditions in which photosensitisers are released into the general circulation. These include the idiopathic photoderma-

toses, such as polymorphic light eruption, and systemic metabolic disorders, as in the porphyrias, as well as the genetic syndromes, such as xeroderma pigmentosum.[14,15]

Although the focus of this review is on those drugs and chemicals that can induce undesired photosensitivity responses, it should be understood that in some special cases a benefit can be gained from the photoreaction.[16] The dominant examples in regular use are the application of blue light irradiation to counteract neonatal jaundice or hyperbilirubinaemia, and methoxsalen plus 365nm UV radiation as a treatment for psoriasis. Still in the experimental development stage is photodynamic therapy (PDT) for a number of serious conditions including various cancers.[17] In this procedure, a photosensitising chemical, usually haematoporphyrin derivative, is administered to the patient who is then selectively irradiated at the site of the lesion. One of the risk factors associated with this type of PDT using systemic photosensitisers is the fact that the patient remains liable to photosensitivity from room lighting and other sources until the sensitiser is eliminated from the body. PDT is now being performed in dermatological treatments with the topical application of aminolevulinic acid on the lesions (in which case the systemic photosensitivity is not a problem for the patients). Aminolevulinic acid is converted *in situ* via the heme biosynthetic pathway into the photosensitiser protoporphyrin IX. To date, aminolevulinic acid–PDT has been used primarily for the treatment of actinic keratoses.

To highlight another source of photosensitising substances, there are a number of plants that contain irritant substances causing an inflammatory response after contact with the skin. Some of these responses may be identified as phytophotodermatitis in that exposure to sunlight is a necessary component of the stimulation. The eruptions are characterised by erythema, pruritus, vesiculation and subsequent hyperpigmentation, 1 to 2 days after contact with the plant and sun exposure. The most common plant families involved are the Apiaceae, Rutaceae and Moraceae, which contain furocoumarins as the phototoxic substances (e.g. psoralen, methoxsalen and 5-methoxypsoralen).[18] In the last 10 years, increasing attention has been directed to alternative therapies involving plant and herbal remedies arising from traditional use in both the Western and Eastern Hemispheres. The most relevant of these in relation to human photosensitivity is the herb *Hypericum perforatum*, commonly known as St John's wort. This herb has raised widespread interest as a treatment for mild depression, but contains the chemical hypericin, a very active photosensitiser *in vitro* and a candidate compound for application in PDT of cancers and photodeactivation of the human immunodeficiency virus.[19]

The undesired photosensitivity responses occur in some people who either ingest the photosensitising agents or apply them topically, and then experience sunlight exposure of their skin in the course of their daily activities. The same drugs are generally regarded as innocuous to skin in the absence of exposure to sunlight. However, certain individuals may experience skin reaction or sensitivity not involving sunlight, rendering difficult a clear diagnosis.

1.4 Clinical Presentation of the Photosensitivity Reaction

Photosensitivity is a general term that describes either the common phototoxic response or the much less frequent photoallergic reaction. While a differentiation between these two types of photosensitivity reactions may be difficult, some principles have been established, based on observation at the clinical presentation.

A phototoxic reaction is essentially immediate and resembles an exaggerated sunburn. The eruptions occur on exposed skin areas, giving a clear delineation of shading caused by clothing. Three general types of phototoxic response have been differentiated, primarily from studies on those agents that have been tested for therapeutic applications:[15,20]

- A strong delayed erythema and oedema with its onset 8 to 24 hours after sun exposure, and last-

ing 2 to 4 days. It may involve hyperpigmentation and be darker red than sunburn, this being typically caused by psoralens.

- A more rapid, transient erythema with an immediate onset (30 minutes), lasting 1 to 2 days. There is no oedema, but localised burning and itching are evident. This type of response is associated with demeclocycline and the coal tar derivatives, such as anthracene and acridine.
- Rapid, transient wheals and flares with a burning sensation. While this type subsides quicker, it is characteristically caused by porphyrins, e.g. haematoporphyrin, which are activated by room lighting.

All phototoxic responses will be dependent on the dose of photosensitiser and the intensity of sunlight experienced. In comparison, a photoallergic reaction has an immunological basis and requires previous exposure to the photosensitising agent. Patients who experience photoallergic responses may present 1 to 14 days after exposure to sunlight with papulovesicular eruption, pruritus, and eczematous dermatitis. Photoallergy represents an acquired altered reactivity either due to an antigen antibody (immediate) or a cell-mediated (delayed) hypersensitivity process.[15]

Cases of drug-induced photosensitivity are frequently diagnosed without specific investigations, if the onset can be traced to the start of a course of therapy with a drug of known photoactivity. When confirmation is needed to exclude dermatitis conditions that appear similar, phototesting with a solar simulator provides the most useful information.[14] This is usually done on a number of shielded and unshielded areas on the upper back of the patient, with epicutaneous administration of the suspected agent. The aim is to determine whether the minimal erythemal dose (exposure to UVR leading to the first faint reddening of the skin) is reduced in the presence of the agent, and to eliminate other dermatological events. Photopatch testing is indicated for the evaluation of photoallergy, with the end-point being the development of vesicles and/or papules. The occurrence of false negatives in photopatch testing of systemic drugs often renders difficult the correct identification of the agent responsible for the photosensitivity.

2. Literature on the Incidence of Drug Photosensitivity

The information on photosensitising drugs is collected by the various national reporting systems for adverse drug reactions. This is usually a voluntary reporting procedure involving physicians, pharmacists and pharmaceutical companies. The major computerised systems include the WHO Programme for International Drug Monitoring database, the database of the UK's 'yellow card' system administered by the Committee on Safety of Medicines/Medicines Control Agency, and the databases of the US Food and Drug Administration.[13]

In his 1976 book,[21] Magnus listed the drugs known at that time to be photosensitisers, but also made the observation that the voluntary reporting procedures for drug-related photosensitivity, as for any drug-induced adverse effect, are biased and inaccurate. The bias enters because a physician or pharmacist is more likely to notice a reaction to a newly marketed drug and then report the incident to the appropriate body (the 'bandwagon effect'). On the other hand, a drug that has been in use for a longer period of time with some adverse reactions already reported, gains the photosensitiser tag, and is less likely to have further reactions reported. The inaccuracy in reporting arises, for example, when the reporter does not appreciate that a photosensitiser should have an absorption spectrum in the sunlight range. In one noteworthy incident, a patient receiving diuretic therapy displayed a photosensitivity response, so the non-UV-absorbing potassium chloride supplement was nominated by the reporter as the cause, rather than the actual diuretic agent hydrochlorothiazide. The true culprit should be obvious to those with some knowledge of chemical structure and UV spectrophotometry. While the voluntary reporting services are simple and cheap to administer, they contribute to significant under-reporting.[13] This is

more likely to be the case for photosensitivity, which can be readily confused with normal sunburn, and is more easily controlled by the patient taking protective actions.

The publication of collections of data from the adverse reaction reporting agencies is very limited on the subject of drug-induced photosensitivity. In the main, the bulletins from these agencies tend to concentrate on monitoring the recently released drugs for severe effects. Photosensitivity has been considered a minor (and preventable) adverse effect in comparison with, for example, liver damage and gastrointestinal bleeding, and is rarely addressed as an issue by the drug regulatory agencies. For example, the most recent summaries on the subject of drug-induced photosensitivity from the Adverse Drug Reaction Advisory Committee of the Australian Therapeutic Goods Administration were in 1983 and 1987.[22] This is remarkably infrequent in a country with a large proportion of the population having a fair skinned complexion living in sub-tropical areas of high insolation.

As a consequence of the low level of reporting, much of the information on drug-induced photosensitivity reactions has to be found by direct scanning of the medical literature, where case reports for individual drugs are given. Several authors have compared the severity of the photosensitivity reactions induced by the members of various therapeutic classes, such as antipsychotics, antidepressants and anxiolytics,[23] antibacterials[24] and nonsteroidal anti-inflammatory drugs (NSAIDs).[25] A compendium of all adverse drug reactions, Meyler's Side effects of Drugs, appears every four years (with annual updates), the latest edition being in 2000.[26] This encyclopaedic work lists the occurrence of reports over the 4-year period, with the relevant index headings of 'Photoallergy', 'Photodermatitis', 'Photosensitivity' and 'Phototoxicity'.

In the current context, a more focussed compendium is the Drug Eruption Reference Manual, which is regularly updated, and its companion guide for pharmacists.[27] This is a cumulative listing for each therapeutic substance of the associated primary reports of all skin and hair effects. A total of 268 drugs have 'photosensitivity' recorded against them. With this excellent source-book one is able to gain a perspective on the incidence of photosensitivity in relation to other dermatological responses. In many cases, photosensitivity represents only a small percentage of the overall skin effects, although the possibility should be considered that sunlight exposure is a contributing factor to many skin eruptions. Generally, the specific type of photosensitivity reaction is not described in the reports, but it is a reasonable assumption that phototoxicity is involved in the majority of cases.

3. Major Classes of Photosensitising Drugs

A listing of drugs that have been more frequently reported to give rise to some form of photosensitivity response is given in table I. Only the generic names of the drugs have been used. The list includes a wide range of disparate substances, including sulfonamides, tetracyclines, quinolones, sulfonylureas, thiazides, phenothiazines, furocoumarins and NSAIDs. Photosensitising chemicals usually have a low molecular weight (200 to 500 Daltons) and are planar, tricyclic, or polycyclic configurations, often with heteroatoms in their structures enabling resonance stabilisation. All absorb ultraviolet and/or visible radiation, a characteristic that has to be regarded as essential for the chemical to be regarded as a photosensitiser.

