15 Phototoxic Dermatitis

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Core Messages

- Phototoxic dermatitis from exogenous chemicals can be polymorphic.
- It is not always easy to distinguish phototoxicity from photoallergy.
- Phytophotodermatitis from plants containing furocoumarins is one of the main causes of phototoxic contact dermatitis.
- Topical and systemic drugs are a frequent cause of photosensitivity, often with phototoxic aspects.
- The main clinical pattern of acute phototoxicity is an exaggerated sunburn.
- Subacute phototoxicity from systemic drugs can present as pseudoporphyria, photoonycholysis, and dyschromia.
- Exposure to phototoxic drugs can enhance skin carcinogenesis.

1 Introduction

Photosensitivity represents an abnormal inflammatory skin reaction to the sun, presenting under a wide spectrum of clinical reaction patterns. It is usually due to the abnormal presence, in the skin, of an endogenous or exogenous substance that is selectively activated by solar radiation – a chromophore. Apart from exogenous photoactive chemicals, there are several causes for photosensitivity: congenital or acquired errors may hinder DNA repair after ultraviolet (UV) aggression (xeroderma pigmentosum, Bloom's syndrome) and reduce the natural UV protection (albinism and vitiligo) or the antioxidative response to UV light (pellagra due to reduced levels of niacin in diet or from alcohol consumption); accumulation of endogenous photoactive chemicals, like in porphyria; idiopathic photodermatosis, inflammatory or immune-mediated reactions whose antigen has not been well characterized, like solar urticaria, polymorphos light eruption, "lucite estvial benigne," actinic prurigo, and chronic actinic dermatitis (Hawk 1999).

Considering only photosensitivity from exogenous agents, both chemicals applied topically or those that reach the skin by the systemic route, there is still a wide spectrum of skin reactions. Some involve predominantly a specific T-cell-dependent response, including photoallergy, both photoallergic contact dermatitis and systemic photoallergy, and autoimmunity with photosensitivity, as in drug-induced photosensitive lupus erythematosus in Ro-positive patients taking terbinafine, thiazide diuretics, calcium channels blockers, or taxanes (Farhi et al. 2006; Sontheimer et al. 2008; Cohen 2009). Phototoxic dermatitis, on the other hand, does not involve specific immune hypersensitivity reactions.

Although these mechanisms are well characterized, their participation in each case of photosensitivity can be more complex. For instance, in chronic actinic dermatitis, the extreme photosensitivity to UV light may be initially triggered by a photosensitive reaction or by contact allergy to perfumes, sesquiterpene lactones, or colophony, but in its evolution, individuals become extremely photosensitive even with no further exposure to the exogenous chromophore or allergen: An autoantigen may be formed during the acute reaction (DNA or RNA modified by plant products) and/or, in the absence of the expected UV-induced immunosuppression, sensitization to a new epidermal autoantigen may occur (Hawk 2004; Béani 2009).

When considering only phototoxic and photoallergic dermatitis there is also an overlap between these two reaction patterns. Except for a few chemicals, as piroxicam and olaquindox, which do not have an intrinsic phototoxic potential and induce only photoallergic reactions (Figueiredo 1994), most substances can induce both photoallergic and phototoxic reactions. For instance, potent phototoxic agents like psoralens can induce photoallergy in some individuals. There is also some overlap between phototoxicity and photoallergy in the clinical characteristics of the reaction and their time course. Most phototoxic reactions are well recognized, are not severe, and do not call medical attention. Others may be severe and are often misdiagnosed, as their relation to sun exposure is not so obvious, namely, the recently described UV-induced skin cancers in patients on voriconazole (McCarthy et al. 2007; Cowen et al. 2010).

Photoallergy from exogenous agents is now considered rare (Darvay et al. 2001; Bryden et al. 2006), but it may be underreported or underdiagnosed (Zeeli et al. 2006). Many photosensitizers have been recognized and

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removed from the market (salicylanilides, PABA) or sun avoidance is recommended when they are used (lomefloxacin). Also, there is an increasing concern on premarketing studies on the photosensitizing potential of chemicals for human use. Nevertheless, photosensitivity is still a field on intense research. New photosensitizers are discovered, either causing skin disease (Chang et al. 2009) or for therapeutic purposes. Also, new mechanisms underlying the photosensitizing potential of chemicals and new aspects of clinical presentation of photosensitivity are recognized, which may be important to understand diseases that course with photosensitivity, as HIV infection (Béani 2009).

2 General Mechanisms of Phototoxicity from Exogenous Chemicals

Normal skin is prepared to live with sunlight and takes benefit from it. Skin chromophores are activated upon sun exposure and undergo chemical reactions which are important for survival under the sun and necessary for human life: 7-dehydrocholesterol is activated by UVB to form pro-vitamin D3 and Vitamin D.

Photosensitivity develops when an abnormal chromophore is present in the skin or when a normal chromophore in present in exaggerated amounts. When excited by a photon these molecules receiving the energy suffer changes within the molecule itself, often also within neighboring molecules, in a cascade of events that result in skin damage and inflammation. The energy received by the molecule excites the electrons in the outer orbits; the molecule becomes reactive and can undergo several types of modifications within itself (isomerization, breaking of double bounds, oxidation) or react with neighboring molecules, eventually forming free radicals or reactive oxygen species (ROS). These ROS and other free radicals damage cellular organelles by modifying unsaturated lipids of cell membranes, aromatic amino acids of proteins, and pyrimidine bases of DNA or RNA. If the repair mechanisms do not act immediately, there is damage of these cellular structures and suffering or death of skin cells. In this process, inflammatory mediators are generated (prostaglandins, leukotrienes, IL-1, 6, 8, other cytokines and chemokines) with consequent visible skin lesions – this is briefly the mechanism of phototoxicity (Hawk 1999; Ferguson 1999). In photoallergy, the energy of the photon transforms the chromophore into a photoproduct or enhances its reaction with an endogenous peptide forming a hapten or an allergen that is specifically recognized by the immune system.

