

Benzophenones

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Abstract: Benzophenones are ultraviolet light filters that have been documented to cause a myriad of adverse cutaneous reactions, including contact and photocontact dermatitis, contact and photocontact urticaria, and anaphylaxis. In recent years, they have become particularly well known for their ability to induce allergy and photoallergy. Topical sunscreens and other cosmetics are the sources of these allergens in most patients, but reports of reactions secondary to use of industrial products also exist. Benzophenones as a group have been named the American Contact Dermatitis Society's Allergen of the Year for 2014 to raise awareness of both allergy and photoallergy to these ubiquitous agents.

Benzophenones are chemical ultraviolet light absorbers. They primarily absorb light in the UV-B range (290–320 nm), whereas 2 benzophenones (benzophenone-3 and benzophenone-4) also absorb UV-AII light (321–340 nm).¹ Benzophenones-1 through benzophenones-12 are substituted derivatives of 2-hydroxybenzophenone and are currently being used for a wide variety of purposes in the United States. These aromatic ketones are planar molecules that are capable of photoabsorption and resonance stabilization, which account for their ability to protect human skin and commercial products from damaging ultraviolet radiation. All benzophenones have slightly different properties based on specific molecular substitutions (Table 1).

Benzophenones were initially used as preservatives in industrial products such as paints, varnishes, and plastics to extend shelf life and reduce photodegradation. In the 1950s, benzophenones were introduced into sunscreens.² Although 6 different benzophenones were initially used as sunscreens, benzophenones-3, -4, -8, and -10 are now the 4 agents most commonly used in personal care products.³ The amount of benzophenone-3 used in US sunscreens is more than all other benzophenones combined; in a 2011 study of the prevalence of known contact allergens in cosmetic and skin care products, benzophenone-3 was found in 68% of the 201

sunscreens assessed.⁴ Cosmetic and toiletry products such as moisturizers, hair sprays, hair dyes, perfumes, shampoos, detergent bars, and nail polishes may also contain benzophenones. Other benzophenones continue to be used in industry, with applications ranging from incorporation into plastic lens filters for color photography, aerosol sprays to protect color prints, transparent shades to protect window displays, and many polystyrene, acrylic, and rubber products to prevent darkening and loss of structural integrity.³

Benzophenones have been documented to cause a myriad of adverse cutaneous reactions, including contact and photocontact dermatitis, contact and photocontact urticaria, and anaphylaxis.^{5–7} In recent years, they have become particularly well known for their ability to induce allergy and photoallergy. Topical sunscreens and other cosmetics are the sources of these allergens in most patients, but reports of reactions secondary to use of industrial products also exist.

ALLERGIC CONTACT DERMATITIS

Allergic contact dermatitis to benzophenone-3 was first documented in 1972.⁸ Today, it is not only the most common benzophenone to cause positive patch test reactions, but also it is the most common UV filter, overall, to cause allergy. The most recent 10-year retrospective analysis of the North American Contact Dermatitis Group Data (NACDG; 2001–2010) found that of the 219 of 23,908 patch tested patients with sunscreen listed as an allergen source, 70.2% had positive patch test reactions to benzophenone-3.⁹ This finding is consistent with data from other geographic locations. Not only was benzophenone-3 the leading allergen in an Australian retrospective analysis of 6292 patients patch tested with suspicion for allergy to sunscreen, causing 28% of positive reactions,¹⁰ but also recent European multicenter studies and a Canadian single-center study have also found benzophenone-3 to be among the most significant sunscreen allergens.^{11–13}

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TABLE 1. Benzophenone Properties, Products, and Patch Test Concentrations

	Other Names	Structure	Properties
Benzophenone-1	2,4-Dihydroxybenzophenone benzoresorcinol, 4-benzoyl resorcinol, (2,4-dihydroxyphenyl)- phenylmethanone, resbenzophenone		-light yellow powder insoluble in water
Benzophenone-2	2,2',4,4'-Tetrahydroxybenzophenone		-yellow crystalline solid -slightly soluble in water and toluene
Benzophenone-3	Oxybenzone 2-hydroxy-4-methoxybenzophenone		-light cream powder -soluble in most organic solvents and insoluble in water -can cross the epidermal barrier -metabolites are excreted in the urine after widespread topical application
Benzophenone-4	Sulisobenzene, 2-hydroxy-4-methoxybenzophenone-5-sulfonic acid		-pale ivory powder -soluble in water
Benzophenone-5	2-Hydroxy-4-methoxybenzophenone-5-sodium sulfonate		-water soluble

TABLE 1.