Because of the inherent bias and inaccuracy of reporting referred to above, only a generalised approach has been made to quantify the incidence level. Not all of the drugs listed in the Drug Eruption Reference Manual have been included in table I. However, within each drug category, an attempt has been made to list the drugs most frequently cited at the head of the group. One of the factors that obviously has a bearing on the incidence of reports is the extent to which the drug is prescribed. Many of the older drugs listed have been supplanted by newer therapeutic regimes. Historically, it was the sulfonamides that were reported in the first photosensitivity reactions in the

Table I. Drugs in current use reported to cause photosensitivity responses[a]

Diuretic agents	**Antimalarials**
Hydrochlorothiazide, furosemide (frusemide)	Chloroquine
Chlorothiazide	Quinine, pyrimethamine
Bendroflumethiazide, benzthiazide, cyclothiazide	Mefloquine
Hydroflumethiazide, methyclothiazide	**Antidepressants**
Trichlormethiazide, polythiazide	Amitriptyline, trimipramine
Amiloride, ethacrynic acid	Nortriptyline, protriptyline, desipramine
Triamterene, spironolactone	Amoxapine, imipramine, doxepin
Acetazolamide, metolazone, quinethazone	**Cardiovascular drugs**
Nonsteroidal anti-inflammatory drugs	Amiodarone, nifedipine
Naproxen, ketoprofen	Quinidine, captopril, enalapril
Suprofen, tiaprofenic acid	Fosinopril, ramipril, disopyramide
Piroxicam, diflunisal	Hydralazine, clofibrate, simvastatin
Diclofenac, mefenamic acid, nabumetone	**Hypoglycaemics**
Sulindac, phenylbutazone	Glibenclamide (glyburide), tolbutamide, glipizide
Indomethacin, ibuprofen	Tolazamide, chlorpropamide
Antipsychotic drugs	Acetohexamide
Chlorpromazine	**Anticonvulsants**
Trifluoperazine, prochlorperazine, thioridazine	Carbamazepine, lamotrigine
Chlorprothixene, promethazine	Phenobarbital (phenobarbitone), phenytoin
Perphenazine, fluphenazine, promazine	**Antihistamines**
Haloperidol, thiothixene	Cyproheptadine
Triflupromazine, trimeprazine	Diphenhydramine, brompheniramine, triprolidine
Antimicrobials	Loratadine
Demeclocycline, nalidixic acid	**Cytotoxic drugs**
Sulfamethoxazole, sulfasalazine	Fluorouracil, vinblastine
Ciprofloxacin, enoxacin, lomefloxacin	Dacarbazine, procarbazine
Ofloxacin, norfloxacin	Methotrexate
Oxytetracycline, tetracycline	**Hormones**
Doxycycline, methacycline, minocycline	Corticosteroids, estrogens, progesterones
Trimethoprim, isoniazid	Spironolactone
Sulfamethizole, gentamicin, clofazimine	**Systemic dermatological agents**
Griseofulvin, nitrofurantoin	Isotretinoin, methoxsalen
	Others
	Gold salts, azathioprine, haematoporphyrin

a Listed by therapeutic class and generic name. The drugs are listed within each grouping in approximate order of frequency of incidence of reports; drugs of equal ranking are listed on the same line.

1940s, while the tetracycline group members were frequently implicated after their introduction in the 1950s.[21] These two groups of compounds contain a large number of individual compounds, many of which are no longer in use therapeutically, and are not included in current listings.

There is also no certainty that all of the drugs reported are indeed photosensitisers. Rigorous proof could only be obtained by photopatch testing of each substance with a solar simulator on healthy individuals. Another important question relates particularly to a number of drugs listed in table I, for example, ibuprofen and the hormonal contraceptives, which do not have absorption spectra that extend into the critical sunlight UVB region. From a photochemical viewpoint, it appears impossible

for these compounds to initiate a photobiological reaction. However, a recent report has associated photosensitivity reactions with the use of the combined oral contraceptive,[28] to reinforce the observations from the 1960s. Thus, the hormonal contraceptives by altering the hormone levels are presumed to alter a person's susceptibility to sunburn, rather than acting as the absorbing molecule in a photochemical process. It is possible that a metabolic conversion could change the absorption characteristics of the molecule to give rise to an extension into the sunlight region. The participation of metabolic conversion has been hypothesised as a component of the mechanism of photosensitivity caused by chlorpromazine[29] and piroxicam[30] (see sections 4.2 and 4.4.2, respectively).

Overall, several trends can be identified. In a qualitative sense, the sulfonamide and tetracycline antibacterials and the phenothiazine-based tranquillising drugs, such as chlorpromazine, are the dominant photosensitisers from the 1950s and 1960s, while three therapeutic groups stand out in the modern era, namely, the diuretic, the anti-inflammatory and the fluoroquinolone antibacterial drugs. one obvious factor that has determined the frequency of reports is the proliferation of new drugs in these categories – the reporting 'peak' occurs in the first 3 years after the introduction of a drug. In addition, the 'greying' of the population has naturally resulted in increased usage of drugs in the diuretic and anti-inflammatory groups for the treatment of hypertension and arthritis. Despite the general indifference to reporting photosensitivity effects, this increasing incidence needs to be monitored and, where possible, the substitution of drugs with a lower propensity to photosensitivity reactions should become a matter of course.

In relation to the key question of whether photosensitising drugs can initiate skin cancer, some pertinent observations are:

- Repeated phototoxic injury caused by drug administration and UVA exposure leads to skin cancer in experimental animals.[31,32]
- PUVA treatment (psoralens +UVA radiation) for psoriasis can cause skin cancer with prolonged use.[33]
- Immunosuppressive therapy with azathioprine is associated with a high skin cancer incidence in renal transplant recipients. Even though the patient's immune system is compromised by the drug treatment, the photosensitivity effect of azathioprine was unequivocally established when cyclosporin was substituted and the incidence of skin cancer diminished markedly.[34]
- Several cases of basal cell carcinoma have been reported in patients receiving long-term treatment with amiodarone for cardiac dysrhythmia.[35]

For the general population, this evidence suggests that phototoxic reactions to drugs have the potential to increase the already high risk of skin cancer from sunburn.

4. Photosensitising Mechanisms

A better understanding of the molecular mechanisms involved in photosensitivity effects will enable the choice of drugs with low photoactivity for sensitive individuals. Additionally, this knowledge will aid the new drug development process by providing the means to assess the potential of a new compound to provoke these adverse effects. As can be seen from table I, the list of phototoxic drugs shows a diverse range of pharmacological activities, and widely differing chemical structures. Thus far, it has not been possible to establish a satisfactory relationship between the chemical structure and photobiological activity for more than a closely related group of drugs.[36-38] Such a structure-activity study would take into account the following properties:

1. Photophysics and photochemistry of the drug (chemical and spectroscopic evidence for the production of highly reactive intermediates upon irradiation; photodegradation pathways in polar and non-polar media).
2. Photochemical interaction of the drug with cellular macromolecules (lipids, proteins, DNA, and their respective building blocks) and circulating

protector molecules (glutathione, tocopherols, coenzyme Q_{10}, etc.).
3. Photosensitised damage caused by irradiation of the drug with bacterial cells, viruses and UVR-resistant cell lines.
4. The ability to induce skin cancers in animal models, such as the hairless mouse, after administration of the drug followed by irradiation with UVR.

In order that the processes (1) to (4) are to be accepted as a validated screening program, it will be necessary that the results for a representative sample of drugs be correlated successfully with a controlled clinical study by objective phototesting using healthy volunteers. Even then, idiosyncratic responses will pass undetected, so that good post-marketing surveillance remains essential.

4.1 Primary Photophysical Mechanisms

In general, the initiation of an adverse photosensitivity response can be postulated to involve one or more of the pathways shown in figure 3.[39] The elucidation of the specific pathways relevant to a particular drug can be achieved by the experiments broadly described under (1) and (2) above.

Any UVR or visible light induced process begins with the excitation of drug molecules or sensitisers from their ground state (D_o) to reactive excited states, by absorption of photons of wavelengths corresponding to the energy separation between the ground and excited states. Upon absorption of radiation, the drug molecule, D_0, in the ground state (in which the valence electrons are paired or antiparallel – a spin singlet state) is raised to a higher energy level, as a valence electron moves to the first available outer shell corresponding to the first excited singlet state ^1D (the electron spins remain antiparallel). When the absorption spectrum shows more than one absorption band, it indicates a corresponding number of excited states which can be reached by irradiation with the appropriate excitation wavelength.

The molecule cannot persist in an excited state indefinitely since it represents a situation that is less stable with respect to the ground state. There are a variety of competing physical processes involving energy dissipation and resulting in deactivation of the excited states. The energy dissipation may be via either internal conversion (IC), which is a non-radiative transition between states of like multiplicity, or via photon emission (fluorescence) resulting in return to D_0. Even if excitation occurs to an excited state higher than the first, IC will always bring the molecule to the ^1D level (within a picosecond) before fluorescence occurs. Thus the fluorescence emission wavelength is the same, irrespective of the irradiating wavelength. Any excess energy within a particular electronic state is dissipated as heat by collision with neighbouring molecules. This is referred to as vibrational relaxation. As the lifetime of the excited singlet state of a molecule is generally of the order of nanoseconds (but up to microseconds for rigid molecular structures), the possibility of interaction with neighbouring molecules leading to chemical change is limited at this stage. However, in the excited singlet state, the ionisation potential of the molecule is reduced, and the excited electron is more easily removed than it is from the ground state molecule, but requires that an appropriate acceptor be present. This process of photoionisation is also more likely to occur if higher energy UVR is used (i.e. wavelengths less than 300nm) and if the molecule is in the anionic state. Alternatively, intersystem crossing (ISC) may occur from the excited singlet state to a metastable excited triplet state ^3D (electron spins parallel). Despite the low probability in general for transfer between states of differing multiplicity, ISC occurs with relatively high efficiency for most photochemically active molecules. The excited triplet state, because of its longer lifetime (normally microseconds to milliseconds, but for certain molecules much longer), may diffuse a significant distance in fluid media and therefore has a much higher probability of interaction with other molecules. If no interaction occurs, it decays back to the ground state by a further ISC event, or by phosphorescence emission.

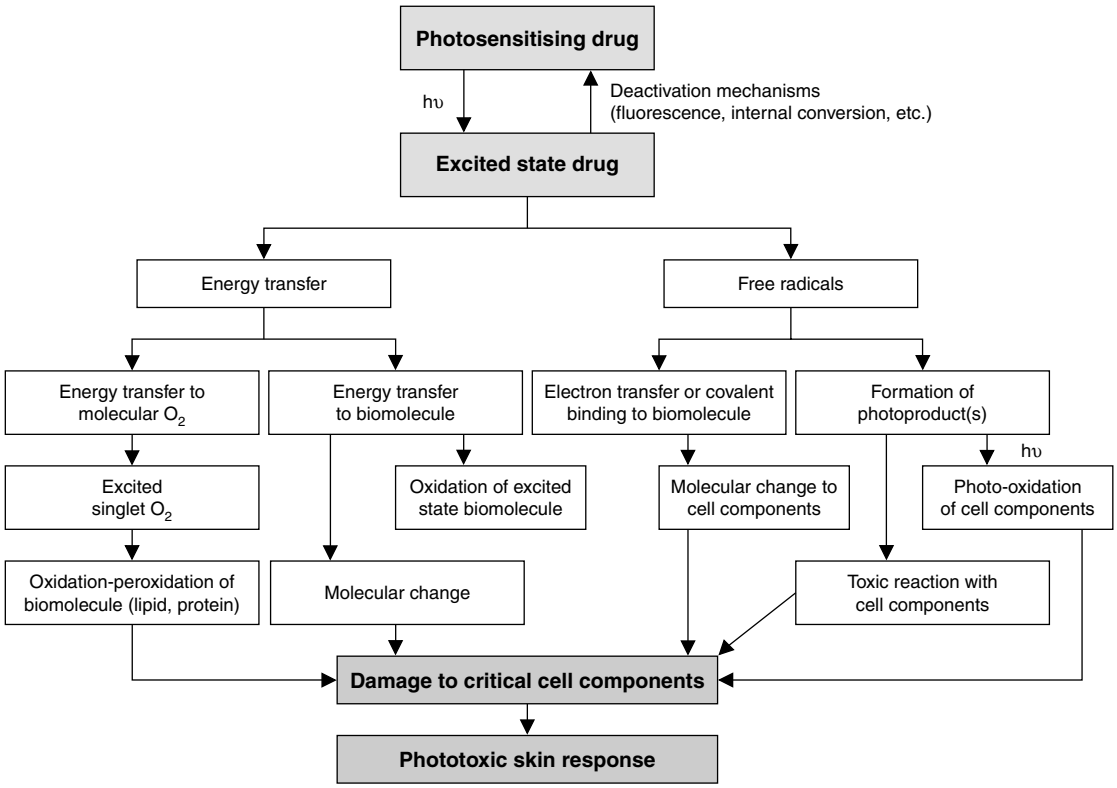

Fig. 3. Schematic representation of the pathways by which photosensitising drugs may produce a phototoxic skin response. **h**υ = light energy.

