Drug photoallergy

Yoshiki Tokura MD, PhD

Department of Dermatology, Hamamatsu University School of Medicine, Hamamatsu, Japan

Correspondence
Yoshiki Tokura, Department of Dermatology, Hamamatsu University School of Medicine, Hamamatsu, Japan.
Email: tokura@med.uoeh-u.ac.jp

Abstract
Drugs are one of the representative exogenous agents that cause photosensitive dermatitis. Both phototoxic and photoallergic mechanisms exist in photosensitivity to exogenous agents. While the phototoxic reaction is mediated mainly by reactive oxygen species, the photoallergic reaction is induced and elicited by immunological consequences. Two hypotheses have been put forward to explain the formation of photoallergen: prohapten and photohapten. The vast majority of clinically photoallergic drugs are photohapten rather than prohapten. Clinically, photocontact dermatitis and drug photosensitivity are the two major disorders caused by topical and systemic exogenous photosensitizers, respectively. The main cause of photocontact dermatitis is nonsteroidal anti-inflammatory drugs. In drug photosensitivity, various causative agents have been reported and are recently represented by hydrochlorothiazide, quinolones, piroxicam, and flutamide. Orally administered drugs diffuse from the blood to the epidermis, and keratinocytes are photoderivatized with a given drug upon ultraviolet (UV) A irradiation, leading to photoantigen formation and cytokine production. In parallel, dendritic cells become photohapten-bearing, T-cell-sensitizing cells. Considering the mechanisms of photoallergy to chemicals, several in vitro assessments have been proposed to detect the photoallergenicity. Finally, a recent observation with newly marketed drugs has demonstrated that drugs may function as immunomodulators and induce photosensitivity as typically seen in anti-CCR4 antibody.

KEYWORDS
drug, photoallergy, photocontact dermatitis, photohapten, photosensitivity

1 | INTRODUCTION

Photosensitivity is clinically recognized as sunlight-induced dermatitis. There are various diseases that manifest as photosensitivity, including photocontact dermatitis, drug photosensitivity, xeroderma pigmentosum, porphyria, pellagra, hydroa vacciniforme, solar urticaria, polymorphous light eruption, lupus erythematosus, and chronic actinic dermatitis. Among them, photocontact dermatitis and drug photosensitivity are disorders caused by topical and systemic exogenous photosensitizers, respectively, and their incidences are higher than the others.7 It is interesting that the mechanisms underlying some of photosensitive diseases have recently been elucidated, as represented by pellagra.2

Recent photoallergic and phototoxic (photoirritable) substances include pharmaceutical drugs, cosmetic ingredients, sunscreens, fragrances, and nutraceuticals.3 Thus, drugs are one of the most important causes of photoallergy,4,5 and the basic and clinical information on the drug photosensitivity is helpful to understand photosensitivity to cosmetics and fragrances.

This review aims to highlight the mechanism of drug photoallergy, focusing on the assessments of photoallergenicity as well as phototoxicity of chemicals. A recent finding that
immunomodulatory drugs can induce photosensitivity is also mentioned.

2 | PROPERTIES OF PHOTOSENSITIZERS

2.1 | Two types of photosensitivity to chemicals

Photosensitive materials have two properties, phototoxicity and photoallergenicity. The phototoxic reaction eventually results in a cellular cytotoxicity, while the photoallergic reaction is induced and elicited by immunological consequences involving various immunocompetent cells and molecules.6-8 Each photosensitive chemical has different dominancy to phototoxicity or photoallergenicity. For example, psoralen and porphyrin derivatives are strong phototoxic agents with scarce photoallergenicity and thus used for photochemotherapy or photodynamic therapy with few photoallergic adverse effects.9 By contrast, ketoprofen and fluoroquinolones (FQs) are causative agents for photocontact dermatitis and drug photoallergy, respectively.7 It is noted, however, that all photoallergic chemicals have a phototoxic property because the photoallergic reaction requires the initial phototoxic step (Figure 1) in which photosensitizers bind to protein via the formation of reactive oxygen species (ROS).1

Historically, it was believed that most cases of photocontact dermatitis and drug photoallergy are induced by the phototoxic reaction, and the incidence of the photoallergic reaction is low. However, recent clinical studies have suggested that the photoallergic type is rather common.7 This misunderstanding seems to be caused by easy evaluation of phototoxicity and difficult assessment of photoallergenicity.