Source	Patch Test Concentration	Allergic Contact Dermatitis Author ^{ref#} -Reactions	Photoallergic Contact Dermatitis Author ^{ref#} -Reactions
-personal care products	1% pet*	NR	NR
-personal care products -herbicides	1% pet.†	NR	1 <i>total reaction</i> ; 1 study Shaw et al ³⁰ –1
-personal care products -agricultural films (such as polyvinyl chloride)	10% pet.‡	45 <i>total reactions</i> ; 15 <i>studies</i> Torres and Correia ²³ –1 Bilsland and Ferguson ²⁴ –2 Szczerko et al ³² –1 Rademaker ²⁵ –1 Darvay et al ²⁶ –8 Crouch et al ²⁷ –1 Nedorost ²⁰ –1 Kiec-Swierczynska et al ³⁶ –1 Bryden et al ³¹ –9 Rodríguez et al ³⁵ –2 Hughes and Stone ¹⁴ –3 Scalf et al ¹⁷ –3 Travassos et al ¹⁸ –5 Sasseville et al ³⁸ –1 EMCPPTS ¹² –6 Greenspoon et al ¹³ –17	153 <i>total reactions</i> ; 13 <i>studies</i> Szczerko et al ³² –35 Horn et al ³⁹ –1 Darvay et al ²⁶ –14 Crouch et al ²⁷ –3 Nedorost ²⁰ –1 Kiec-Swierczynska et al ³⁶ –1 Bryden et al ³¹ –27 Rodríguez et al ³⁵ –22 Scalf et al ¹⁷ –5 Cardoso et al ³⁴ –3 Shaw et al ³⁰ –1 Victor et al ²⁸ –3 EMCPPTS ¹² –37 Greenspoon et al ¹³ –12
-personal care products -hair care products	10% pet* 2% pet.†	46 <i>total reactions</i> ; 6 <i>studies</i> Ramsay ⁸ –1 Bryden et al ³¹ –18 Hughes and Stone ¹⁴ –13 Scalf et al ¹⁷ –6 Travassos et al ¹⁸ –7 Sasseville et al ³⁸ –1 Greenspoon et al ¹³ –3	26 <i>total reactions</i> ; 6 <i>studies</i> Bryden et al ³¹ –7 Rodríguez et al ³⁵ Scalf et al ¹⁷ Cardoso et al ³⁴ –3 Victor et al ²⁸ –3 EMCPPTS ¹² –3
-personal care products	NR	NR	NR

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TABLE 1. (Continued)

	Other Names	Structure	Properties
Benzophenone-6	2,2'-Dihydroxy-4,4'-dimethoxybenzophenone, bis(2-hydroxy-4-methoxyphenyl) methanone		-light yellow solid -insoluble in water
Benzophenone-7	5-Chloro-2-hydroxybenzophenone, 2-hydroxy-5-chlorobenzophenone		
Benzophenone-8	Dioxybenzone, 2,2'-dihydroxy-4-methoxybenzophenone		-yellow crystalline solid -slightly soluble in water
Benzophenone-9	Sodium 2,2'-dihydroxy-4,4'-dimethoxy-5-sulfo benzophenone		-light yellow powder -water soluble
Benzophenone-10	Mexenone, 2-hydroxy-4-methoxy-4'-methylbenzophenone		
Benzophenone-11	(mixture of benzophenone-6 and other tetra-substituted benzophenones)		-yellow or tan powder
Benzophenone-12	Octabenzene, 2-hydroxy-4-(octyloxy)benzophenone, (2-hydroxy-4-(octyloxy)phenyl)phenylmethanone		

*De Groot.

†As seen in Shaw et al⁸⁰ 2010.

‡Chemotechnique recommended primary patch test concentration.

TABLE 1. (Continued)

Source	Patch Test Concentration	Allergic Contact Dermatitis Author ^{ref#} -Reactions	Photoallergic Contact Dermatitis Author ^{ref#} -Reactions
-personal care products	2% pet.*	NR	NR
-commercial grain fungicide	NR	NR	NR
-personal care products	2% pet.*	2 total reactions; 2 studies Pariser ¹⁹ —1 Sasseville et al ³⁸ —1	NR
-personal care products -grain insecticide	NR	NR	NR
-personal care products	10% pet.†	33 total reactions; 8 studies Millard and Barrett ²¹ —2 English et al ²² —6 Torres and Correia ²³ —1 Bisland and Ferguson ²⁴ —6 Rademaker ²⁵ —1 Darvay et al ²⁶ —13 Crouch et al ²⁷ —3 Hughes and Stone ¹⁴ —1	16 total reactions; 7 studies Burry ²⁹ —1 Torres and Correia ²³ —1 Szczurko et al ³² —1 Darvay et al ²⁶ —9 Kiec-Swierczynska et al ³⁶ —1 Rodríguez et al ³⁵ —2 Cardoso et al ³⁴ —1
-personal care products	2% pet.*	NR	NR
-food stabilizer in petroleum wax -antioxidant/stabilizer in olefin polymers	NR	NR	NR