The nature of the excited state decay processes is studied by the technique of laser flash photolysis,[40] which involves irradiating a sample with a short (nanosecond) intense pulse from a laser, then observing by rapid response spectrophotometry the subsequent spectral changes that occur on the time scale of nanoseconds to milliseconds. Several standard tests have been established to aid in the identification of the transient species, which can be the drug triplet state, and/or cation radical with solvated electron generated by photoionisation. The efficiency, or quantum yield, of each of the excited state decay processes, is defined as the fraction of the molecules, excited by absorption, which then undergo that particular mechanism of deactivation. Knowledge of the excited state processes is important to gaining an understanding of the possible pathways of the photochemical and biological processes.

From figure 3 it can be seen that there are two major photochemical pathways, involving either the excited triplet state or free radical entities. The free radicals are derived from the excited state drug by photoionisation (yielding a cation radical and solvated electron) or by bond dissociation (direct cleavage of the least stable covalent bond of the molecule). The relative yield of each process is dictated to some extent by the solvent – generally, aqueous systems are required to support photoionisation, whereas bond dissociation occurs in less polar solvents. The pathways have been classified as photodynamic when they are oxygen de-

pendent, or non-photodynamic when oxygen is not required for the effect.[41] Free radical and singlet oxygen generation by photoexcited drug molecules appear to be the principal intermediate species in the processes.[42] Since the primary event in any photosensitisation process is the absorption of a photon, a critical property of the photosensitising drug is its absorption spectrum, and the extent of overlap of that spectrum with the sunlight spectrum. The overlap spectrum is synonymous with the action spectrum for the compound, as was explained for the sunburn erythemal effectiveness in figure 2. As with sunburn, the potential for increase in exposure at the shorter wavelength end of the sunlight spectrum (<300nm) with decrease in the level of stratospheric ozone protection is a cause for concern with photosensitising drugs unless adequate protection measures are adopted.

As an example, the sulfonamide antibacterial drug sulfamethoxazole has an absorption spectrum (figure 4) which is maximal at around 270nm, but extends through the UVB region. Also shown in figure 4 is the overlap of the sunlight spectrum in midsummer and midwinter at latitude 33°S. Because the overlap occurs on the steeply rising side of the sulfamethoxazole absorption, the difference between summer and winter is substantial, and emphasises the effect of different path lengths through the ozone layer. Thus continuing ozone depletion will move the sunlight curves to slightly lower wavelength and dramatically increase the interaction with drugs such as sulfamethoxazole. The particular sensitivity of sulfamethoxazole to sunlight at the UVB cut-off has been investigated, with the conclusion that this drug could be used in an actinometer system to monitor the changing intensity of this important region.[43] Sulfamethoxazole degrades under the action of UVB radiation, via a free radical mechanism that is clearly relevant to the photosensitivity associated with this drug.

In the following sections, some examples have been selected from the major classes of photosensitising drugs (diuretic, antibacterial and anti-inflammatory agents), and the information

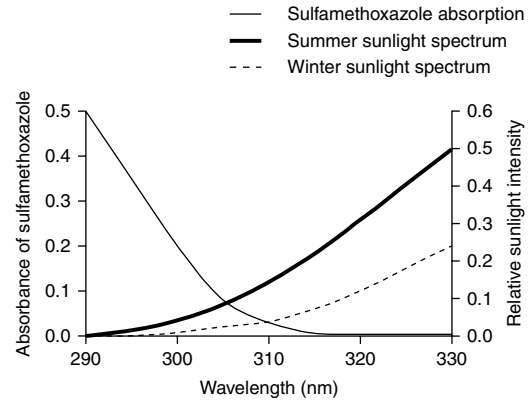

Fig. 4. Sulfamethoxazole absorption spectrum showing overlap with sunlight spectrum in summer and winter at latitude 33°S.

that has been gleaned concerning the photochemical basis for their action is presented.

4.2 Photochemical Mechanisms – Chlorine Containing Drugs

It is no coincidence that many of the most photoactive drugs as shown in figure 5, have the common feature of an aromatic chlorine substituent. The key pathways of their photochemical action can be traced to dissociation of this bond. Hydrochlorothiazide and furosemide (frusemide) are widely used diuretic agents, and the most reported of this therapeutic class in regard to photosensitivity. Hydrochlorothiazide can be used alone but is mostly co-formulated with a potassium-sparing agent such as amiloride or triamterene to yield a better-balanced diuretic effect. It is the combination formulation of (hydrochlorothiazide plus amiloride) that has headed the most recent list of photosensitivity reports in Australia.[22] Chlorpromazine is the archetype of photosensitising drugs, being recognised as such soon after its introduction in the 1950s. It remains as the benchmark against which others can be compared.

The intermediate processes of photoionisation and bond dissociation have been reported to occur in the irradiation of a number of different chlorine-containing drugs, such as chlorpromazine,[44] hy-

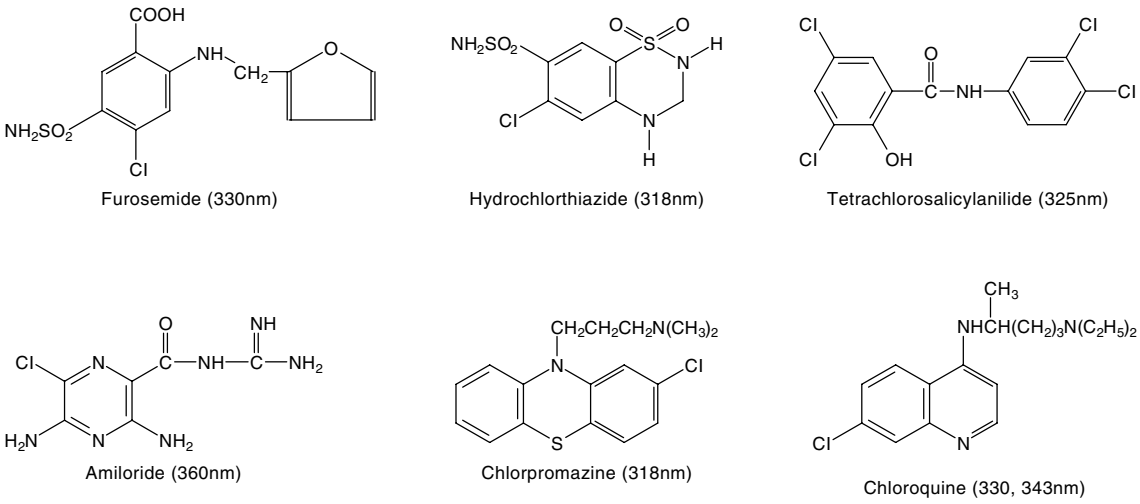

Fig. 5. Chemical structures of photoactive drugs containing chlorine substituents. The wavelength values in parentheses refer to the maximum absorbance in the ultraviolet (UV) A or UVB region.

drochlorothiazide,[45] chloroquine,[46] furosemide,[47] diclofenac [48] and amiloride.[49] In each case, when the drug (designated as Aryl-Cl) is photolysed in aqueous or alcoholic (ROH) solution, HCl is liberated and a mixture of reduction (Aryl-H) and substitution (Aryl-OR) products is obtained. The photodechlorination occurs for these compounds more strongly in de-oxygenated solution. When oxygen is present, it promotes ISC to the triplet state and the production of singlet oxygen (see section 4.1).

The mechanism is by no means completely clear, but the photodehalogenation reaction is postulated to occur through the formation of a pair of radical ions from an exciplex resulting in the excited state.[50] The precursor of the reduction product (Aryl-H) is suggested to be a radical anion ($Aryl\text{-}Cl^{-}$) while a radical cation ($Aryl\text{-}Cl^{+}$) is postulated as the precursor of the substitution product (Aryl-OR). In a less polar solvent, e.g. 2-propanol, direct homolysis of the C-Cl bond occurring from the triplet state has been suggested based on flash photolysis experiments with chlorpromazine.[44] 3,3′,4′,5-Tetrachloro-salicylanilide represents a class of antibacterial agents formerly used in cosmetics and soaps. These compounds were found to undergo sequential photodehalogenation, which was presumed to be related to their capacity to induce skin rashes upon sunlight exposure.[51]

Not all chloroaromatic drugs appear to follow this type of reaction. For example, free chloride ion is not formed on irradiation of chlordiazepoxide for which an oxaziridine is the major photoproduct.[52] There is a variability among reports on other drugs which contain chlorine substituents. This can arise due to differences in the irradiation conditions. If an unfiltered mercury arc source is used, the sample will receive higher energy UVC irradiation and the C-Cl bond will certainly break, while under longer wavelength irradiation (>300nm) the bond may be stable.

All of the chlorine-containing drugs that undergo photodechlorination figure strongly in the list of photosensitisers, leading to the implication that the free radicals play a major role in initiating the adverse response. A considerable amount of work has been done to demonstrate the photoreactivity of chlorpromazine and related phenothiazines, in the presence of biological substrates.[53] The phenothiazine drugs can form

molecular complexes *in vitro* with DNA, by intercalation between two adjacent base pairs, and then achieve an irreversible binding upon irradiation with UVR. When experiments were performed with rats, however, it was found that irradiation produced a greater amount of binding of chlorpromazine to lipids and proteins, with little binding to DNA that could initiate mutagenesis. A photoinduced reaction with a protein is clearly important to the development of photoallergic responses that are presumed to occur through formation of a hapten via change in a protein's structure and properties.