Several phototoxic substances, like psoralens, chlorpromazine, and fluorquinolones, apart from the capacity to generate free radicals and cell death responsible for acute phototoxicity, also enhance chromosomal damage in the presence of UVR, both in vitro and in vivo (Seto et al. 2010). Therefore, they are photogenotoxic and photomutagenic, which is usually associated with photoimmunosupression, and have consequent implications in animal photocarcinogenesis (Klecak et al. 1997; Marrot et al. 2003; Lhiaubet-Vallet et al. 2009; Müller et al. 1998). Epidemiological studies and recent reports also show enhancement of photocarcinogenesis in humans exposed to photoactive chemicals (Cowen et al. 2010; Placzek et al. 1999; Miller et al. 2010).

From the solar spectrum that reaches the earth, UV radiation, and particularly UVA (320–400 nm), is responsible for most cases of photosensitivity. Even though some chromophores absorb in the UVB (290–320 nm) and UVB is more energetic, UVA penetrates the skin more deeply and, particularly for systemic chromophores, this is certainly the most important spectrum for inducing photodermatosis (Hawk 1999). Only exceptional cases have a well-documented exogenous photosensitivity exclusively from UVB (Fujimoto et al. 2009).

2.1 Phototoxicity Versus Phototoallergy

In theory, it is easy to differentiate photoallergy from phototoxicity, but there are many overlapping aspects, as presented below.

Classically, photoallergy develops only in a limited number in individuals, needs previous sensitization but occurs also with cross-reactive chemicals, is not dose-dependent, develops on low UV dose, appears as eczema that can spread to nonexposed sites and, on skin biopsy, there is mainly T-cell infiltration, spongiosis, and vesicles. Phototoxicity is more frequent, develops in every individual, as long as enough photosensitizer and sun exposure are present, occurs on a first and single contact, with no flare-ups or cross-reactions, appears mainly as well-demarcated erythema exclusively on sun-exposed areas (mimicking sunburn), resolves with hyperpigmentation and, on histology, apoptotic keratinocytes (sunburn cells) are abundant (*Table 15.1*).

These are the two polar aspects of photosensitivity, but, as referred previously, some molecules may induce both phototoxic and photoallergic reactions and, in the

Table 15.1
Distinction between phototoxicity and photoallergy

	Phototoxicity	Photoallergy
Frequency	High	Low
Latency period/ sensitization	No	Yes
Doses of UV/ photosensitizer	High	Low
Cross-reactions	No	Yes
Morphology of lesions	Sunburn, polymorphic	Eczema, erythema multiforme
Sharp limits	Yes	No
Covered areas	Not involved	Possibly involved
Resolution	Quick	May recur, persistent reactors
Residual hyperpigmentation	Yes	No
Histology	Sunburn cells	Eczema
Pathomechanism	DNA/cell damage ROS/ inflammation	Type IV hypersensitivity Photoproduct

same patient, aspects that resemble phototoxicity may coexist with others that suggest photoallergy.

After contact with plant furocoumarins (*Ruta graveolens, Ficus carica, Umbelliferae*) or during photochemotherapy, some individuals can become reactive to very low concentrations of psoralens (Karimian-Teherani et al. 2008) and with phototoxic drugs like promethazine and lomefloxacin, patients may develop photoallergy, reacting to very low doses of the drug or sun exposure (Gonçalo 1998; Oliveira et al. 1996; Kurumajin and Shono 1992). Very probably, as for contact allergens that have an inherent "irritant" potential to awaken the innate immune system promoting sensitization (Neves et al. 2008), photoallergens are photoactive molecules with some inherent phototoxicity. This innate inflammatory reaction can work as the "danger signal" necessary to initiate the sensitizing process.

Although phototoxicity can occur on a first contact and photoallergy needs previous sensitization, individuals previously sensitized by contact or photocontact to a similar molecule can react on a first exposure. This occurs in individuals with contact allergy to thimerosal and its moiety thiosalicylic acid who develop photoallergy to piroxicam on the first drug intake and patients allergic to perfumes (cinnamic alcohol) who may have photoallergic contact dermatitis from ketoprofen on a first exposure (Foti et al. 2008). Upon UVA irradiation, piroxicam is photodecomposed into a molecule very similar antigenically and structurally to thiosalicylic acid (Gonçalo et al. 1992; Hariva et al. 1993) and there are conformational similarities between cinnamate derivatives and ketoprofen photoproducts (Foti et al. 2008; Pigatto et al. 1996)

Phototoxicity is considered to occur in every patient as long as enough chromophore and sun are present at the same time, but even in drug phototoxicity and phytophotodermatitis there is some individual susceptibility, even though the parameters that characterize this susceptibility are not precisely known.

3 Clinical Patterns of Photosensitivity from Exegenous Chemicals

As referred, clinical and evolutive aspects suggesting of a phototoxic dermatitis from exogenous chemicals can coexist with signs of photoallergy or other photo-immune reactions; therefore, in most instances it is best to call photosensitivity. Nevertheless, in this chapter, clinical patterns that are more suggestive of phototoxicity will be described.

The clinical patterns of phototosensitivity from exogenous chemicals vary from urticaria through eczema or subacute lupus erythematosus up to vitiligo-like lesions or squamous cell carcinomas (Gonçalo 1998; Ferguson 1999; McCarthy et al. 2007). They can be very typical, like phytophotodermatitis or acute exaggerated sunburn from a phototoxic drug, but sometimes, the diagnosis or even the suspicion of photosensitivity is not so obvious. It is the example of cases involving nonexposed areas, which occurs mainly in photoallergy, or when there is no immediate or evident relation with exposure to the sun and exogenous chemicals, as in actinic keratosis and skin cancer in patients chronically exposed to photoactive drugs (*Table 15.2*).

Skin reactions can occur immediately after sun exposure, as in photocontact urticaria, but the appearance of skin lesions may be delayed 1 or 2 days, as in most phototoxic or photoallergic contact dermatitis or systemic photoallergy, several days or weeks, as in pseudoporphyria or subacute lupus erythematosus, or even years, in photocarcinogenesis enhanced by a long exposure to the sun and the photoactive chemicals.