Allergic contact dermatitis to the other benzophenones commonly used in personal care products is also well documented. Benzophenone-4 was “an emerging allergen in cosmetics and toiletries” 10 years ago because the reports of sensitized patients continued to surface secondary to its incorporation into sunscreens, hair care products, and shower gels.^{14,15} This UV filter has also recently been implicated in allergic contact dermatitis to printing ink, highlighting the importance of considering these compounds in occupational settings.¹⁶ Recent literature now points to benzophenone-4 as having “emerged” because it is repeatedly one of the leading 5 sunscreen allergens in large multicenter patch test studies and cross-sectional surveys.^{18,31} A few smaller studies have found more positive patch reactions to benzophenone-4 than benzophenone-3.^{14,17}

Although benzophenones-8 and -10 were commonly used in topical sunscreens in the past, the literature regarding adverse reactions to these agents is scarce. Only 2 case reports of allergic contact dermatitis to benzophenone-8 have been published.^{17,18} Although this may reflect the relative less frequent use of this chemical filter in sunscreen preparations today, it may also be due to difficulty in obtaining the allergen for testing.⁷ A number of positive patch reactions to benzophenone-10 have been reported,^{13,19–25} although more recent studies in both the United States and the European Union have not documented reactions to this agent.^{12,26}

The remainder of the benzophenones has not been documented in the literature as eliciting allergic contact dermatitis. This could be due to infrequent use in products or lack of routine testing to these agents.

PHOTOALLERGIC CONTACT DERMATITIS

Photoallergic contact dermatitis to benzophenone-3 was first reported in 1980, 8 years after the first report of non-light-related contact dermatitis.²⁷ Benzophenone-3 is implicated in more PACD reactions than any other UV filter available. Although photoallergy to this agent has been demonstrated in studies conducted in the United States,^{16,27,28} the number of positive photopatch reactions in Europe has been even greater.^{11,12,29} Benzophenone-3 was also the leading UV filter photoallergen in a recent 10-year retrospective Canadian study, causing reaction rates similar to those of known strong photoallergens promethazine and chlorpromazine.¹³ It is also important to note that reactions to this agent often stem from its use in cosmetics not marketed as sunscreens. One study found that most patients with positive photopatch reactions to benzophenone-3 had their daily moisturizer as the allergen source.³⁰ Another recently reported case of PACD to benzophenone-3 was secondary to contact with magazine printing ink. The patient developed positive reactions to benzophenone-3, octocrylene, and ketoprofen on photopatch testing, but of these, only “benzophenones” was a component of the ink used in the making of the magazine that she was reading on the beach.³¹

A number of large photopatch studies have suggested that benzophenone-4 is also a leading cause of photoallergy in patients with adverse reactions to sunscreens, both in the United States

and abroad.^{27,30,32} In fact, 1 recent US study found benzophenone-4 to be the most frequently implicated photoallergen of the 11 tested UV filters in 182 photopatch tested patients with suspected photodermatoses or sunscreen allergy.¹⁶

Benzophenone-10 was the second leading photoallergen in a European retrospective study investigating the results of photopatch testing in 2715 patients from 1983 to 1998.²⁵ However, the authors note that benzophenone-10 was rarely used in sunscreen manufacture by the time they published these results. This is reflected in the relatively small number of case reports documenting photoallergy to this substance.^{22,28,31–34}

Benzophenone-2 has been reported to cause a photopatch test reaction in a patient with self-proclaimed “sunscreen allergy.”¹⁶ No reports of photoallergy to benzophenone-8 have been documented. However, neither of these agents is routinely included in photopatch testing series.

A literature search found no reports of photoallergic reactions to benzophenones -1, -5, -6, -7, -9, -11, or -12.

PATCH TESTS

The US Food and Drug Administration now regulates the concentrations of ultraviolet filters allowed in topical sunscreen preparations. The Food and Drug Administration Code of Federal Regulations for Sunscreen Drug Products for Over-the-Counter Human Use lists maximum concentrations in personal care products, which are as follows: benzophenone-3 up to 6%, benzophenone-4 up to 10%, and benzophenone-8 up to 3%.³⁵ Neither benzophenone-2 nor -10 are approved for use in topical sunscreens. The recommended concentrations of each benzophenone for patch testing differ from the product concentrations. Suggested patch test concentrations are listed in Table 1. A literature search found no recommended patch test concentrations for benzophenones-5, -7, -9, or -12.