Another observation was that photobinding of chlorpromazine *in vivo* can be induced by long wavelength UVA (320 to 380nm) rather than at its maximum absorption of 310nm. This has been attributed to the possibility referred to above, that it is the metabolite chlorpromazine sulfoxide (absorption maximum 345nm) that is responsible for the initiation.[29]

4.3 Biological Acceptors for Photodynamic Action

Amongst the macromolecules that make up the normal cell, most have been shown to be susceptible to oxidative degradation of the type occurring in photodynamic action. Membrane lipids are the most readily oxidised since they can react at their unsaturated sites through both free radical (type I) and singlet oxygen (type II) mediated processes. While there is a difference in the nature of the oxidation products resulting from the two mechanisms, the net effect is a splitting of the lipid molecule into shorter fatty acids and a disruption of the cellular membrane.[54]

Proteins are oxidised specifically via their amino acid side chains, of which the two most reactive are histidine and tryptophan. The imidazole group of histidine is a specific substrate for singlet oxygen while the indole group of tryptophan experiences both type I and II reactions.[55] The susceptible residue in the nucleic acids is guanine, but both its reactivity and concentration are small relative to lipid and protein reactive sites, so this cannot be regarded as a major mechanism in dynamic action.[56] On the other hand, non-photodynamic action is exemplified by substances that intercalate within the DNA strands, and then bind covalently after photochemical activation. The psoralen group of compounds typically act this way while the phenothiazines photobind to DNA effectively *in vitro*, but competing reactions with lipids and proteins dominate when *in vivo* experiments are performed (see section 4.1).[57]

4.4 Photochemical Mechanisms – Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

It has frequently been noted as paradoxical that a group of therapeutic agents, NSAIDs which are designed to alleviate inflammatory responses, are themselves a significant cause of inflammation when combined with sunlight exposure.[58] The NSAIDs as a group are diverse in chemical structure but are consistent in their ability to inhibit to varying degrees the cyclo-oxygenase (COX) enzymes, regarded as markers for inflammation.[59] The older NSAIDs were developed at a time when only the constitutive isoform COX-1 was known. While gastrointestinal irritation is the dominant adverse effect of their use, a significant number of these drugs are associated with photosensitivity responses in patients. The new generation of anti-inflammatory drugs have been designed specifically or preferentially to inhibit the recently discovered isoform COX-2, whose formation is induced by tissue damage.[59] A significant advantage of these new drugs is that they have less frequent adverse effects on the gastrointestinal tract, yet three of them, celecoxib, etodolac and rofecoxib, are already recorded as causing photosensitivity.[27] Since the latter drugs have not been subjected to photochemical and photobiological study to this point, the focus of the following discussion is on the older non-selective NSAIDs.

4.4.1 2-Arylpropionic Acid NSAIDs

A number of investigations of the photochemistry and photobiology of NSAIDs have shown that

the most photoactive are the 2-arylpropionic acid derivatives (naproxen, ibuprofen, ketoprofen and suprofen).[60-66] Figure 6 shows the chemical structures of some of the NSAIDs that contain this substituent grouping.

In the context of sunlight-derived photosensitivity, the most photoactive (and strongest absorbing) member of this structural group is benoxaprofen (λ_{max} 315nm, ε_{max} 23 000 M^{-1} cm^{-1}). This drug was available in Europe for a brief time only, yet caused serious liver damage and other adverse effects including photosensitivity, thereby stimulating the start of a concerted study of the photochemistry and photobiology of the NSAID group.

The photochemistry of the 2-arylpropionic acids is dominated by an efficient photodecarboxylation process, although the specific aryl chromophore influences the nature of the primary photoprocess. For example, naproxen (λ_{max} 330nm, ε_{max} 2200 M^{-1} cm^{-1}) in neutral aqueous solution undergoes photoionisation and the resulting radical readily decarboxylates to the benzylic radical whence oxidative products are obtained in aerated solutions and reductive products in deaerated solutions.[60-62] On the other hand, for ketoprofen (λ_{max} 262nm, ε_{max} 16 400 M^{-1} cm^{-1}) the primary reaction under similar conditions involves an intramolecular electron transfer from the carboxyl to the carbonyl group as the pathway to decarboxylation.[63,64] Ibuprofen is unusual among this group of drugs in that its absorption spectrum is very weak and does not reach into the sunlight region (λ_{max} 265nm, ε_{max} 380 M^{-1} cm^{-1}). Nonetheless, ibuprofen has been reported as a photosensitiser, and is photoreactive when irradiated with UVC light, giving products analogous to those obtained with the other aryl propionic acids.[65] Ibuprofen is now available without prescription in many countries, leading to widespread use.

The generation of free radicals from the irradiation of naproxen and ketoprofen has been demonstrated by spin trapping experiments and the initiation of free radical polymerisation of acrylamide.[60,66] The radicals trapped were the decarboxylated drug and the free electron. In flash photolysis experiments with naproxen, the electron was detected in relatively high concentration,[60] whereas more detailed studies on ketoprofen showed that photoionisation is not a major process when the irradiation was performed at 355nm.[64] Singlet oxygen yields on irradiation of the 2-arylpropionic acids (determined by time-resolved near-infrared emission) were very strong for naproxen, ketoprofen, carprofen, suprofen, tiaprofenic acid and indoprofen.[67]

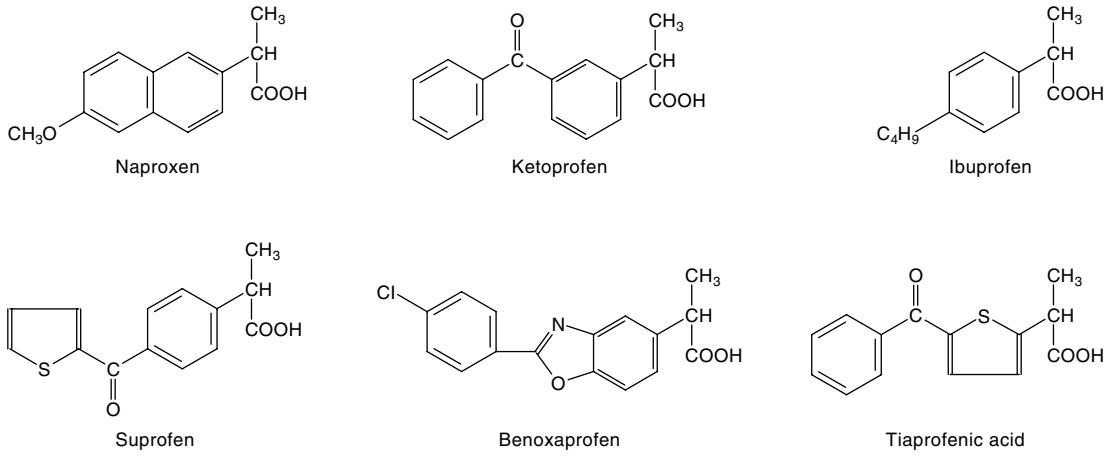

Fig. 6. Chemical structures of nonsteroidal anti-inflammatory drugs containing the 2-arylpropionic acid group.

Thus the 2-arylpropionic acids are capable of producing significant yields of singlet oxygen and free radical species upon irradiation with sunlight-simulating radiation. The photo-oxidation of susceptible biological substrates, such as membrane lipids and proteins, by singlet oxygen or free radical pathways is widely believed to lead to cell disruption and the initiation of oxidative stress leading to the adverse responses.[68] Oxygen may also be involved as an electron carrier in the form of the superoxide anion radical. However, it is possible that, in conditions of low oxygen concentration, or when the sensitiser is located close to susceptible substrates, direct electron transfer between sensitiser and substrate may become a significant contributor.

Photo-induced binding of tiaprofenic acid and suprofen to proteins and cells occurs in an oxygen-free system, thereby providing a mechanism for the initiation of the photoallergic response.[69] Additionally, irradiation of fenofibrate or ketoprofen with DNA leads to cleavage of the DNA by a radical mechanism. Although these compounds have the same benzophenone chromophore, ketoprofen was about 50 times more effective in promoting the formation of pyrimidine dimers. The difference in photoactivity of these two drugs was attributed to the relative ratio of ionic versus radical pathways in their photolysis. Ketoprofen was suggested to have a higher efficiency of radical production in the photodecarboxylation process.[70]

Naproxen was shown to donate electrons to cytochrome-*c* and Nitro Blue Tetrazolium (NBT) when irradiated with UV light in deoxygenated aqueous buffer solution (pH 7.4, 30ºC). The electron transfer process facilitates the decomposition of naproxen at a rate approximately 20-fold faster than when irradiated alone. The strength of the electron donating capability of naproxen is therefore embodied in the decarboxylation of the propionic acid group, with the photoreaction proceeding more rapidly in the presence of a suitable electron acceptor.[71]

In view of the extensive photochemistry of the 2-arylpropionic acid-derived NSAIDs, involving as it does the generation of singlet oxygen, free radical and electron transfer reactions, it is not surprising that these drugs are high on the list of photosensitivity reports.

4.4.2 Other NSAIDs

The structural component that is common to some of the other NSAIDs is the acetic acid side chain, as in indomethacin, diclofenac and sulindac (figure 7). Diflunisal and piroxicam do not have any commonality of structure, but are both acids like all the NSAIDs mentioned so far. Benzydamine is a novel member of this drug group because it is a base, and also has some local anaesthetic properties.

Piroxicam (λ_{max} 345nm, ε_{max} 2200 M^{-1} cm^{-1}) has recorded the most photosensitivity adverse effects of this sub-group of NSAIDs.[22,72] It has been proposed that a metabolite is responsible for phototoxicity caused by piroxicam, due to the low level of photoactivity of the drug itself in polar solvent systems [30,73] but this has been challenged following a study of its photodegradation, suggesting that photo-oxidation products may be involved.[74]

Diclofenac (λ_{max} 275nm, ε_{max} 10 400 M^{-1} cm^{-1}) is a chlorine-containing NSAID that undergoes dechlorination readily in aqueous solution on irradiation with UVR.[48] Following the sequential loss of the chlorine substituents, ring closure occurs and carbazole-1-acetic acid is the major product. Despite having a rigid chromophore with absorption at 360nm, the carbazole photoproduct is a weak phototoxic agent. It is able to generate singlet oxygen more efficiently than diclofenac, but it is postulated that the radical formation is a more likely mechanism of initiation of the *in vivo* photosensitivity responses. Nonetheless the fact that the organic radical readily promotes the intramolecular process suggests that this radical is short-lived and thus limited in its ability to reach appropriate biological substrates. The retention of the carboxyl group after photodegradation also means that the photoproduct is readily excreted from the physiological circulation.

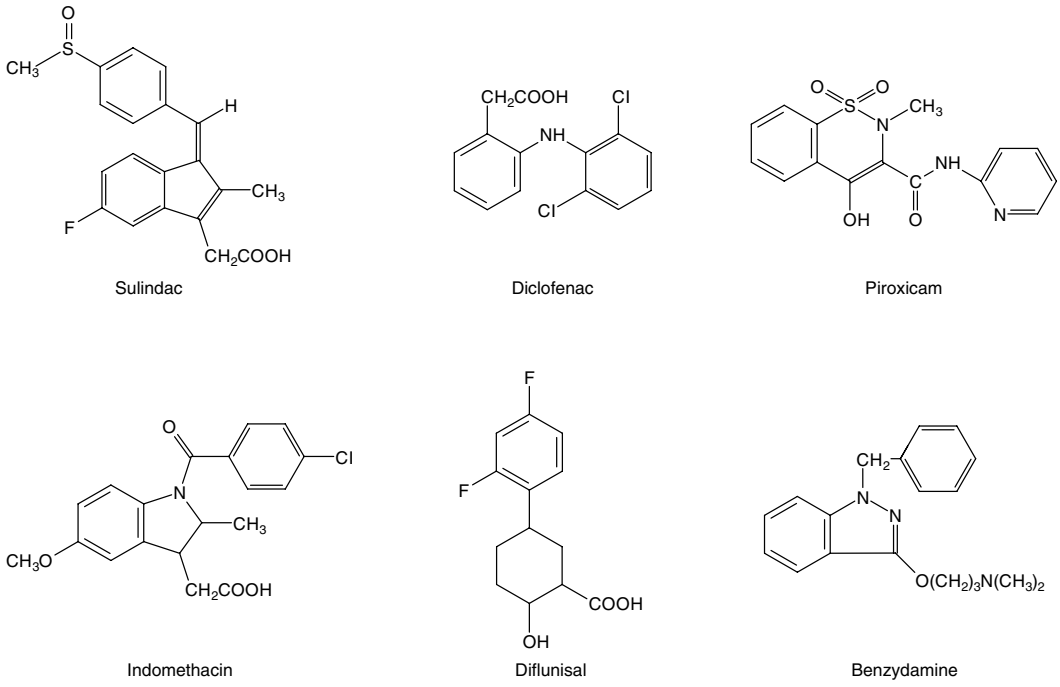

Fig. 7. Chemical structures of selected nonsteroidal anti-inflammatory drugs not containing the 2-arylpropionic acid group.