Table 15.2
Clinical patterns of photosensitivity

Predominant in phototoxicity	In photoallergy
Exaggerated "sunburn"	Urticaria in sun-exposed area
Pseudoporphyria	Acute or subacute eczema
Photoonycholysis	Cheilitis
Hyperpigmentation	Erythema multiform-like
Hypopigmentation (vitiligo-like lesions)	Lichenoid reactions
Telangiectasia Purpura	Subacte or chronic lupus erythematosus
Pellagra-like reactions	
Actinic keratosis and squamous cell carcinoma	

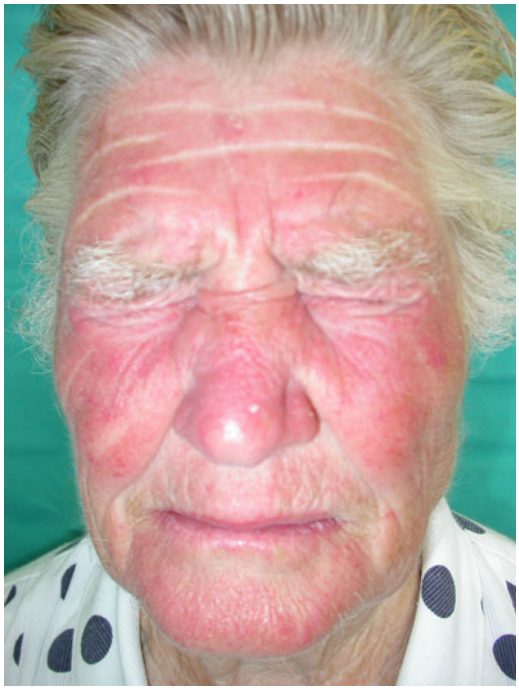

Fig. 15.1
Acute phototoxicity from amiodarone, mimicking sunburn and sparing the deep wrinkles

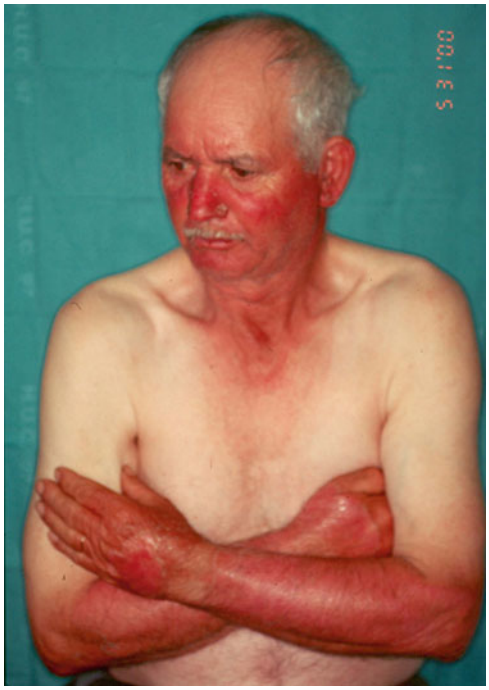

Fig. 15.2
Photosensitivity from systemic lomefloxacin, sparing the sunshaded areas and the wrist protected from the watch

Localization of the lesions depends on whether the photoactive chemical is applied on the skin (photocontact dermatitis) or the photosensitizer is a systemic drug. In photocontact dermatitis from a topical agent, dermatitis draws the area of application and concomitant sun exposure, but distant lesions can occur in areas of accidental contact, as in a contralateral limb (kissing faces of the legs) or in areas of inadvertent spread by the hands or contaminated objects (Hindsén et al. 2004). Some topical drugs, as nonsteroidal anti-inflammatory drugs (NSAIDs), are considerably absorbed through the skin and lesional distribution can be similar to systemic photosensitivity.

In systemic photosensitivity the reaction usually involves, in a symmetric distribution, all exposed areas of the face, the V-shaped area of the neck and upper chest, dorsum of the hands and forearms, while shaded areas are spared. This corresponds, in the face, to the upper eyelids, upper lip, deep wrinkles (*Fig. 15.1*), retroauricular areas, submandibular area, and areas covered by the beard or hair. Large body folds, like the axillae, groins, finger webs, and areas covered by clothing or other accessories (watch strip, shoes) (*Fig. 15.2*) are also usually spared. Involvement of these shaded areas suggests dermatitis from an airborne allergen or irritant.

In exceptional cases where sun exposure is asymmetric, this pattern can be different, as in car drivers who only expose the left arm. Sometimes, in systemic

photosensitivity, the lower lip is mainly or almost exclusively involved, because of its higher exposure and, very probably, because of the thinner corneal layer more prone to phototoxic reactions (Auffret et al. 2006; Cardoso et al. 2009).

3.1 Acute Patterns of Phototoxicity

3.1.1 Immediate Reactions

Apart from idiopathic solar urticaria, for which a chromophore is not identified, immune or nonimmune urticaria as a manifestation of photosensitivity from an exogenous substance has been rarely described with 5-aminolevulinic acid, used in photodynamic therapy (Kerr et al. 2007), with oxybenzone in sunscreens (Collins and Ferguson 1994) and chlorpromazine (Lovell et al. 1986). Nevertheless for some drugs, like amiodarone and benoxaprofen (already removed from the market), immediate prickling and burning with transient erythema may occur as a manifestation of photosensitivity (Ferguson 1999).

3.1.2 Acute Phototoxic Dermatitis, Mimicking Sunburn

The main clinical pattern of acute phototoxicity, mimicking exaggerated sunburn develops within 12–24 h of sun exposure. It consists on a well-demarcated erythema with prickling and burning, eventually with skin pain but typically without pruritus. Erythema can progress to vesicles and bullae, but eczematous lesions with small vesicles or multiforme-like lesions involving also covered areas is not usual in phototoxicity and recalls mainly photoallergy.

Like in exaggerated sunburn, acute phototoxicity progresses to large sheets of epidermal detachment within the next days and resolves with residual hyperpigmentation. In this pattern of phototoxicity, there is typically a very sharp limit between affected and nonaffected shaded area (*Fig. 15.2*).