The action spectrum (the provocative light wavelength) of these two types of photosensitivity is mostly ultraviolet A light (UVA; 320-400 nm).1 Ultraviolet B light (UVB; 290-320 nm) rarely evokes the diseases, as represented by photosensitivity to drugs, such as sulfanilamide,10 ranitidine,11 and bicalutamide.12 Photoaugmentation by UVA and UVB is occasionally seen in some drugs.13

2.2 | Phototoxicity

Phototoxicity is mainly caused by generation of ROS.1,13,14 Singlet oxygen is most important for chemical phototoxicity and the generally termed type II photodynamic reaction.14 The target molecules of phototoxic chemicals include proteins or amino acids, lipids, and DNA,1,13,14 and their alterations lead to cellular damage or even cellular death (Figure 1). Therefore, cellular cytotoxicity has been used as a classical method to evaluate phototoxicity. Both necrosis and apoptosis occur in cells phototreated with chemicals and UV.15 Various cells have been utilized for cytotoxicity assessments, including erythrocytes, fibroblasts, keratinocytes, macrophages, lymphocytes, and even fungi, but the reduction in neutral red uptake (NRU) in phototreated fibroblasts (3T3) has been the standard assessment.16

Phototoxicity can also be evaluated using target molecules, and such tests include protein (histidine, lysine, and cysteine) degradation, lipid oxidation, and plasmid DNA-breaking activity.13 In addition, the binding capacity of chemicals to protein upon exposure to UV is a phototoxicity test.17 Although this reaction is derived from a phototoxic moiety of chemicals, the resultant chemical-protein complex affords a photoantigenic
determinant. Thus, it is now thought that photobinding of agents with protein represents a photoallergic potency of a given chemical (Figure 1).

2.3 | Photoallergenicity

Photoallergy is a well-organized immunological reaction. The pathogenesis of contact dermatitis and drug hypersensitivity is based on the hapten hypothesis: A hapten binds covalently to protein, and the resulting conjugate can be recognized as immunogenic determinants. Likewise, photosensitive materials have a haptenic moeity. Two hypotheses have been put forward to explain the formation of photoallergens (Figure 2). The initially proposed one is the prohapten, which is converted to a complete hapten by UV irradiation, and the resultant hapten can bind to protein. Another theory is the photohapten, which needs to coexist with protein, and upon UV irradiation, a covalent bond is formed via the formation of ROS. In the case of the photohapten, UVA-preirradiated photosensitive chemicals are incapable of binding to protein. In a clinical photopatch test, a causative chemical is applied to the skin and UVA is irradiated to the site. This method is to examine the photohaptenic property. In the case of prohaptenes, however, an UV-preirradiated chemical should be applied to the skin as a patch test. Empirically, photopatch test has been performed to examine photoallergy. This fact, together with our studies, demonstrates that the vast majority of clinically photoallergic sensitizers are photohaptenes rather than prohaptenes. Accordingly, patients usually exhibit a positive photopatch test to culprit chemicals but negative patch test to UVA-preirradiated chemicals. UVA is the action spectrum of photoderivatization of proteins or cells with photoallergic chemicals.

3 | CLINICAL MANIFESTATIONS OF DRUG PHOTOALLERGY

3.1 | Allergic photocontact dermatitis

Photocontact dermatitis is a specialized form of contact dermatitis and exhibits an eczematous eruption consisting of erythema, papules/vesicles, and occasionally bullae, at the skin sites where a photocontactant is applied. The action spectrum of this photosensitivity is mainly UVA. The sensitivity is divided into two, phototoxic and photoallergic, types. Recent attention to phototoxic materials has decreased the incidence of the phototoxic type of photocontact dermatitis. Therefore, the incidence of photoallergy is now thought to be higher than that of phototoxicity.

Various agents have been reported to evoke allergic photocontact dermatitis. Historically, halogenated salicylanilide, such as 3,3′,4′,5-tetrachlorosalicylanilide (TCSA), and related compounds, which were contained in soaps/detergents and used as topical antimicrobial agents, yielded a large number of patients with photocontact dermatitis. Elimination of these germicides from the market reduced the frequency of the patients. Perfumes, such as musk ambrette and 6-methylcoumarin, and sunscreen agents, especially benzophenone-3 (oxybenzone), had been causative thereafter.

