

# Benzophenone 4: an emerging allergen in cosmetics and toiletries?

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Chemical ultraviolet (UV) filters have, over the last few decades, been increasingly used not only in conventional sunscreen products but also in many cosmetics and toiletries. Allergic contact dermatitis as well as photoallergic contact dermatitis reactions have been well documented as a consequence of such use. Over a 3-year period, we recorded the number of positive patch test reactions to a selection of chemical UV filters that we added to our usual cosmetics/facial series. Our objective was to investigate whether any of these filters produced significant numbers of positive patch test results in the absence of photostimulation. Our results show that not only did benzophenone 4 (2-hydroxy-4-methoxybenzophenone-5-sulphonic acid: sulisobenzene) produce significantly more positive patch test results than the other UV filters that were tested, but also it was the third most frequently positive result overall. Our findings would support the inclusion of benzophenone 4 when patch testing to investigate likely contact dermatitis from cosmetics and toiletries.

**Key words:** allergic contact dermatitis; benzophenone 4; chemical UV filters; cosmetics; 2-hydroxy-4-methoxybenzophenone-5-sulphonic acid; patch testing; sulisobenzene; toiletries. © Blackwell Munksgaard 2007.

*Accepted for publication 25 September 2006*

Awareness of the damaging effects of sun exposure, in particular the carcinogenic effects on the skin, has resulted in the promotion and greater use of sunscreen products. The majority of the individual's lifetime exposure to the sun's harmful rays is, however, usually on an incidental daily basis rather than as a result of periodic holidaying (1). Chemical ultraviolet (UV) filters have thus been incorporated into everyday use cosmetics, such as skin moisturizers and facial makeup, with the intention of guarding against UV light exposure and reducing photoageing of the skin. Personal hygiene products such as hair shampoos, conditioners and shower/bath gels often also contain these sunscreens for the purpose of extending the product's shelf life by retarding photodegradation, rather than for any direct health benefit to the consumer.

Unless the patient is known to suffer from a photodermatosis, or gives a classical history of an adverse reaction to a sunscreen product, it is unlikely that photopatch testing will be carried out. Allergic contact dermatitis (ACD) reactions to photoallergens are usually only detected when the non-irradiated control series gives positive results during the course of photopatch testing or when

the individual constituents of a commercial product are secondarily patch tested. Thus, if patch testing with chemical UV filters is seldom undertaken, then a possible diagnosis of ACD, due to skin contact with products containing these allergens, would likely be missed.

## Materials and Methods

Over the 3-year period, between January 2003 and December 2005, 1693 patients underwent patch testing to our extended British Contact Dermatitis Society (BCDS) standard series. 553 of these patients (33%) were also patch tested to an extended facial/cosmetic series that included a selection of chemical UV filters supplied by Trolab (Hermal, Reinbek, Germany) and Chemotechnique (Crawford Pharmaceuticals, Milton Keynes, UK). These additional UV filters are numbered 27–35 inclusive at the bottom of Table 1.

Prior to this study, we routinely used a modified BCDS facial/cosmetics series, which included two commonly encountered photoallergens, namely benzophenone 3 (2-hydroxy-4-methoxybenzophenone: oxybenzone) and avobenzone (4-tert-butyl-4-methoxydibenzoylmethane).

Table 1. Extended British Contact Dermatitis Society facial/cosmetic series. Positive patch test results 2003–2005 inclusive

| Allergens                                                                 | Number of positives |
|---------------------------------------------------------------------------|---------------------|
| 1. 2,6-ditert-butyl-4-cresol 2%                                           | 1                   |
| 2. 2-tert-butyl-4-methoxyphenol 2%                                        | 2                   |
| 3. Toluenesulfonamide formaldehyde resin 10%                              | 3                   |
| 4. Amerchol L101 50%                                                      | 22                  |
| 5. Cocamidopropylbetaine 1%                                               | 4                   |
| 6. Sorbic acid 2%                                                         | 2                   |
| 7. Hydroquinone 1%                                                        | 1                   |
| 8. Triclosan 2%                                                           | 0                   |
| 9. Propyl gallate 1%                                                      | 2                   |
| 10. Abitol 10%                                                            | 1                   |
| 11. Benzyl alcohol 1%                                                     | 0                   |
| 12. 2-hydroxy-4-methoxybenzophenone 10% (benzophenone 3)                  | 3                   |
| 13. Triethanolamine 2%                                                    | 2                   |
| 14. 1,3-Dimethylol-5,5-dimethylhydantoin 2%                               | 3                   |
| 15. Ethylenediaminetetraacetic acid 1%                                    | 1                   |
| 16. Propolis 10%                                                          | 8                   |
| 17. Tea tree oil 5%                                                       | 4                   |
| 18. Chloroacetamide 0.2%                                                  | 5                   |
| 19. Iodopropynyl butyl carbamate 0.1%                                     | 5                   |
| 20. Oleamidopropyl dimethylamine 0.1%                                     | 7                   |
| 21. Sorbitan sesquioleate 20%                                             | 1                   |
| 22. Coconut diethanolamide 0.5%                                           | 2                   |
| 23. 4-tert-butyl-4-methoxydibenzoylmethane 10% (avobenzone)               | 0                   |
| 24. Sodium metabisulfite 1%                                               | 17                  |
| 25. Compositae mix 5%                                                     | 11                  |
| 26. Propylene glycol 20%                                                  | 5                   |
| 27. 2-ethylhexyl-p-dimethylaminobenzoate 10%                              | 1                   |
| 28. 2-hydroxy-4-methoxybenzophenone-5-sulphonic acid 10% (benzophenone 4) | 13                  |
| 29. Isoamyl-p-methoxycinnamate 10%                                        | 0                   |
| 30. 2-ethylhexyl-p-methoxycinnamate 10%                                   | 0                   |
| 31. 3-(4-methylbenzylidene)-camphor 10%                                   | 0                   |
| 32. 2-phenylbenzimidazol-5-sulphonic acid 10%                             | 1                   |
| 33. p-aminobenzoic acid 10%                                               | 1                   |
| 34. 2-hydroxy-4-methoxy-4-methylbenzophenone 10% (benzophenone 10)        | 1                   |
| 35. 6-methyl coumarine 1%                                                 | 0                   |