The reported incidence in Australia of phototoxic reactions involving sulindac is about 60% that of naproxen, whereas for indomethacin it is negligible in comparison.[22] When tested by two *in vitro* assays – photohaemolysis of erythrocytes and growth inhibition of *Candida albicans* [75] – as well as an *in vivo* assay (the mouse tail technique),[76] no activity was found for sulindac and indomethacin. These studies are in accord with the minimal photosensitising activity in aqueous solution, in terms of singlet oxygen and free radical generation.[60] From that study it was clear that indomethacin (λ_{max} 320nm, ε_{max} 7300 M^{-1} cm^{-1}) is relatively stable when irradiated in aqueous solution, even though irradiation in non-polar solvents leads to decomposition by an oxygen-independent mechanism.[77-79] A free radical intermediate, formed by decarboxylation of indomethacin, was detected by radical trapping experiments, and a weak triplet state by flash photolysis of non-polar benzene solutions of the drug.[77] The stability of the indomethacin molecule in polar solvents may be attributed to a resonance-stabilised chromophore extension through the amide link between the indene and *p*-chlorophenyl groups. Free rotation about this link apparently provides an efficient pathway for internal conversion or triplet state decay to occur at room temperature. The very low level of photochemical activity recorded for indomethacin despite its strong UV absorption spectrum, has led to studies which show that this drug has a capacity to act as a sunscreening or photoprotective agent when applied to the skin externally.[80,81] This is a fortunate outcome given the appearance of new formulations of indomethacin designed for topical application to affected joints.

Sulindac (λ_{max} 327nm, ε_{max} 13 000 M^{-1} cm^{-1}) is yellow in colour and has an extensive absorption

spectrum across the UVA range. There is some structural analogy to indomethacin, except that the chromophore is clearly seen to extend through the molecule via the olefinic bond without the need for resonance stabilisation. The process of photoisomerisation about this olefinic bond was found to occur, thereby dissipating the excited state energy and accounting for the very limited photochemical activity of sulindac.[71] When sulindac or indomethacin was used as photosensitiser in electron transfer experiments, the reactions were much slower than for naproxen. It can be concluded that direct electron transfer from the excited state of sulindac or indomethacin can occur in deoxygenated conditions. Because of the effect that oxygen has on the electron transfer process, it is probable that it is the triplet excited state that is involved. This is particularly evident for naproxen, which has a relatively strong capacity to generate singlet oxygen, whereas indomethacin and sulindac did not display such ability.[60]

Benzydamine (λ_{max} 308nm, ε_{max} 5800 M^{-1} cm^{-1}) has widespread availability as an over-the-counter medication even though it has recorded many cases of photosensitivity reactions following topical application or oral ingestion.[82-88] Studies of benzydamine photodegradation[89] and photosensitisation[90] revealed a significant photoactivity. The drug decomposes under the effects of sunlight, and in aerated solutions competing pathways of photosensitisation are possible. These are both singlet oxygen mediated oxidation and electron-transfer mechanisms, detected by the methods outlined above.

One of the notable considerations is that each drug has a different prescribing regimen, determined for the NSAIDs by the relative efficiency of inhibition of the cyclo-oxygenase enzymes. Thus naproxen is typically given in a daily dose of 500mg, while the diclofenac and indomethacin dose is 100mg daily for a similar therapeutic effect. A consequence is that there is a higher circulating concentration of naproxen than for the others, a factor that may contribute to a higher incidence of photosensitivity for naproxen. When benoxaprofen was available, the recommended daily dose was 600mg. Given that its absorption characteristics are more than 10 times stronger than those of naproxen, and that it is more photoactive *in vitro*, it is perhaps not surprising that so many severe photosensitivity reports were experienced with benoxaprofen.

4.5 Antibacterial Drugs

Within the antibacterial group of drugs, photosensitivity responses have been reported most for sulfonamides, tetracyclines, nalidixic acid and the fluoroquinolones.[24] The chemical structures for a representative sample of these groups are shown in figure 8. Among the sulfonamides most activity has been reported over a long period in relation to sulfapyridine, which is released from sulfasalazine absorbed from the intestine in patients with inflammatory bowel disease.[91] Such reactions are characterised by a burning, painful, blistering erythema of the exposed skin with sparing of the protected sites.[24]

4.5.1 Tetracyclines

The tetracyclines have been the subject of more examination in a photochemical context, probably because of their extensive absorption spectrum across the UVA region. However, given the complex structures of the tetracyclines, it is not surprising that fully detailed studies of their photochemistry have not been completed. Demeclocycline has the reputation as the strongest photosensitiser of the group, and is now rarely used. Doxycycline is better absorbed orally and has resulted in far fewer phototoxic effects, as also is minocycline. However, neither is totally free of drug-sunlight eruptions, including some persistent pigmentation of exposed skin.[24] In correlation with the clinical observations, it was found that the tetracyclines are effective generators of singlet oxygen mediated oxidation, with demeclocycline and chlortetracycline being twice as effective as minocycline and doxycycline.[92] Free radical activity has also been demonstrated in the photodegradation of tetracycline.[93]

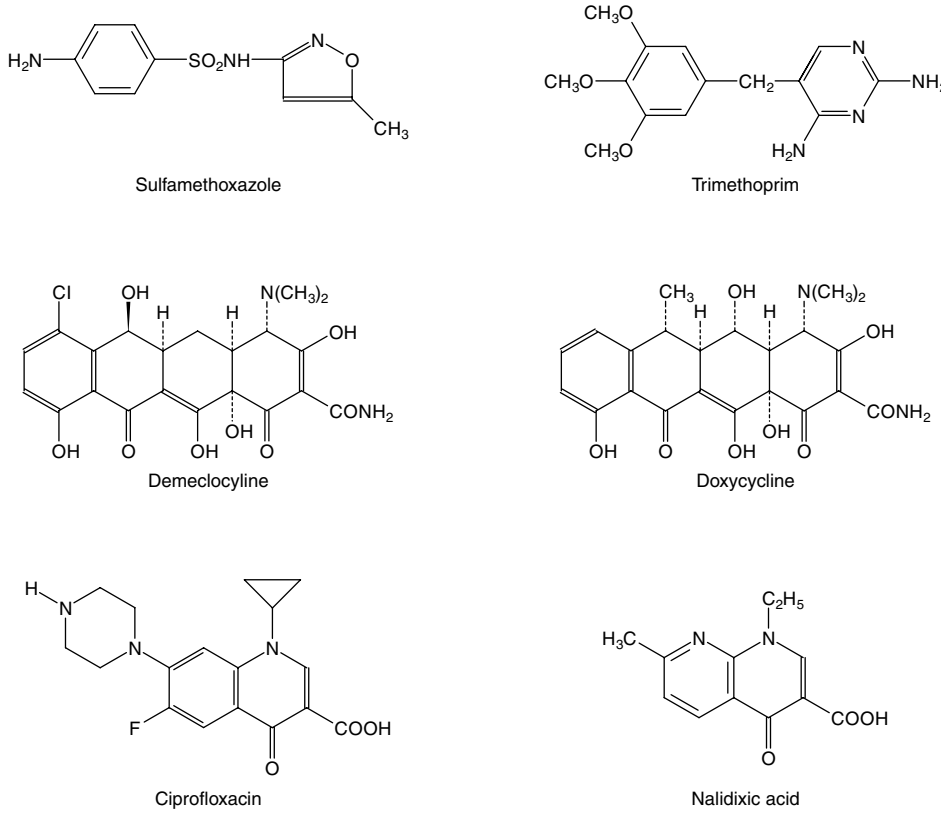

Fig. 8. Chemical structures of selected photoactive antibacterial agents.

4.5.2 Fluoroquinolones

The fluoroquinolones, examples of which are ofloxacin and ciprofloxacin, are a relatively new group of antibacterial agents with activity against a variety of Gram-positive and Gram-negative organisms. Photosensitivity is one of the main adverse effects of these drugs and introduces a serious limitation to their use. Overall they have been shown to have phototoxic, photoallergenic, photomutagenic and phototumourigenic outcomes *in vitro* and *in vivo*, summarised in several reviews.[32,94,95] An examination of the photochemical reactivity of four members of the group revealed heterolytic C-F bond cleavage with its efficiency in the sequence ofloxacin < norfloxacin < enoxacin < lomefloxacin.[96] This sequence can be compared with the quantitative data for the generation by these drugs of activated oxygen species. Sensitised formation of singlet molecular oxygen in aqueous solution is low and uniform along the series, while superoxide anion formation varies, although only narrowly.[97] Thus the photochemical data is not sufficiently clear to enable an expression of the mechanism of the photobiological effect. Nevertheless, it may be hypothesised that the photodefluorination produces an aggressive radical that is able to attack biological cell constituents, in essentially the same way that the chlorinated compounds are believed to act (see section 4.2).