Recently emerging causative agents of photocontact dermatitis are topical nonsteroidal, anti-inflammatory drugs (NSAIDs), such as ketoprofen, suprofen, suprofen, dexketoprofen, and piketoprofen. Diclofenac rarely induces photosensitivity. Benzydamine, a nonaspirin-like anti-inflammatory topical agent, provokes photocontact dermatitis on the skin and lips. Sunscreens are still very important photoallergens in cosmetics. In this regard, not only benzophenone and para-amino benzoic acid (PABA) derivatives, which are now rarely

![Figure 2](https://example.com/figure2.png)

**Figure 2** Two hypotheses on the formation of photoallergens
used, but also dibenzoylmethanes, such as PARSOL 1789,32-34 may be causative.

It is notable that there is a photoallergic cross-reactivity between ketoprofen, suprofen, benzophenone, tiaprofenic acid, and antilipidemic drug fenofibrate.

3.2 | Drug photosensitivity (photosensitive drug eruption)

Drug photosensitivity is one of the adverse reactions of systemically administered drugs35 and is clinically recognized as skin eruptions on sun-exposed areas, including cheeks, nose, forehead, posterior nuchal area, V area of neck, dorsal aspect of hands, extensor surface of forearms, and lower legs. The action spectrum is usually UVA, although UVB may exceptionally induce the sensitivity or augment the level of UVA-induced sensitivity.13 It should be noted that the absorption spectrum and the action spectrum are same in phototoxicity; however, the action spectrum is shifted from the absorption spectrum to longer wave range in photoallergy.

Drug photosensitivity usually shows erythematous eruption and lichenoid eruption, and occasionally bullous eruption and leukomelanoderma. The erythematous eruption is the common type of drug photoallergy and may have scaling on the surface. The lichenoid eruption is occasionally similar to lichen planus.36 This type is clinically characterized by erythematous but dark-colored papules and histologically by CD8+ T-cell infiltration in the upper dermis and attacking keratinocytes.37 Leukomelanoderma displays a unique clinical appearance of a mixture of pigmentation and depigmentation and occurs in dark-colored individuals such as Japanese. In some patients with the erythematous, lichenoid, and bullous eruptions, biopsied specimens exhibit infiltration of eosinophils as well as lymphocytes.38

Various drugs have been reported to induce photosensitivity, including quinolones as represented by fluoroquinolones (FQs),7,39,40 afloqualone (AQ),17,41 NSAIDs24,26,42,43 and others. In the period of 1980-2006 (total of 718 cases in the Japanese literature), the top 25 drugs with high incidence of photosensitivity are as follows: sparfloxacin, piroxicam, fleroxacin, AQ, griseofulvin, enoxacin, lomefloxacin, tegafur, ampiroxicam, tilisolol, mequitazine, meticrane, flutamide, chlorpromazine, furosemide, chlorella, doxycycline, carbamazepine, thiaprofen, diltiazem, salazosulfapyridine, hydrochlorothiazide, dactarbazine, isoniazid, pyridoxine, promethazine, and dibucaine. However, highly incident drugs are recently represented by the major histocompatibility complex (MHC).6 On the one hand, mice with H-2b,d alleles are high responders, whereas the H-2k haplotype is closely associated with low responders.6 On the other hand, in allergic photocontact dermatitis to ketoprofen, H-2b is associated with high responders and H-2b,d with low responders.42 Therefore, high responder H-2 haplotypes are different between photohaptenic chemicals.

We have taken several different approaches to establish mouse models of drug photoallergy with the use of AQ17,41 and FQs.39 Drug photoallergy is successfully induced and elicited by systemic administration of a drug and subsequent UVA irradiation of the skin,17,39 which is mimircy of clinical drug photoallergy. In another system, photoallergy is induced by sensitization and elicitation with subcutaneous injections of epidermal cells that are photomodified in vitro with a drug under UVA exposure.17 The essential role of T cells in drug photoallergy has been clearly demonstrated by mouse models of photoallergy to AQ and FQ.39,41 Drug photoallergy is mediated by CD4+ T cells,39,41 and dendritic cells (DCs) are photomodified with a given drug and are capable of inducing the proliferation of primed CD4+ T cells.39 CD8+ T cells may be required for the full-blown sensitivity.41,42