3.2 Subacute Patterns of Phototoxicity

Some clinical patterns of photosensitivity develop within days or weeks after exposure to the photosensitizer and the sun. These patterns that evoke mainly a phototoxic reaction are pseudoporphyria, photoonycholsys, hyper or hypopigmentation, telangiectasia, and purpura.

3.2.1 Pseudoporphyria

Pseudoporphyria presents as chronic skin fragility with flaccid bullae on non-inflamed exposed skin, occasionally with later milia formation, that resembles porphyria cutanea tarda both clinically and on histopathology (bullae formation below the lamina densa). It occurs in individuals with no inborn error in porphyrin metabolism and no increase of endogenous porphyrins.

It was observed in individuals regularly exposed to solarium (Kochs et al. 2009) or to some systemic drugs. Nalidixic acid, furosemide, and naproxen predominantly in children (Ferguson 1999; Figueiredo 1994) were initially described as causing pseudoporphyria but, more recently, many others drugs are associated with this phototoxic reaction: ciprofloxacin (Schmutz et al. 2008), celecoxib (Cummins et al. 2000; Schmutz et al. 2006), voriconazole (Auffret et al. 2006), torasemide (Pérez-Bustillo et al. 2008), and imatinib (Timmer-de Mik et al. 2009). This represents a typical phototoxic reaction where the drug, as the uroporphyrin in the hereditary disease, probably induces phototoxicity through singlet oxygen (Ferguson 1999; Figueiredo 1994).

3.2.2 Photoonycholysis

Photoonycholysis, with a half-moon distal onycholysis of one or several nails, is a typical pattern of phototoxicity, occurring most often as the single manifestation of phototoxicity (*Fig. 15.3*). It appears late (2–3 weeks after drug intake and sun exposure), sometimes preceded by pain in the nail apparatus. It occurs mainly with tetracyclines (demethylchlortetracycline or doxycycline)

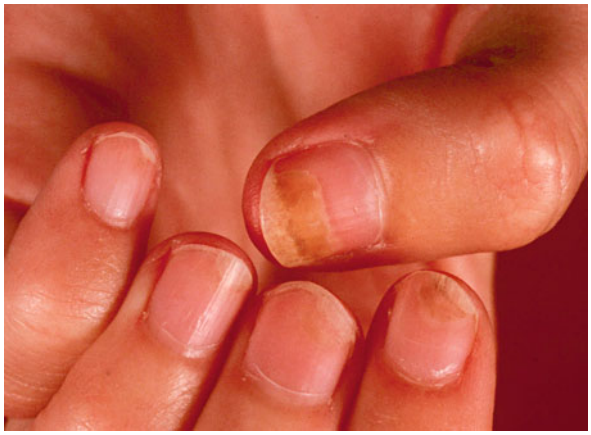

Fig. 15.3
Photoonycolysis from chlortetracycline

(Passier et al. 2004), psoralens, and fluorquinolones (Baran and Juhlin 2002). There is no definite explanation for the single involvement of the nail: The nail bed is relatively unprotected from sunlight, it contains less melanin, the nail plate may work as a lens, and the inflammatory reaction induces detachment of the nail plate from the nail bed (Passier et al. 2004; Baran and Juhlin 2002; Gregoriou et al. 2008).

3.2.3 Dyschromia

Hyperpigmentation that follows mainly an acute phototoxic reaction is frequently due to the residual melanocytic hyperpigmentation, and is very typical in phytophotodermatitis (*Fig. 15.3*).

In rare occasions, like in flutamide-induced photosensitivity, vitiliginous lesions with sharp limits occur after the acute reaction (Gonçalo et al. 1999; Vilaplana et al. 1990).

Dyschromia from the accumulation of the photoactive drug or its metabolites in the dermis occurs in a smaller percentage of patients after acute phototoxicity from amiodarone, minocycline, or phenothiazines (Ammoury et al. 2008; Vassileva et al. 1998). Some patients with lower phototypes also develop a golden-brown, slate gray, or bluish color on sun-exposed areas, that persists much longer than residual melanocytic hyperpigmentation (Ferguson 1999; Ammoury et al. 2008).

3.2.4 Other Clinical Patterns

Telangiectasia as a manifestation of photosensitivity has been reported with calcium channel blockers (Ferguson 1999) and the telangiectatic pattern of photoaging with lesions mainly in the lateral folds of the neck, sparing the shaded skin under the chin, is frequently observed in patients chronically exposed to the sun or to photoactive drugs. In rare cases, petechial purpura with sharp limits on the transition to the shaded areas was described with ciprofloxacin (Urbina et al. 2006).

Pellagra is associated with the prolonged use of isoniazid, that consumes niacin for its metabolization, and pellagroid reactions were reported with the anticancer agents, like 6-mercaptopurine and 5-fluorouracil.

3.3 Delayed and Late Effects of Phototoxicity

Patients that are chronically exposed to photoactive drugs may develop other patterns of skin lesions, like chronic actinic dermatitis and lupus erythematosus where autoimmune reactions are predominantly involved, or accelerated photoaging and skin cancers, that are explained by the photogenotoxic effect of some phototoxic molecules.

There is a consensual agreement on the increased risk of skin cancers after longtime therapeutic exposure to PUVA phototherapy (Ferguson 1999) but, apart from psoralens, other drugs like naproxen, chlorpromazine, and the fluorquinolones, particularly lomefloxacin, also augment in vitro UV-induced DNA aggression and increase epidermal neoplasia in animals (Klecak et al. 1997). Recent reports and epidemiological data also correlate chronic human exposure to photoactive drugs with an increased risk of developing actinic keratoses, nonmelanoma skin cancer and, even, malignant melanoma (Placzek et al. 1999; McCarthy et al. 2007; Jensen et al. 2008). In 1999, the group of Przybilla showed an association between actinic keratosis and the use of potentially photosensitizing chemicals (Placzek et al. 1999). More recent studies tend to confirm an increased risk for skin cancer in patients chronically exposed to psoralens, fluoroquinolones, and diuretics (Jensen et al. 2008) and voriconazole (McCarthy et al. 2007; Cowen et al. 2010; Miller et al. 2010). Also, patients with severe chronic photosensitivity may develop skin cancers in the photoexposed areas, like squamous cell carcinoma with ciprofloxacin (personal experience) and both squamous cell carcinoma and melanoma with voriconazole (Cowen et al. 2010; Miller et al. 2010).