4.5.3 Sulfamethoxazole

Cotrimoxazole is a combination antibacterial product containing sulfamethoxazole and trimethoprim in a fixed 5 : 1 ratio. The combination is regularly applied in the treatment of upper and lower respiratory tract infections such as bronchitis and *Pneumocystis carinii* pneumonia with AIDS, severe urinary tract infections and enteric infections. However, cotrimoxazole has been implicated in adverse phototoxic and photoallergic skin reactions in patients exposed to sunlight and sulfamethoxazole is believed to be the prime suspect in causing such adverse effects.[22,27,98]

Sulfamethoxazole in its non-ionised form in aqueous solution has UV absorption which is maximal at 268nm but extends into the UVB region (see figure 4). It was found to be extremely susceptible to photodegradation when exposed to artificial UV radiation through a Pyrex filter or to unfiltered natural sunlight.[43] The sulfamethoxazole anion was more stable. Sulfamethoxazole photodegrades in aqueous solution by several pathways, the most important of which is a rearrangement of the isoxazole ring resulting from photolytic rupture of the labile N-O bond. The minor products, sulfanilic acid, 3-amino-5-methylisoxazole and aniline, are postulated as being formed from free radicals following homolytic fission.[99] Both thermal and photochemical degradation of trimethoprim has been reported to occur by a radical mechanism.[100]

Sulfamethoxazole was found to be an efficient photosensitiser particularly with respect to free radical and electron transfer mechanisms. On the other hand, trimethoprim shows only a minor reactivity, thereby implicating sulfamethoxazole as the more likely cause of the photosensitivity effects.[101]

4.6 Photoreactions in Hydrophobic Systems

An interesting observation is that the photoreactions of many of the drugs are pH-dependent. Two important examples are sulfamethoxazole and frusemide. The neutral forms of each molecule are predominant at pH values below the pKa of 5.6 and 3.9, respectively. In both cases, the neutral form is at least twice as photoreactive (in terms of degradation, singlet oxygen oxidations and free radical reactions) compared with the anion existing at more alkaline pH. The neutral molecule is much more capable of partitioning into hydrophobic regions of cells and biomolecules where the photosensitiser can interact very closely with the acceptor substrates. Using surfactant micelles as model cellular systems, it has been shown that ionisation of frusemide may be suppressed in the hydrophobic environment, such that a greater proportion of the more photoactive species is present close to physiological pH values.[102]

As an approach to understanding how photodamage to cell membranes can occur, the capability of a drug to photosensitise lipid peroxidation can be investigated using linoleic acid, a polyunsaturated fatty acid. By measuring the progressive increase in absorbance at 233nm corresponding to the formation of dienic hydroperoxides, a substantial peroxidation rate of linoleic acid was observed upon irradiation in the presence of a number of drugs under aerobic conditions. This ability to photosensitise lipid peroxidation in this way leads to the prediction that the drug is capable of causing cell membrane damage when irradiated. Recently, in several laboratories, a correlation has been observed between photohaemolysis of human erythrocytes and the photoperoxidation of linoleic acid mediated by NSAIDs, diuretics and antibacterials.[101,103]

The haemolysis of human erythrocytes was readily induced by UV irradiation in the presence of the different drugs under aerobic conditions, and was negligible under anaerobic conditions. Free radical scavengers such as glutathione, vitamin E and 2,6-di-t-butylhydroxyanisole (BHA) offered efficient protection against photodynamic haemolysis of human erythrocytes, suggesting that free radical reactions are very important in the photodynamic action. It is not clear whether the inhibition afforded by the free radical scavengers arises from cellular uptake or from solution-phase reactions of the inhibitors. The erythrocytes were

also partially protected by the singlet oxygen quenchers, sodium azide and diazabicyclo-octane (DABCO). The photosensitising capabilities of chlorpromazine, frusemide, sulfamethoxazole and naproxen were experimentally compared under the same conditions. At the same drug sensitiser concentration (1.0×10^{-5} mol) a 30 minute irradiation was performed for each drug solution at its own absorption maximum in the presence of either linoleic acid or human erythrocytes under oxygenated conditions. There is a broad correlation between the ability of these drugs to photosensitise in both systems, suggesting that the lipid peroxidation reaction is a useful model or benchmark upon which the photosensitising potential of a drug or chemical can be usefully compared. Chlorpromazine has long been recognised as a potent photosensitising drug, and it was clearly the strongest sensitiser of those tested. Sulfamethoxazole has approximately the same intrinsic photosensitising ability as furosemide and naproxen. However, sulfamethoxazole is not a strong sunlight absorber and therefore it is not expected to show the same frequency of photosensitivity adverse effects as the others.[101]

4.7 Photosensitisation by Topical Agents

A large number of adverse effects are diagnosed as photocontact dermatitis – skin eruptions resulting from the interaction of sunlight and substances applied to the skin for various reasons. There are two types of photo-related reactions that are secondary effects to the use of topical agents. The first is topical phototoxicity due to, for example, coal tar or topical psoralens, while the second is photocontact allergic dermatitis, due to agents such as sunscreens.[104,105] Table II contains a list of some of the substances implicated. These include many cosmetic and sunscreen ingredients, as well as drugs such as NSAIDs that are now being used via cutaneous application. In the past, some antibacterial creams, ointments and soaps have contained photosensitising agents such as the various chlorinated salicylanilides.[21] Now very extensive premarket testing of such products as well as cosmetics and sunscreens has resulted in very few reports of photosensitivity for this type of formulation. The exceptions are the retinoid creams, such as tretinoin, used in the treatment of acne. Users of the creams are warned by package labelling to avoid sun exposure because of the high photoreactivity of the retinoids.

The application of an effective sunscreen formulation is the basis for protection of the patient against photosensitivity reactions caused by drugs. The majority of drug substances giving rise to photosensitivity have an absorption (action) spectrum across the UVB and UVA regions of sunlight. Hence a so-called broad spectrum sunscreen is needed to block this important part of the harmful radiation. Most sunscreen formulations currently available in the marketplace include a cinnamate ester such as 2-ethylhexyl p-methoxycinnamate for coverage of the UVB region, and a compound such as 4-methoxy-2-hydroxybenzophenone for the UVA region. These are referred to as organic absorbers, since they absorb the sunlight energy and are raised to excited states, but dissipate the energy by internal conversion pathways. An inorganic absorber such as microparticulate titanium dioxide, may also be added to provide a barrier layer for protection. A fraction with particle diameters of 80 to 120nm blocks the UVB and UVA up to about 340nm. Zinc oxide with the larger particle size (>200nm) is an alternative inorganic absorber, providing a layer that is opaque right across the UV and visible ranges.[106]

The particulate screens have recorded essentially no skin eruptions, while the cinnamate and benzophenone sunscreen ingredients have resulted in a few adverse reports. However, these are orders of magnitude fewer than have been associated with p-aminobenzoic acid (PABA) and its esters. In the 1970s 2-ethylhexyl-N,N-dimethylaminobenzoate was the principal sunscreen component, but the large number of cases of photosensitivity associated with it led to replacement by the cinnamate ester.[105] When one considers that the application of a sunscreen formulation is a preliminary to extended sunlight exposure by a large proportion of

Table II. Examples of drugs and chemicals reported as causing photo-contact dermatitis

Sunscreen ingredients
Para-aminobenzoic acid (PABA)
6-Acetoxy-2,4-dimethyl-m-dioxane (preservative in sunscreens)
Isoamyl-p-n,n-dimethylaminobenzoate
Glyceryl-p-aminobenzoate and other PABA esters
Oxybenzone and other benzophenones
2-Ethoxyethyl-p-methoxycinnamate
Topical antiseptic and antifungal agents
5-Bromo-4-chlorsalicylanilide
Tetrachlorosalicylanilide
Hexachlorophene
Chlorhexidine
Bithionol
Erythromycin
Buclosamide
Topically applied agents
Tretinoin
Benzocaine
Benzydamine
Dibucaine
Hydrocortisone
Ketoprofen
Coal tar (derivatives)
Coumarin (derivatives)
Zinc pyrithione
Methoxsalen (8-methoxypsoralen)
Cosmetic ingredients
6-Methylcoumarin (used in perfumes, shaving lotions, and sunscreens)
Musk ambrette (used in perfumes)
β-Carotene
Essential oils
Bergamot oil, oils of citron, lavender, lime, sandalwood, cedar
Dyes
Brilliant lake red R
Methylene blue
Fluorescein
Rose bengal
Acridine orange
Acriflavin
Neutral red

the light-skinned population of the world, the conclusion must be reached that these are very safe compounds in the photosensitivity context. Indeed, laboratory experiments have been unable to demonstrate any photosensitising ability for the cinnamate ester, while the PABA ester does display a small triplet state population on irradiation, indicative of potential reactivity (unpublished observations).

5. Management and Prevention of Photosensitised Responses

It has been stated long ago that a phototoxic reaction would occur in everyone if enough of the appropriate wavelength of non-ionising radiation (the action spectrum) is absorbed by enough of the specific chromophore for that reaction.[107] On that basis, photosensitivity responses are not as common as might be expected given the propensity of such a large proportion of the population towards sun exposure. Public health campaigns have clearly played a role in educating people to control their level of tolerance. Those individuals who are affected by photosensitivity are usually able to alter their habits and/or lifestyle to find a regime that minimises the occurrence.

Treatment is necessary when a severe burning occurs. In the case of a phototoxic reaction, the treatment is usually the same as would be applied to sunburn. Within 24 to 48 hours the stinging and burning sensations will subside, with some relief gained from soothing creams or gels. Antibacterial creams should be applied to prevent infection if the skin blisters and is broken. Avoidance of the offending photosensitising agent and/or sunlight exposure is clearly required. Antihistamines and corticosteroids may be required to treat the inflammation arising from photoallergic reactions. There is often a definite history of the rash appearing in spring or summer, so regular skin examination needs to be done in patients at risk of developing skin cancers secondary to chronic phototoxicity.[14,15]

In many cases of photosensitivity responses, it is not be an option on therapeutic grounds to withdraw or substitute the photosensitising drug. Hence two lines of approach are considered as means of prevention of the adverse response. The first of these is obvious as it involves protection from sun exposure, while the second relates to the chemical/biochemical mechanisms of photosensitivity. This latter approach is by no means fully

documented and may be considered controversial at this stage.

5.1 Sunscreens, Protective Clothing and Eyewear

Quite obviously, photosensitivity reactions can be minimised by avoidance of the combination of sunlight and a photosensitising drug. Thus the wearing of fully protective clothing and eyewear and the application of a sunscreen formulation of a high protection rating are the most important measures that can be adopted when some sunlight exposure is inevitable in a person's daily routine. Sunscreen formulations are legally required to carry a sun protection factor (SPF) rating, e.g. 15+, 30+, etc. The SPF rating is determined by phototesting on healthy volunteers, and is calculated from the ratio of the MED with sunscreen to the MED without sunscreen. The standard for sunscreen testing specifies the spreading of a 20μm layer such that it contains 2 mg/cm^2 of the absorbing ingredients. It is important that people use sunscreens according to the instructions supplied, which includes application about 15 minutes before exposure, and repeat applications at least every 2 hours.[108]

The degree of protection that a sunscreen affords against photosensitivity reactions depends upon the action spectrum of the drug in question. The Australian/New Zealand specification for a broad spectrum sunscreen is that it should transmit no more than 2% of the UVB region and no more than 20% across the 320 to 360nm portion of the UVA region. It is important to recognise that a sunscreen acts as a filter, and is simply reducing the amount of the potentially damaging UVR that is reaching the skin. For photosensitising substances whose absorption (action) spectrum stretches above 360nm, the level of protection achievable by sunscreens is reduced proportionately. Fortunately there are very few compounds in that category, the most notable being the porphyrins and various dyes. Note that window glass transmits sunlight above about 330nm, and artificial room lighting contains wavelengths above 370nm, so the precautions need to be taken indoors according to the sensitiser's absorption properties.