We have also established a murine model of eosinophil-infiltrating drug photoallergy by administration of AQ in combination with UVA.
irradiation. Repeated sensitization (>ten-times) with AQ plus UVA successfully induced eosinophil infiltration upon challenge with subcutaneous AQ plus UVA irradiation in AKR/J mice. CD4+ T cells are responsible for this sensitivity, but CD8+ T cells induce this sensitivity at a lower level. AQ-photoimmunized lymph node cells produce a higher level of IL-4 and a lower level of IFN-γ. The skin of AQ-photochallenged site exhibits high expression of CCL24/eotaxin-2, a chemokine for eosinophils. Thus, eosinophilic drug photoallergy is mediated by sensitized Th2 cells and locally produced eosinophil-attracting chemokines.

5 IMMUNOLOGICAL MECHANISMS OF DRUG PHOTOALLERGY

5.1 Photobinding of drugs to protein

The main sequential events in allergic photocontact dermatitis and drug photosensitivity are virtually the same as those of ordinary contact dermatitis and drug eruption, except for the requirement of UV irradiation in sensitization and challenge. Photobinding of chemicals to skin constituents is the initial step of drug photoallergy (Figure 3). In photocontact dermatitis, a chemical is applied to the skin from the outside. Meanwhile, in drug photosensitivity, a systemically administered drug diffuses to the epidermis from the blood. Protein is covalently bound to a photodegraded site of photohapten to form an allergic photohapten-protein complex. Lysine is a preferential amino acid to allow binding to FQs, but other amino acids possibly afford the binding sites.

UVA is the action spectrum of photoderivatization of protein with photosensitizers. This is in accordance with the historical notion that in the case of photoallergic reaction to exogenous agents, the action spectrum is shifted from its absorption wavelength to a longer wavelength. Thus, even if the absorption spectrum of a given material is UVB, its action spectrum falls in UVA wave range.

5.2 Photomodification of epidermal keratinocytes with drugs

Upon photobinding of photosensitizers to protein, epidermal cells (possibly even dermal cells) can be photoconjugated with
photosensitizers. Various proteins, including key signaling proteins, on the surface of epidermal keratinocytes are photomodified with drugs, leading to production of cytokines, such as tumor necrosis factor-α (TNF-α), interleukin (IL)-1α, and granulocyte macrophage colony-stimulating factor (GM-CSF). These proinflammatory cytokines induce maturation of epidermal Langerhans cells (LCs), which are professional antigen-presenting dendritic cells (DCs).

In addition, uptake of drugs by keratinocytes and irradiation with UVA would produce ROS, leading to activation of antioxidant response element.

5.3 | Photomodification of DCs with drugs

In parallel with photoconjugation of keratinocytes, DCs, including epidermal LCs and dermal DCs, are also photoderivatized. The photohapten-bearing LCs migrate to the draining lymph nodes in the induction phase of allergic photocontact dermatitis. In our murine model of FQ photoallergy, systemically administered FQ diffuses to the epidermis. Upon UVA exposure, LCs are photomodified with a given FQ in their MHC class II-associated peptides. Notably, recent studies suggest that dermal DCs play a positive role, and LCs serve as regulatory antigen-presenting cells for sensitization of contact hypersensitivity to hapten. This provides an implication that dermal DCs photomodified with chemicals can sensitize specific T cells.

Photosensitive chemicals and UVA irradiation not only yield photoantigens but also promote the antigen-presenting ability of DCs. The expression of MHC class II, CD54, CD80, and CD86 is elevated to antigens but also promote the antigen-presenting ability of DCs. Therefore, as ordinary haptens, photohaptns are capable of inducing immunocompetent molecules on antigen-presenting cells when irradiated with UVA.

5.4 | Sensitization of T cells by photohapten-bearing DCs in draining lymph nodes

Migration and maturation of DCs are induced directly by photoderivatization of DCs with photohapten and indirectly by cytokines released from photohapten-stimulated keratinocytes. In the draining lymph nodes, DCs sensitize naïve T cells to be memory/effector T cells. Recent findings with conventional hapten suggest the differential roles of dermal DCs and LCs for effector T cells and regulatory T cells, respectively.