Also the photoaging process may be enhanced by the exposure to topical or systemic photosensitizers.

4 Main Sources of UV Exposure

The sun is the main source of UV exposure even in the occupational setting. Farmers, gardeners, construction workers, fishermen, sailors, policemen, ski instructors, oil-field workers, and road workers are occupations where sun exposure can be heavy, prolonged, and begin at an early age.

Artificial sources of UV exposure are present in several occupational settings and, even though protective measures and instructions for UV avoidance are active, UV exposure can be relevant in some of them. Some examples are the rooms for solarium and phototherapy, plants for UV curing of printing inks, lacquers, dental acrilates, or nail modeling acrilates, indoor working places artificially illuminated with UVA light sources with no plastic/glass

cover, and areas of food cooking where insect traps have UVA emission to attract the insects.

The highest artificial UV exposure in occupational setting occurs in welders, particularly in electric arc welding. These individuals may suffer UV-induced erythema, burns, and keratitis (welder's flash) during inadvertent exposure during the arc welding process (Hawk 1999).

Exposure to the more energetic UVC rays (260–265 nm) can also occur during sterilization or disinfection of water for drinking, for cosmetic or pharmaceutical industries or for swimming pools, during sterilization of the air in cabinets, research laboratories, and operating theaters and during the treatment of sewage effluents (Hawk 1999).

5 Main Topical and Systemic Photosensitizers

There is a large and increasing list of photoactive molecules to which we can be exposed to in our daily life and that can induce photosensitivity (*Table 15.3*). But there has been a higher concern on the evaluation of the phototoxic potential of cosmetics and consumer products before marketing and many photosensitizers have been removed or highly reduced in our ambience.

These "historical" photosensitizers include some predominantly photoallergic others mainly phototoxic: musk ambrette and natural bergamot oil were removed by the perfume industry, the sunscreen isopropyl–dibenzoylmethane was withdrawn in 1994, the sunscreen PABA (para-aminobenzoic acid) which sensitized about 4% of the American population in the 1950s is no longer used (Lowe 2006), the antibiotic olaquindox, a swine feed additive, was banned in 1998 by the European Commission (Emmert et al. 2007), and the halogenated salicylanylides were removed from disinfectants and hygiene products in most countries, since 1976. Nevertheless, even though some products are not available in Europe, they can be "imported" from other countries and induce photosensitivity (Emmert et al. 2007; Waters et al. 2009).

In most reports from Europe and the USA, the main topical photosensitizers are the UV filters (Darvay et al. 2001; Sheuer and Warshaw 2006) which represent 5.6–80% of the cases diagnosed by photopatch testing (Darvay et al. 2001; Cardoso et al. 2009; Bakkum and Heule 2002; Leonard et al. 2005), but they represent photoallergic reactions in the vast majority of cases. Furocoumarin-rich plants are an important source of phototoxicity, mainly in more sunny countries, and

Table 15.3
Main agents causing exogenous photosensitivity

1. Sunscreens[c]	
2. Plants[b]	**Umbelliferae** *Ammi majus* *Apium graveolens* (celery) *Pastinaca sativa* (parsnip) *Petroselinum crispum* (parsley) *Heracleum mantegazzianum* (giant hogweed)
	Rutacea Citrus spp, *Citrus aurantica v. bergamia* (bergamot) *Citrus aurantifolia* (lime) *Citrus limon* (lemon) *Ruta graveolans* (common rue) *Dictamus albus* (burning bush)
	Moracea *Ficus carica* (fig)
3. Drugs	**Antimicrobials**
	Tetracyclines[b] (doxycycline, minocycline)
	Sulphonamides (sulfametoxazole)
	Fluorquinolones (lomefloxacin[b], ciprofloxacin[b])
	Voriconazole[b], griseofulvin[b], efavirenz
	Nonsteroidal anti-inflammatory drugs (NSAIDs)
	Arylpropionic acids: Ketoprofen[a], tiaprofenic acid[b], suprofen, naproxen, ibuprofen, ibuproxam, carprofen Piroxicam[a], benzydamine, etofenamate[a] azapropazone, diclofenac, fenilbutazone, indometacine
	Phenotiazines
	Chlorpromazine, thioridazine Promethazine[a], Chorproethazine[a]
	Antidepressants
	clomipramine, imipramine, sertraline
	Cardiovascular drugs
	Amiodarone[b], quinidine, Furosemide and thiazide diuretics
	Anticancer agents
	Paclitaxel, 5-fluoruracil, Dacarbazine, methotrexate
	Miscellaneous
	Flutamide, sulfonylureas, fenofibrate, simvastatin

Table 15.3 (Continued)

4. "Historical" photosensitizers	**Perfumes:** musk ambrette and bergamot oil[b]
	Halogenated salicylanilides: tetrachlorsaliiynilide trichlorocarbanilide tribromsalicylanide
	Sunscreens: isopropyldibenzoylmethane, PABA
	Antibiotics: Olaquindox[a]

[a]Mainly photoallergic
[b]Mainly phototoxic
[c]Sunscreens are not detailed as they are responsible mainly for photoallergy

drugs, both phototoxic and photoallergic are, by far, the most frequent photosensitizers in Southern Europe (Cardoso et al. 2009; La Cuadra-Oyanguren et al. 2007; Leonard et al. 2005; Pigatto et al. 2008)

5.1 UV Filters

Due to the increased awareness of the sun-damaging effects, sunscreens are widely used, and UV filters are also included in moisturizing and facial creams, lipstick, nail varnish, shampoos, and other hair products, but adverse skin reactions from UV filters are not reported proportionally (Darvay et al. 2001). Also, as referred, most represent allergic, photoallergic, or photoaggravated allergic contact dermatitis, not phototoxicity (Bryden et al. 2006; Berne and Ros 1998; Pigatto et al. 2008; Leonard et al. 2005; La Cuadra-Oyanguren et al. 2007; Cardoso et al. 2009).