Standards for sunglasses are in place in many countries, requiring UV transmission to be minimal below 380nm and many types of clothing have been categorised as to their UVR protection rating. These points are important as some sunglasses have been found to not comply with the standard, and samples of lightweight fabrics used in summer clothing have been shown to be less protective than a sunscreen.[109]

The human immune system plays an important role in UV carcinogenesis by contributing to host resistance against tumour growth. Persons sensitive to immunosuppression that is induced by UVR are at increased risk for skin cancer. UVR alters antigen-presenting cell function directly by affecting epidermal Langerhans cells, or indirectly by inducing keratinocytes to release immunomodulatory cytokines. Exposure of the skin to UVB impairs the induction of contact hypersensitivity to hapten applied to the irradiated skin surface in certain strains of mice and in humans. Chemical sunscreens are effective in preventing sunburn, erythema and solar keratoses. The issue has been confused by some variable results in studies that examined the use of sunscreens in preventing UVB tumour susceptibility and immunologic effects of UVR in mice, leading to some controversial suggestions that sunscreens may not be so beneficial.[110,111] Recent studies however, have clarified this and confirmed the benefit of sunscreens in protecting humans from immunosuppression.[112] At this point there have been no investigations as to whether a drug-induced photosensitivity incident also involves immunosuppression, but the expectation is that it would, since many of the same photobiological reactions appear to be involved as occur in sunburn.

5.2 Antioxidants

An additional preventative measure that merits consideration is diet supplementation with antioxidants, on the basis that the widely demonstrated photochemical and photobiological mechanisms

involve free radical and singlet oxygen mediated damage to biomolecules. Many disease states, as well as the natural process of aging, have been linked to free radical processes with active oxygen species, thereby drawing forth theories of the connection between a 'good diet rich in antioxidants' and good health.[55] Antioxidant therapy is suggested as a new approach in shock, inflammation and ischaemia/reperfusion injury.[113] Antioxidants can be presented in many ways – as the bioflavonoid components of a diet with a high vegetable and fruit content, or as supplements of vitamins A, C and E, and specific plant extracts such as that from grape seed. As an example of this concept in the field of UVR-induced damage, a pine bark extract was given as an oral supplement to 21 healthy volunteers over a period of 4 weeks. The MED for those volunteers measured by phototesting doubled over the period, and expression of a UV-responding nuclear factor gene in the keratinocytes was modulated, thereby indicating that a level of protection was provided by the supplement.[114]

A number of animal model experiments, as well as small scale clinical studies and some epidemiological evidence appear to support the value of antioxidants, but there are some contradictory results, so it remains an equivocal, albeit logical, proposition at this time.

6. Conclusions

For the majority of drugs that have been implicated in adverse photosensitivity reactions, it has been possible to demonstrate by *in vitro* experiments a level of photochemical activity that relates to the severity of the observed *in vivo* effects. The mechanisms that prevail for the most photoactive drugs involve free radical intermediates derived by bond cleavage of the excited state drug molecule. On this basis, there is strong evidence that the development phase for new drugs should include a screening of the photochemical reactivity. Future research in this area should be directed towards gaining a better understanding of the secondary reaction phase, i.e. the period in which the activated species derived from the drug after light absorption interacts with the cellular macromolecules to initiate the biological effects.

References

1. International Agency for Research on Cancer (IARC). Solar and ultraviolet radiation. IARC Monogr Eval Carcinog Risks Hum 1992; 55: 1-316
2. Marks R. Epidemiology of non-melanoma skin cancer and solar keratoses in Australia: a tale of self-immolation in Elysian fields [review]. Australas J Dermatol 1997; 38 Suppl. 1: S26-9
3. Rusonis ES, Rusonis PA, Miller C, et al. Skin cancer detection and prevention: a community program promoting sun safe behaviours. Md Med J 1999; 48 (4): 169-72
4. Whiteman DC, Whiteman CA, Green AC. Childhood sun exposure as a risk factor for melanoma: a systematic review of epidemiologic studies [review]. Cancer Causes Control 2001; 12 (1): 69-82
5. Jagger J. Solar-UV actions on living cells. New York: Praeger Scientific, 1985: 1-10
6. Loomis WF. Rickets. Sci Am 1970; 223 (6): 76-82
7. Parrish JA, Anderson RR, Urbach F, et al. UV-A: Biological effects of ultraviolet radiation with emphasis on human responses to longwave ultraviolet. New York: Plenum Press, 1978
8. Epstein JH. Photomedicine. In: Smith KC, editor. The science of photobiology. 2nd ed. New York: Plenum Press, 1989: 155-92
9. Kocsard E. Solar keratoses and their relationship to non-melanoma skin cancers [review]. Australas J Dermatol 1997; 38 Suppl. 1: S30
10. Russell DH. Ornithine decarboxylase: a key regulatory enzyme in normal and neoplastic growth. Drug Metab Rev 1985; 16: 1-88
11. Dahlback A, Henriksen T, Larsen SHH, et al. Biological UV-doses and the effect of an ozone layer depletion. Photochem Photobiol 1989; 49: 621-5
12. Sobolev I. Effect of column ozone on the variability of biologically effective UV radiation at high southern latitudes. Photochem Photobiol 2000; 72: 753-65
13. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis and management. Lancet 2000; 356: 1255-9
14. Baker CS. Photosensitivity. Med J Aust 1996; 165: 96-101
15. Epstein JH. Phototoxicity and photoallergy. Semin Cutan Med Surg 1999; 18: 274-84
16. Dall'Acqua F, Jori G. Photochemotherapy. In: Foye WO, Lemke TL, Williams DA, editors. Principles of medicinal chemistry. 4th ed. Baltimore: Williams and Wilkins, 1995: 893-907
17. Ackroyd R, Kelty C, Brown N, et al. The history of photodetection and photodynamic therapy. Photochem Photobiol 2001; 74 (5): 656-69
18. Avalos J, Maibach HI, editors. Dermatologic botany. Boca Raton: CRC Press, 1999: 51-65
19. Diwu Z. Novel therapeutic and diagnostic applications of hypocrellins and hypericins. Photochem Photobiol 1995; 61: 529-39
20. Gould JW, Mercurio MG, Elmets CA. Cutaneous photosensitivity diseases induced by exogenous agents. J Am Acad Dermatol 1995; 33: 551-73

21. Magnus IA. Dermatological photobiology. London: Blackwells, 1976: 213-215
22. Australian Department of Health. Adverse Drug Reactions Advisory Committee (ADRAC). A sunburnt country. Adverse Drug Reactions Bulletin. Canberra, Mar 1983, Feb 1987
23. Harth Y, Rapoport M. Phototoxicity associated with antipsychotics, antidepressants and anxiolytics. Drug Saf 1996; 14: 252-9
24. Wainwright NJ, Collins P, Ferguson J. Photosensitivity associated with antibacterial agents. Drug Saf 1993; 9: 437-40
25. Mammen L, Schmidt CP. Photosensitivity reactions: a case report involving NSAIDs. Am Fam Physician 1995; 52: 575-9
26. Dukes MNG, Aronson JK, editors. Meyler's side effects of drugs. 14th ed. Amsterdam: Elsevier, 2000
27. Litt JZ. Drug eruption reference manual 2000. New York: Parthenon, 2000, The Pharmacists guide to drug eruptions and interactions
28. Cooper SM, George S. Photosensitivity reaction associated with use of the combined oral contraceptive. Br J Dermatol 2001: 144, 641-2
29. Schoonderwoerd SA, Beiersbergen van Henegouwen GMJ, Luijendijk HJ. Photobinding of chlorpromazine and its sulfoxide *in vitro* and *in vivo*. Photochem Photobiol 1988; 48: 621-6
30. Western A, Van Camp JR, Bensasson R, et al. Involvement of singlet oxygen in the phototoxicity for a metabolite of piroxicam. Photochem Photobiol 1987; 46: 469-75
31. Kelly GE, Meikle WD, Moore DE. Promotion of UV-induced skin carcinogenesis by azathioprine: role of photochemical sensitization. Photochem Photobiol 1989; 49: 59-65
32. Johnson BE, Gibbs NK, Ferguson J. Quinolone antibiotic with potential to photosensitise skin tumorigenesis. J Photochem Photobiol B 1997; 37: 171-3
33. Stern RS, Laird N. The carcinogenic risk of treatments for severe psoriasis. Cancer 1994; 73: 2759-64
34. Sheil AGR. Cancer in dialysis and transplant patients. In: Morris PJ, editor. Kidney transplantation. 2nd ed. London: Grune and Stratton, 1984: 491-507
35. Monk B. Amiodarone-induced photosensitivity and basal cell carcinoma. Clin Exp Dermatol 1990; 15: 319-20
36. Monk B. Basal cell carcinoma following amiodarone therapy. Br J Dermatol 1995; 133: 148-9
37. Beiersbergen van Henegouwen GMJ. The interference of light in pharmacotherapy. Pharm Weekblad Sci 1981; 3: 85-95
38. Miranda MA. Assessment of the phototoxicity risk of new drugs. In: Seiler JP, Vilanova E, editors. Applied toxicology: approaches through basic science. Berlin: Springer-Verlag, 1997: 249-58
39. Moore DE. Mechanisms of photosensitization by phototoxic drugs. Mutat Res 1998; 422: 165-73
40. Bensasson RV, Land EJ, Truscott TG. Flash photolysis and pulse radiolysis. Oxford: Pergamon Press, 1983: 1-19
41. Spikes JD. Photosensitization. In: Smith KC, editor. The science of photobiology. 2nd ed. New York: Plenum, 1989: 79-110
42. Moore DE. Photophysical and photochemical aspects of drug stability. In: Tonnesen HH, editor. Photostability of drugs and drug formulations. London: Taylor and Francis, 1996: 9-38
43. Moore DE, Zhou W. Photodegradation of sulfamethoxazole: a chemical system capable of monitoring seasonal changes in UVB intensity. Photochem Photobiol 1994; 59: 497-502
44. Davies AK, Navaratnam S, Phillips GO. Photochemistry of chlorpromazine (2-chloro-N-(3-dimethylaminopropyl)phenothiazine) in propan-2-ol solution. J Chem Soc [Perkin] 1976; 2: 25-9
45. Tamat SR, Moore DE. Photolytic decomposition of hydrochlorothiazide. J Pharm Sci 1983; 72: 180-3
46. Moore DE, Hemmens VJ. Photosensitization by antimalarial drugs. Photochem Photobiol 1982; 36: 71-7
47. Moore DE, Sithipitaks V. Photolytic degradation of frusemide. J Pharm Pharmacol 1983; 35: 489-93
48. Moore DE, Roberts-Thomson S, Dong Z, et al. Photochemical studies on the anti-inflammatory drug diclofenac. Photochem Photobiol 1990; 52: 685-90
49. Li YNB, Moore DE, Tattam BN. Photodegradation of amiloride in aqueous solution. Int J Pharm 1999; 183: 109-16
50. Grimshaw J, de Silva AP. Photochemistry and photocyclization of aryl halides. Chem Soc Rev 1981; 10: 181-203
51. Davies AK, Hilal NS, McKellar JF, et al. Photochemistry of tetrachlorosalicylanilide and its relevance to the persistent light reactor. Br J Dermatol 1975; 92: 143-7
52. Cornelissen PJG, Beijersbergen Van Henegouwen GMJ, Gerritsma KW. Photochemical decomposition of 1,4-benzodiazepines. Chlordiazepoxide. Int J Pharm 1979; 3: 205-20
53. Beiersbergen van Henegouwen GMJ. Systemic phototoxicity of drugs and other xenobiotics. J Photochem Photobiol B 1991; 10: 183-210
54. Gorman AA, Rodgers MAJ. Singlet molecular oxygen. Chem Soc Rev 1981; 10: 205-31
55. Matheson ICB, Lee J. Chemical reaction rates of amino acids with singlet oxygen. Photochem Photobiol 1979; 29: 879-81
56. Cadet J, Berger M, Douki T, et al. Oxidative damage to DNA: formation, measurement and biological significance. Rev Physiol Biochem Pharmacol 1997; 31: 1-87
57. Kochevar IE, Garcia C, Geacintov NE. Photoaddition to DNA by nonintercalated chlorpromazine molecules. Photochem Photobiol 1998; 68: 692-7
58. Kochevar IE. Phototoxicity of non-steroidal anti-inflammatory drugs: coincidence or specific mechanism? Arch Dermatol 1989; 125: 824-6
59. Vane JR, Botting RM. New insights into the mode of action of anti-inflammatory drugs. Inflamm Res 1995; 44: 1-10
60. Moore DE, Chappuis PP. A comparative study of the photochemistry of the non-steroidal anti-inflammatory drugs, naproxen, benoxaprofen and indomethacin. Photochem Photobiol 1988; 47: 173-81
61. Costanzo LL, De Guidi G, Condorelli G, et al. Molecular mechanism of naproxen photosensitization in red blood cells. J Photochem Photobiol B 1989; 3: 223-5
62. Bosca F, Miranda MA, Vano L, et al. New photodegradation pathways of naproxen, a phototoxic non-steroidal anti-inflammatory drug. J Photochem Photobiol A – Chemistry 1990; 54: 131-4
63. Bosca F, Miranda MA, Carganico G, et al. Photochemical and photobiological properties of ketoprofen associated with the benzophenone chromophore. Photochem Photobiol 1994; 60: 96-101
64. Monti S, Sortino S, De Guidi G, et al. Photochemistry of 2-(3-benzoylphenyl)-propionic acid (ketoprofen). Pt 1. A picosecond and nanasecond time resolved study in aqueous solution. J Chem Soc Faraday Trans 1997; 93: 2269-75
65. Castell JV, Gomez-Lechon ML, Miranda MA, et al. Photolytic degradation of ibuprofen: toxicity of the isolated pho-