5.5 | Elicitation of sensitivity by sensitized T cells

Upon challenge with the same chemical plus UV as induction, skin eruption is elicited by sensitized T cells. An adaptive transfer study using immune T cells showed that transfer of CD4⁺ T cells induced ketoprofen photosensitivity in naïve recipient mice, but transfer of both CD4⁺ and CD8⁺ T cells produced the full-blown sensitivity reaction. Murine photoallergic contact dermatitis to TCSA involves both positive and regulatory immunologic pathways. The suppressive pathway is mediated by IL-10-producing Th2 cells, which had been known as suppressor T cells and may correspond to recently named regulatory T cells (Tregs). Sensitization with TCSA plus UVA is more prone to induce Th2 cells compared with ordinary haptns, suggesting that the suppressive immunologic pathway is clearly detectable in this sensitivity. The low responsiveness of allergic photocontact dermatitis in the H-2k strain is due to the preferential activation of Th2 cells or Tregs.

6 | PHOTOSAFETY ASSESSMENTS OF CHEMICALS

6.1 | History of photosafety evaluation and phototoxicity assessments

Photosafety assessments of chemical materials were initiated with methods to evaluate phototoxicity. In vivo animal tests have been used to assess phototoxicological properties by skin application of materials and subsequent UV irradiation in guinea pigs and mice. Investigators often examine the photoallergenicity in parallel with the phototoxicity. However, due to regulatory constraints and ethical concerns, the development of alternative in vitro assays is necessary, following the 7th amendment (2003) of the European Cosmetics Directive.

Guidance on the photosafety testing of medical products was established by the regulatory agencies in the United States and EU in the early 2000s. ICH S10 guidelines on photosafety evaluation reached step 5 of the ICH process in 2014, describing detailed photosafety assessment strategies. However, the current ICH S10 guideline "photosafety evaluation of pharmaceuticals" is intended to de-risk the photoirritation of new drug candidates, and the risk management on photoallergy and photogenotoxicity is currently out of scope because of limited best practice.

There have been various in vitro phototoxicity tests. Cytotoxic assays are common and evaluated using fibroblasts (3T3), erythrocytes, Candida albicans, macrophages, lymphocytes, and keratinocytes. 3T3 NRU phototoxicity test was adopted by OECD guideline in 2004. ROS assay was adopted in the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) S10 guideline (2013). Plasmid DNA-breaking activity was proposed as a sensitive method. The phototoxicity of chemicals also can be assessed by their activities to bind to protein and amino acids, and resultant reduction in certain amino acids. It is notable that the ability to bind to proteins/amino acids also indicates photoallergenicity of chemicals.

6.2 | Photoallergenicity assessments

As for photoallergy, several in vitro methods have been proposed, but none of them has yet been accepted for prediction tests (Table 1). In vitro assessments of photoallergenic potentials of chemicals reflect one or two steps of the sensitivity. The major
Antioxidant response element (ARE) assay is used to test sensitizers or photosensitizers, and it targets guideline. Uptake of a chemical by keratinocytes and irradiation with UVA would produce ROS, leading to activation of ARE. Therefore, photosensitizer plus UVA activates Keap1-Nrf2-ARE pathway in keratinocytes (Figure 4). Keap1 is a sensor protein and cytochrome-rich. Photosensitizers bind to Keap1 by UVA, and activated Keap1 is dissociated from Nrf2, leading to activation of ARE promoter. Original reporter cell line is AREc32 reporter breast cancer cells, and KeratinoSens™ is currently used reporter cells, which are HaCaT cells with stable insertion of a luciferase reporter gene. It was shown that accuracy of predicting photoallergenicity/phototoxicity was 70% with AREc32 cells and 67% with KeratinoSens™, and specificity was 100%.58

In photo-h-CLAT, monocyte cell line THP-1 cells are incubated in a test chemical solution and irradiated with UVA. The expression of CD54, CD86, and HLA-DR (MHC class II molecule) is measured by flow cytometry (Figure 5). This preincubation method is to see the photosensitization capacity. When THP-1 cells are incubated UVA-preirradiated chemical solution and then subjected to flow cytometric analysis, the photoactivated ability can be evaluated. Simple incubation with the solution represents the haptenic capacity. In our study, ketoprofen as well as TCSA shows the pattern of photohapten.59 As haptenic materials, it may be reasonable that the estimated concentration that yields a stimulation index of two (EC2) is appropriate for CD54 expression and EC1.5 is for CD86.59 When the phototreated cells express higher levels of MHC class II and costimulatory molecules, such as CD86, CD80 or CD40, the substance would have an ability to photosensitize and photoelicit T cells.