The newer UV filters – Mexoryl SX (terephtalydene dicamphor sulfonic acid), Tinosorb M (methylene-bis-benzotriazolyl tetramethylbutylphenol or bisoctrizole), and Tinosorb S (bis-ethylhexyloxyphenol methoxyphenyl triazine) – are photostable molecules and, in mixtures of several sunscreens, are able to photostabilize older photolabile UV filters, like butyl-methoxydibenzoylmethane and cinnamates. Therefore, they seem to be more efficient in protecting from the harmful effects of UVR (Lowe 2006) and, eventually, in reducing photosensitivity from the other UV filters.

5.2 Plants Causing Phytophotodermatitis

Photoactive furocoumarins, e.g., bergapten (5- methoxypsoralen), 8-methoxypsoralen, 5,6 dimethoxyisopsoralen, sphondin (6-methoxyisopsoralen), and isobergapten (5-methoxyisopsoralen) run in the sap of several plants, in variable amounts. They are beneficial for the plant which uses them as a protection against fungus and insects.

Since the antiquity, these substances have been used in folk medicine in the treatment of vitiligo and, more recently, in photochemotherapy (PUVA), but their acute and chronic phototoxic potential is well known and measures are regularly considered to avoid these adverse effects: A low UV dose is used in the beginning of therapy and in patients with lower phototypes, children under 16 are not usually admitted on PUVA therapy, and a cumulative dose below 1,000–1,500 J/cm^2 of UVA is advised for patients on photochemotherapy to reduce the potential risk of photocarcinogenesis and photoaging.

Aromatic oils rich in furocoumarins were used by the cosmetic industry in tanning oils, but their use has been considerably reduced as this accelerated tanning is harmful – the photosensitizer in the oil enhances UV-induced DNA aggression.

The natural bergamot oil, extracted from the rind of *Citrus bergamia,* previously included in oils and perfumes, was responsible for a very particular type of phototoxic dermatitis, "breloque dermatitis," or berlock dermatitis. It presented as erythema followed by hyperpigmentation, in a very particular shape of a pendant-like figure simulating a breloque, beginning in the face or neck and descending down to the collar. It corresponded to the place where the first drop of perfume is applied and the adjacent and dependent draining area. The natural oil of bergamot is no more used in perfumes and breloque dermatitis is an image of the past, but citrus oils containing psoralens can still induce phototoxicity when used in aromatic oils in sauna or in massages (Lovell 2000).

Nowadays, phototoxic dermatitis from psoralens occurs mainly from inadvertent contact with plants, either during recreation or in occupational settings. Main occupational exposures occur in rural workers or gardeners who harvest fruits or vegetables (parsnip, figs) or cut bushes and weeds (common rue – *Ruta graveolens*, burning bush – *Dictamnus albus*, or fig trees – *Ficus carica*) (Gonçalo et al. 1989; Lovell 2000) and in barmen who squeeze and peal the lime (*Citrus aurantifolia*) and other citrus fruits to prepare cocktails in the sunny weather (Wagner et al. 2002; Gonçalo 2004; Lovell 2000) (*Fig. 15.4*).

The most typical pattern of phytophotodermatitis was described by Oppenheim in 1934 – *dermatosis bullosa striata pratensis.* Corresponding to the contact with the damaged leaves of the plant, prickling linear erythematous

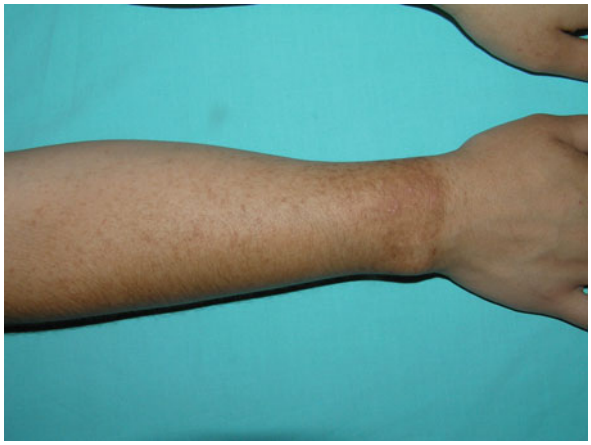

Fig. 15.4
Residual pigmentation in the forearms in a barman who squeezed limes and lemons for cocktails, during an outdoor summer festival (note limit due to glove protection)

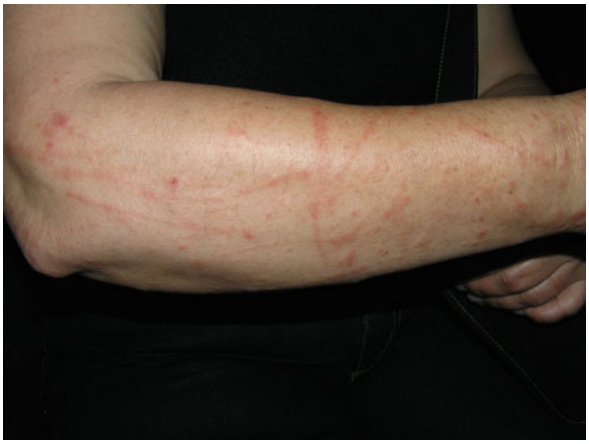

Fig. 15.5
Phytophotodermatitis with linear streaks of erythema and hyperpigmentation in a patient who contacted Ruta graveolens from her garden

skin streaks develop within 24–48 h followed by painful vesicles and bullae (*Figs. 15.5* and *15.6*). This gradually gives rise to long-lasting typical browny linear hyperpigmentation which, sometimes, allows a retrospective diagnosis (Gonçalo 2004).