toproducts on fibroblasts and erythrocytes. Photochem Photobiol 1987; 46: 991-6
66. Costanzo LL, De Guidi G, Condorelli G, et al. Molecular mechanism of drug photosensitization-II. Photohemolysis sensitized by ketoprofen. Photochem Photobiol 1989; 50: 359-65
67. De la Pena D, Marti C, Nonell S, et al. Time-resolved near infrared studies on singlet oxygen production by the photosensitizing 2-arylpropionic acids. Photochem Photobiol 1997; 65: 828-32
68. Halliwell B, Gutteridge JM. Free radicals in biology and medicine. 3rd ed. Oxford: Oxford University Press, 1999: 544-616, 784-859
69. Castell JV, Hernandez D, Gomez-Lechon MJ, et al. Photobinding of tiaprofenic acid and suprofen to proteins and cells. Photochem Photobiol 1998; 68: 660-5
70. Marguery MC, Chouini-Lalanne N, Ader JC, et al. Comparison of the DNA damage photoinduced by fenofibrate and ketoprofen, two phototoxic drugs of parent structure. Photochem Photobiol 1998; 68: 679-84
71. Moore DE, Ghebremeskel KA, Chen BBC, et al. Electron transfer processes in the reactivity of nonsteroidal anti-inflammatory drugs in the ground and excited states. Photochem Photobiol 1998; 68: 685-91
72. Stern RS, Bigby M. An expanded profile of cutaneous reactions to non-steroidal anti-inflammatory drugs. JAMA 1984; 252: 1433-7
73. Becker RS, Chakravorti S, Yoon M. Photochemical and photophysical properties of piroxicam and benoxaprofen in various solvents. Photochem Photobiol 1990; 51: 151-4
74. Miranda M, Vargas F, Serrano G. Photodegradation of piroxicam under aerobic conditions: the photochemical keys of the piroxicam enigma? J Photochem Photobiol B 1991; 8: 199-202
75. Ljunggren B. Propionic acid-derived non-steroidal anti-inflammatory drugs are phototoxic in vitro. Photodermatol 1985; 2: 3-9
76. Ljunggren B, Lundberg K. In vivo phototoxicity of non-steroidal anti-inflammatory drugs evaluated by the mouse tail technique. Photodermatol 1985; 2: 377-82
77. Dabestani R, Sik RH, Davies DG, et al. Spectroscopic studies of cutaneous photosensitizing agents. XVIII. Indomethacin. Photochem Photobiol 1993; 58: 367-73
78. Pawelczyk E, Knitter B. Kinetics of indomethacin degradation. Pharmazie 1977; 32: 698-9
79. Weedon AC, Wong DF. The photochemistry of indomethacin. J Photochem Photobiol -A Chem 1991; 61: 27-33
80. Lim HW, Thorbecke GJ, Baer RL, et al. Effect of indomethacin on alteration of ATPase-positive Langerhans cell density and cutaneous sunburn reaction induced by ultraviolet-B radiation. J Invest Dermatol 1983; 81: 455-8
81. Schwartz T, Gschnait F, Greiter F. Photoprotective effect of topical indomethacin - an experimental study. Dermatologica 1985; 171: 450-8
82. Ikemura I. Contact and photocontact dermatitis due to benzydamine hydrochloride [letter]. Japanese J Clin Dermatol 1971; 25: 129
83. Fernandez De Corres L. Photodermatitis from benzydamine. Contact Dermatitis 1980; 6: 285-303
84. Balato N, Lembo G, Patruno C, et al. Contact dermatitis from benzydamine hydrochloride [letter]. Contact Dermatitis 1986; 15: 105
85. Bruynzeel DP. Contact allergy to benzydamine. Contact Dermatitis 1986; 14: 313-4
86. Motley RJ, Reynolds AJ. Photodermatitis from benzydamine cream [letter]. Contact Dermatitis 1988; 19: 66
87. Foti C, Vena GA, Angelini G. Occupational contact allergy to benzydamine hydrochloride. Contact Dermatitis 1992; 27: 328-9
88. Goday BJJ, Ilardia LR, Soloeta AR. Allergic contact dermatitis from benzydamine with probable cross-reaction to indomethacin. Contact Dermatitis 1993; 28: 111-2
89. Wang J, Moore DE. A study of the photodegradation of benzydamine in pharmaceutical formulations. J Pharm Biomed Anal 1992; 7: 535-40
90. Moore DE, Wang J. Electron transfer mechanisms in photosensitization by the anti-inflammatory drug benzydamine. J Photochem Photobiol B 1998; 43: 175-80
91. Nielson OH. Sulfasalazine intolerance: a retrospective survey of use in patients with chronic inflammatory bowel disease. Scand J Gastroenterol 1982; 17: 389-93
92. Wiebe JA, Moore DE. Oxidation photosensitized by tetracyclines. J Pharm Sci 1977; 66: 186-9
93. Moore DE, Fallon MP, Burt CD. Photo-oxidation of tetracycline – a differential pulse polarographic study. Int J Pharm 1983; 14: 133-42
94. Ferguson J. Fluoroquinolone photosensitization: a review of clinical and laboratory studies. Photochem Photobiol 1995; 62: 954-8
95. Ball P, Tillotson G. Tolerability of fluoroquinolone antibiotics. Drug Saf 1995; 13: 343-58
96. Fasani E, Profumo A, Albini A. Photochem photobiol 1998; 68: 666-74
97. Martinez LJ, Sik RH, Chignell CF. Fluoroquinolone antimicrobials: singlet oxygen, superoxide and phototoxicity. Photochem Photobiol 1998; 67: 399-403
98. Berger TG, Dhar A. Lichenoid photoeruptions in human immunodeficiency virus infection. Arch Dermatol 1994; 130: 609-13
99. Zhou W, Moore DE. Photochemical decomposition of sulfamethoxazole. Int J Pharm 1994; 110: 55-63
100. Bergh JJ, Breytenbach JC, Wessels PL. Degradation of trimethoprim. J Pharm Sci 1989; 78: 348-50
101. Zhou W, Moore DE. Photosensitizing activity of the antibacterial drugs sulfamethoxazole and trimethoprim. Photochem Photobiol 1997; 39: 63-72
102. Moore DE, Burt CD. Photosensitization by drugs in surfactant solutions. Photochem Photobiol 1981; 34: 431-9
103. Miranda MA, Castell JV, Gómez-Lechón MJ, et al. *In vitro* photoperoxidation as an indicator of the potential phototoxicity of non-steroidal anti-inflammatory 2-arylpropionic acids. Toxicol In Vitro 1993; 7: 523-6
104. de Leo VA, Harber LC. Contact photodermatitis. In: Fisher AA, editor. Contact dermatitis. 3rd ed. Philadelphia (PA): Lee and Febiger, 1986: 454-69
105. Funk JO, Dromgoole SH, Maibach HI. Contact sensitisation and photocontact sensitisation of sunscreening agents. In: Lowe NJ, Shaath NA, Pathak MA, editors. Sunscreens. 2nd ed. New York: Dekker, 1997: 631-53
106. Fairhurst D, Mitchnick MA. Particulate sun blocks: general principals. In: Lowe NJ, Shaath NA, Pathak MA, editors. Sunscreens. 2nd ed. New York: Dekker, 1997: 313-51

107. Epstein JH. Adverse cutaneous reactions to the sun. In: Malkinson FD, Pearson RW, editors. Year book of dermatology. Chicago: Year Book Medical Publishers, 1971: 5-43
108. Standards Australia/Standards New Zealand. Sunscreen products – evaluation and classification. Sydney/Wellington, 1993. Report no. AS 2604
109. Gies PH, Roy CR, Toomey S, et al. Protection against solar ultraviolet radiation. Mutat Res 1998; 422: 15-22
110. Reeve VE, Bosnic M, Boehm-Wilcox C, et al. Differential protection by two sunscreens from UV radiation-induced immunosuppression. J Invest Dermatol 1991; 97: 624-8
111. Wolf P, Donawho CK, Kripke ML. Effect of sunscreens on UV radiation-induced enhancement of melanoma growth in mice. J Natl Cancer Inst 1994; 86: 99-105
112. Serre I, Cano JP, Picot MC, et al. Immunosuppression induced by acute solar-simulated ultraviolet exposure in humans: prevention by a sunscreen with SPF 15 and high UVA protection. J Am Acad Dermatol 1997; 37: 187-94
113. Cuzzocrea S, Riley DP, Caputi AP, et al. Antioxidant therapy: a new pharmacological approach in shock, inflammation and ischemia/reperfusion injury. Pharmacol Rev 2001; 53: 135-59
114. Saliou C, Rimbach G, Moini H, et al. Solar UV induced erythema in human skin and nuclear factor-κB-dependent gene expression in keratinocytes are modulated by a French maritime pine bark extract. Free Radic Biol Med 2001; 30: 154-60

Correspondence and offprints: Dr *Douglas E. Moore*, Faculty of Pharmacy, The University of Sydney, Building A15, Sydney, NSW 2006, Australia.
E-mail: demoore@pharm.usyd.edu.au