By photo-SH/NH2 test, changes in cell-surface thiols and amines can be monitored. The SH in vitro sensitization test is useful to measure changes in cell-surface thiols induced by a hapten and is a model of activation of intracellular signal transduction. Alterations of cell-surface thiols might be mainly caused by hapten-protein binding. Thus, we can predict photosensitization, including photoallergenicity, by assessing the changes in both cell-surface thiols and amines. Using the criterion of more than 15% change in cell-surface thiols and/or amines, 22 of 26 known photosensitizers (15 of 18 photoallergens, 7 of 8 photoirritants) were judged positive. The accuracy for predicting photosensitizers was 87.9% (sensitivity/specificity; 84.6%/100%), and the accuracy for predicting photoallergens was 69.7% (sensitivity/specificity; 83.3%/53.3%).60

The capacity of photosensitizing chemicals with ultraviolet A light (UVA) to induce apoptosis is one of the methods to assess their phototoxic and potentially photoallergenic properties, as apoptotic cells may be easily presented by antigen-presenting cells. Significant apoptosis was found in TCSA, bithionol, chlorpromazine, sparfloxacin, and enoxacin, as well as 8-MOP as assessed by both annexin V and active caspase-3 stainings in HaCaT keratinocytes.15

### 7 NEW TYPE OF DRUG PHOTOALLERGY

Recently marketed drugs may induce a new type of photosensitivity by serving as an immunomodulator but not a photohapten.
Mogamulizumab (Mog) is a defucosylated, therapeutic monoclonal antibody, targeting CCR4, and was first approved in Japan for the treatment of adult T-cell leukemia/lymphoma (ATLL), followed by cutaneous T-cell lymphoma and peripheral T-cell lymphoma. We treated 7 cutaneous lymphoma patients with Mog. Upon combination treatment with narrow-band UVB, 4 of 7 patients developed photosensitivity dermatitis following Mog therapy, including 2 cases of mycosis fungoides and others. Phototest revealed that the action spectrum of the photosensitivity was UVB in 3 cases and both UVB and UVA in one case. The photosensitive lesions were characterized by a lichenoid tissue reaction with a CD8+ T-cell–dominant infiltrate, sharing the feature with chronic actinic dermatitis (CAD), an autoreactive photodermatosis with a cytotoxic T-cell response. Foxp3+ regulatory T cells (Tregs) were decreased in the photosensitivity lesions compared with the lymphoma lesions.61

Mog-induced photosensitivity is an immune-related adverse effect (irAE) and virtually identical to CAD. Treg depletion by Mog may induce the photosensitivity. It should be kept in mind that phototherapy exerts an adverse effect in combination with Treg-suppressing Abs or immune checkpoint inhibitors.
The most important issue in drug photoallergy is its diagnosis and identification of causative drugs. Photopatch test, clinically used for the diagnosis, may be false negative, because some drugs are trapped in the stratum corneum. We have therefore attempted to establish in vitro tests to diagnose drug photoallergy and used a modified lymphocyte stimulation test using drug-photomodified cells. This response reflects the proliferative response of T cells to a photohaptenic moiety of chemical. There are a large number of drugs causative for photoallergy, and even newly marketed drugs could evoke photoallergy.

Attention should be paid to new types of photosensitivity, which are represented by the immune-related adverse effect of mogamulizumab. Our recent observation on voriconazole photocarcinogenesis further suggests that a produg and its metabolite play different roles in conjunction with UV and construct a photodisordered condition. Finally, recently marketed drugs, such as pirfenidone, show that a long-term photosensitivity by releasing IL-10. J Immunol. 1996;156:1824–1831.

CONFLICT OF INTEREST
The author declares no conflict of interests.

REFERENCES


**How to cite this article:** Tokura Y. Drug photoallergy. J Cutan Immunol Allergy. 2018;00:1–10. [https://doi.org/10.1002/cia2.12017](https://doi.org/10.1002/cia2.12017)