Other patterns of phytophotodermatitis are the "strimmer dermatitis," a more diffuse involvement as the sap of the plant is sprayed all over the body by the string trimmer (Lovell 2000), a leg dermatitis in walkers who develop lesions only above the socks, and skin lesions in children who make trumpets or pea shooters from the

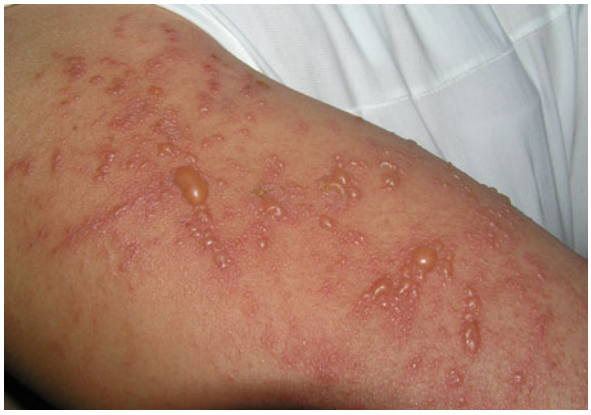

Fig. 15.6
Phytophotodermatitis with linear bullous lesions in the arms, after cutting a fig tree during a sunny day

hollow stems of the giant hogweed (*Heracleum mantegazzianum*) and developed blisters around their mouth (Lovell 2000).

Very occasionally, the ingestion of these plants can induce a systemic photosensitivity as in the cases of celery, parsnip or infusions of St. John's wort (*Hypericum perforatum L.*) used to treat depression (Lovell 2000). Also, they are occasionally used topic drug as a "folk medicine" with impressive adverse effects, as in a recent report where an infusion of *Ruta graveolens* was applied topically to relieve pain in fibromyalgia (Arias-Santiago et al. 2009).

Plants rich in furocoumarins causing phytophotodermatitis occur all over the globe and belong mainly to the families of Umbelliferae, Rutacea, and Moracea (*Table 15.3*)

5.3 Photosensitive Drugs

Drugs used systemically or applied topically are the main cause of exogenous photosensitivity, particularly in Southern European countries (Cardoso et al. 2009; La Cuadra-Oyanguren et al. 2007; Leonard et al. 2005; Pigatto et al. 2008).

Drugs manipulated in an occupational setting can induce photosensitivity: carprofen, a NSAID no more used in humans, induced photoallergic contact dermatitis in workers who manufacture the drug for animals (Kerr et al. 2008a; Walker et al. 2006), and photosensitivity has been reported in nurses and family members who smashed the tablets of chlorpromazine to give to their patients/relatives (Cardoso et al. 2009).

The main systemic drugs inducing photosensitivity are antimicrobials, particularly tetracyclines, fluorquinolones, sulfonamides, and some antifungals, NSAIDs, phenothiazines, and cardiovascular drugs. After topical application, NSAIDs are by far the most frequent cause (Cardoso et al. 2009; La Cuadra-Oyanguren et al. 2007; Leonard et al. 2005; Pigatto et al. 2008).

5.3.1 Antimicrobials

Systemic tetracyclines, particularly doxycycline and minocycline, are highly phototoxic, induce photoonycholysis and pseudoporphyria and, the latter, can also induce a bluish persistent pigmentation (Vassileva et al. 1998; Ferguson 1999).

The fluorquinolones induce phototoxic reactions, in some cases presenting as pseudoporphyria (Schmutz et al. 2008), as initially described for the first quinolone antibiotic, nalidixic acid (Vassileva et al. 1998). Ciprofloxacin was also responsible for purpura in photo-exposed areas (Urbina et al. 2006). Phototoxicity is particularly important and frequent (4–15% of treated patients) with fleroxacin, lomefloxacin, sparfloxacin, pefloxacin, and less frequent with ciprofloxacin, norfloxacin, ofloxacin, and enoxacin (Ferguson 1999). The recommendation to take the drug by the end of the day, therefore reducing drug concentrations in the circulation and in the skin during midday, can reduce this phototoxic reaction.

Although in vitro and in vivo tests prove the high phototoxic potential of fluorquinolones, photoallergy has also been reported with lomefloxacin (Oliveira et al. 1996; Kurumajin and Shono 1992) and enoxacin (Vassileva et al. 1998), sometimes with cross-reaction to other fluorquinolones (ciprofloxacin and flerofloxacin) (Kimura and Kawada 1998; Correia et al. 1994), positive lymphocyte stimulation tests, and drug-specific Th1 cells that recognize skin cells combined with UV irradiated fluorquinolone (Tokura et al. 2001). Moreover, the fluorquinolones also photosensitize DNA and may be photomutagenic and photocarcinogenic (Klecak et al. 1997). A patient on long-term ciprofloxacin therapy for multiresistant tuberculosis developed photosensitivity and highly aggressive squamous cell carcinomas of the face (personal experience).

Sulfonamide antibacterials, as well as sulfa-drug analogs (thiazide diuretics, hypoglycemic sulfonylureas, and celecoxib) and dapsone (diaminodiphenylsulfone) have been reported to cause photosensitivity within the spectrum both of UVB and UVA (Vassileva et al. 1998; Yazici et al. 2004) but this side effect is not so frequent with cotrimoxazole (trimethoprim/sulfamethoxazole) (Vassileva et al. 1998; Ferguson 1999).

Grisefulvin is a known phototoxic drug and can aggravate lupus erythematosus, as the more recent antifungal, terbinafine, which also induced subacute lupus erythematosus in patients with anti-Ro antibodies (Farhi et al. 2006). Another antifungal from a different chemical group, voriconazole, has recently been reported to cause severe photosensitivity (Béani 2009; Frick et al. 2010) and was considered responsible for skin cancer, including malignant melanoma (Auffret et al. 2006; McCarthy et al. 2007; Cowen et al. 2010; Miller et al. 2010).