CROSS-REACTIONS

Because of the shared chemical structure, cross-reactions within the benzophenone family are plausible, whereas an extensive literature search found no confirmed documented case.^{19,37} Although there are a few reports that demonstrated multiple allergies to benzophenones, 1 author postulated that this could be due to separate exposure to each implicated allergen or photoallergen, whereas the significance of reaction to benzophenone-8 could not be determined.³⁶ Given the ubiquitous nature of benzophenones-3 and -4 in cosmetics and toiletries, exposure to both agents in separate products is likely. Most patients patch tested to multiple benzophenones only react to one.

Also of importance, benzophenone-3 shows high rates of cross-reactivity with octocrylene (a UV filter structurally similar to sunscreen agents in the cinnamate family) and ketoprofen (a topical nonsteroidal anti-inflammatory drug [NSAID]). A large European multicenter study across 12 countries found ketoprofen to cause the most photopatch reactions of all agents

tested. It is notable that octocrylene and benzophenone-3 were the third and fourth leading photosensitizers in this study, perhaps reflective of cross-reactivity rather than separate sensitization.¹² Not only do these 3 chemicals have similar structures, but also ketoprofen is broken down into various benzophenones structurally related to benzophenone-3 when it is irradiated with sunlight.³⁷ Benzophenone's cross-reaction with octocrylene may be of increasing interest in the future, given the increasing use of octocrylene in sunscreens as a stabilizer for butyl methoxy dibenzoylmethane (Parsol 1789). All 3 of these chemicals have been labeled as strong photosensitizers. Other topical and systemic agents containing a benzophenone nucleus may result in cross-reactivity. These include other topical NSAIDs (eg, tiaprofenic acid) and the cholesterol-lowering agent fenofibrate.³⁸ Topical NSAIDs are frequently used in European countries but are far less common in the United States.

BENZOPHENONES AND SYSTEMIC REACTIONS

Systemic exposure to UV filters is a result of dermal or gastrointestinal absorption. Studies have shown bioaccumulation of UV filters in wildlife (eg, fish) because of the lipophilic nature of these chemicals. Benzophenone-3 and its metabolites have been detected in human urine 4 hours after widespread topical application.⁵ Benzophenone-3 has also been detected in human breast milk after topical application.³⁹ At least 2 cases of anaphylaxis from topical application of benzophenone-3 have been published. Both cases resulted in a generalized wheal and flare reactions and syncope after widespread application of a sunscreen or sunless tanning product with this filter. Contact urticaria developed after more limited exposure to benzophenone-3 in both cases.^{5,40} The evidence of bioaccumulation in wildlife and humans also raises the possibility of long-term exposure, including effects on reproduction and ontogeny. Benzophenone-3, in particular, has displayed significant dose-dependent estrogenic activity.⁴¹ More recent studies have also demonstrated the estrogenic effects of other benzophenone derivatives. Kerdivel et al⁴² recently examined the effects of 10 different benzophenones on the proliferation of estrogen receptor-positive breast cancer cells and on the transcriptional activity of E2 target genes and found that among the 10 benzophenones tested, benzophenone-8 was high activity about proliferation potential and benzophenone-2 was of moderate activity. Another recent study suggested that exposure to elevated benzophenone-1 levels may be associated with increased odds of an endometriosis diagnosis.⁴³ A comprehensive literature search did not reveal any evidence that systemic absorption of benzophenone-3 or any other of the benzophenones has been linked to dermatitis or photosensitivity.

SUMMARY

The benzophenones are a group of chemical UV filters, which protect against UV-B and some UV-A. Although the general public

has become more aware of the dangers of both UV-A and UV-B radiation, these broad-spectrum agents have increasingly been incorporated into topical sunscreens and various cosmetics. This expanded use has undoubtedly contributed to the increased prevalence of benzophenone sensitization seen when comparing the positive patch test rates to benzophenone-3 in 1995–1996 NACDG data with 2009–2010 NACDG data.^{44,45} Benzophenone-3 is the most common sunscreen contact and photocontact allergen in North America. Allergic and photoallergic contact dermatitis to benzophenone-4 is also increasing, both in the United States and abroad. This underscores the importance of inclusion of these allergens in routine screening series, such as the ACDS Core Screening Series.⁴⁶ Benzophenones as a group have been named the American Contact Dermatitis Society's Allergen of the Year for 2014 to raise awareness of both allergy and photoallergy to these ubiquitous agents.

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