5.3.2 Nonsteroidal Anti-inflammatory Drugs

Benoxaprofen marketed between 1980 and 1982 called the attention to photosensitivity from this class of drugs. Thereafter, photosensitivity was reported with all the other arylpropionic derivatives (carprofen, naproxen, suprofen, tiaprofenic acid, ketoprofen, and ibuprofen) and NSAIDs from other groups (azapropazone, diclofenac, piroxicam, fenilbutazone, celecoxib, benzydamine, and etofenamate) (Figueiredo 1994). The in vitro and in vivo phototoxic potential has been documented particularly for tiaprofenic acid (Figueiredo 1994). In humans, photopatch testing showed typically phototoxic reactions in more than half patients tested with tiaprofenic acid (5% pet) and 5 J/cm^2 of UVA (Gonçalo and Figueiredo 1992; Neumann et al. 1994, 2000), but in other studies tiaprofenic acid was typically photoallergic (Pigatto et al. 1996; LeCoz et al. 1998; Foti et al. 2008), therefore calling the attention to the concomitancy of both patterns of photosensitivity with the same drug.

Most topically applied NSAIDs are absorbed through the skin and cause distant lesions, resembling systemic photosensitivity. Benzydamine, widely used in the oral or genital mucosa, causes photosensitivity at distant sites (Elgezua et al. 2004), eventually after systemic absorption (Cardoso et al. 2009; La Cuadra-Oyanguren et al. 2007) and, when used in the mouth, can induce cheilitis and chin dermatitis as a manifestation of photoallergy (Cardoso et al. 2009).

Although ketoprofen and piroxicam are not the most sold NSAIDs, they cause most cases of photosensitivity (Cardoso et al. 2009; La Cuadra-Oyanguren et al. 2007; Leonard et al. 2005), particularly photoallergy and with a peculiar pattern of cross-reactions (Imai et al. 2005) (Béani 2009; Cardoso et al. 2009): cinnamic alcohol and

aldehyde, oxybenzone, octocrylene, and fenofibrate for ketoprofene (Pigatto et al. 1996; LeCoz et al. 1998; Devleeschouwer et al. 2008; Foti et al. 2008), and thimerosal and thiosalicylic acid for piroxicam (Gonçalo et al. 1992; Hariva et al. 1993).

5.3.3 Other Drugs as Photosensitizers

Phenothiazines used systemically (chlorpromazine and thioridazine) can induce photosensitivity, often with a lichenoid pattern and with residual pigmentation (Ferguson 1999). They are typically phototoxic, both in vitro and in vivo, but some cases of photoallergy also occur (Cardoso et al. 2009). Promethazine is a highly phototoxic drug that is still used as a topical antipruritic, at least in Portugal and Greece. In this setting, it induces many cases of photosensitivity, many of them photoallergic (Cardoso et al. 2009; Katsarou et al. 2008). Its analogue, chlorproethazine, marketed in France as Neuriplege® cream for muscle pain (Genevrier, Antibes, France), is also a frequent cause of photoallergic contact dermatitis (Barbaud et al. 2001a; Kerr et al. 2008b).

The antiarrhythmic amiodarone is a well-known photosensitizer that is still widely used. Apart from erythema in sun-exposed areas, it induces a bluish-gray hyperpigmentation in sun-exposed areas due to the accumulation of drug metabolites in the dermis (Ammoury et al. 2008).

The list of drugs causing photosensitivity is very large and always increasing, with the recent inclusion of biologics, namely, vandetanib, an orally effective VEGF-inhibitor used in oncology (Chang et al. 2009). Therefore, whenever a patient has a photosensitive eruption a systematic inquiry for drugs should be carefully conducted.

6 Diagnostic Procedures in Photosensitivity

Sometimes the lesions are so typical for a dermatologist, as in phytophotodermatitis or in exaggerated sunburn after the use of a systemic phototoxic drug, that no further diagnostic procedures are needed. A simple questionnaire can find the responsible agent. Also, in typical phototoxic reactions, both photopatch and photoprovocation tests are positive in the great majority of tested individuals. Therefore, they are not particularly useful for confirming the etiology of a phototoxic reaction, but they can disclose a hidden photoallergy.

Photopatch testing should be performed according to a standardized procedure (Bruynzeel et al. 2004), using a photoallergen series adapted to the geographic area (Cardoso et al. 2009; Gonçalo 2011) with additions according to patient exposure. Irradiation of one set of allergens at day 1 or day 2 with 5 J/cm2 of UVA is advised and readings should be performed immediately after irradiation and also 48 and/or 72 h thereafter (Bruynzeel et al. 2004).

Photopatch tests results have to be carefully interpreted. A reaction only in the irradiated side mainly with erythema and edema, without pruritus, exclusively limited to the test chamber area, with very sharp limits that begins shortly after irradiation, has its highest intensity by 24 h and regress by 48/72 h (decrescendo reaction) with hyperpigmentation, suggests a phototoxic reaction. A similar reaction may be observed in many individuals tested in the same conditions and, if histology is performed, there are many sunburn cells in the epidermis. On the other hand, a pruritic erythema with vesicles, diffuse limits extending beyond the chamber limit, that increases in intensity until 48–72 h after UV irradiation (crescendo reaction), suggests photoallergy (Neumann et al. 1994). But sometimes the photopatch test pattern is not so typical and the difficulties previously referred in the interpretation of clinical cases also occur in the interpretation of the photopatch tests.

The main indication for photopatch testing is the diagnosis of photallergic contact dermatitis, but photopatch testing can also be useful in the study of systemic drug photosensitivity (Gonçalo 1998, 2010; Barbaud et al. 2001b).

7 Conclusions

Phototoxic, photoallergic, and overlapping photosensitive reactions are still a frequent problem. They have a highly polymorphic clinical presentation, with different time courses and variations in the responsible agents depending on geographic areas and over times. Therefore, the dermatologist must be highly alert to search for a possible involvement of an exogenous chromophore in a photosensitive patient and try to confirm its contribution to photosensitivity. A correct questionnaire should be conducted and, although not so important in typical phototoxic cases, complementary tests including photopatch and photoprovocation tests may contribute to the final etiologic diagnosis and, consequently, allow an adequate patient advice concerning further eviction of the photosensitizer and related chemicals.

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