Patch testing followed the standard protocol using Finn Chambers on Scanpor tape (Bio-Diagnostics Ltd., UK) with results being recorded at 48 hr (D2) and 96 hr (D4). Positive reactions were graded from + to +++ according to international recommendations. Photopatch testing was not carried out as a standard procedure in this study.

### Results

The most frequently positive patch test results in the extended facial/cosmetic series were to amerchol (4%), sodium metabisulfite (3%), benzophenone 4 (2.3%), compositae mix (2%) and propolis (1.5%).

Benzophenone 4 was the most frequently positive chemical UV filter that was tested (13 patients,

shown in Table 2). It also produced the third most frequently positive patch test results overall. Of the 13 patients who patch tested positively to benzophenone 4, 5 were male and 8 were female. None of the other UV filters that we added, for this study, gave any appreciable numbers of positive results. Benzophenone 3, which previously had been routinely patch tested in our BCDS facial/cosmetic series, gave positive results in 3 patients (0.5%). However, with avobenzone, there were no positive results. In 12 of the 13 patients who tested positive to benzophenone 4, there was no other positive UV filter result. 1 patient patch tested positive to 3 UV filters. This patient was known to have systemic lupus erythematosus and had frequently been using sunscreens. Only 1 patient patch tested positive to both benzophenone 3 and benzophenone 4. These results would support previous reports that benzophenone 3 and benzophenone 4 do not appear to cross-sensitize.

The majority of side-effects to chemical UV filters are considered to be irritant (2), especially in patients with healthy skin (3). False-positive irritant reactions are known to be produced on patch testing. Our experience in this study was that benzophenone 4 invariably produced unequivocally positive (+) results at D4 with the D2 readings being negative (–) in every case. Moreover, because of the number of patients who were tested to benzophenone 4, there was an adequate inbuilt system of controls.

### Discussion

The benzophenones are a group of chemical UVA filters whose broad spectrum of protection extends into the UVB range. 4 benzophenones namely benzophenone 3, benzophenone 4, benzophenone 8 (2,2-dihydroxy-4-methoxybenzophenone: dioxibenzone) and benzophenone 10 (2-hydroxy-4-methoxy-4-methylbenzophenone: mexenone) have historically been incorporated into sunscreens and cosmetics with benzophenone 3 being by far the most commonly used (4). Such a frequency of use has, no doubt, contributed to the finding that benzophenone 3 has been the most commonly reported UV filter producing positive patch test results (3, 5–8). However, with changing product formulations, there is every opportunity for the emergence of newer or more frequently occurring allergens.

Benzophenone 3 and benzophenone 10 have been included in some photopatch series for over 20 years (6, 9) with equal numbers of combined photoallergic contact dermatitis (PACD) reactions and ACD reactions being produced by each

Table 2. Patient details with positive patch test reactions

| Patient no. | Age | Sex    | Site                           | Atopic? | Patch test reactions                                                                                                                                   |
|-------------|-----|--------|--------------------------------|---------|--------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1           | 11  | Female | Generalized                    | Yes     | Benzophenone 4                                                                                                                                         |
| 2           | 32  | Female | Face, hands, feet, generalized | Yes     | Benzophenone 4                                                                                                                                         |
| 3           | 42  | Female | Face                           | Yes     | Benzophenone 4                                                                                                                                         |
| 4           | 30  | Female | Face                           | No      | Benzophenone 4                                                                                                                                         |
| 5           | 36  | Male   | Hands                          | Yes     | Benzophenone 4                                                                                                                                         |
| 6           | 48  | Male   | Scalp                          | Yes     | Benzophenone 4                                                                                                                                         |
| 7           | 74  | Male   | Arms, legs, back               | Yes     | Benzophenone 4, caine mix 3                                                                                                                            |
| 8           | 35  | Female | Axillae, scalp                 | No      | Benzophenone 4, myroxylon pereirae                                                                                                                     |
| 9           | 58  | Male   | Face, arms, legs               | No      | Benzophenone 4, caine mix 3, formaldehyde, MCI/MI, 2-bromo-2-nitropropane, diazolidinyl urea, imidazolidinyl urea, myroxylon pereirae, fragrance mix 2 |
| 10          | 71  | Male   | Face, arms, back               | Yes     | Benzophenone 4, triethanolamine, MCI/MI                                                                                                                |
| 11          | 33  | Female | Face, feet, hands              | Yes     | Benzophenone 4, compositae mix, MCI/MI, paraphenylenediamine, thiuram mix, carba mix                                                                   |
| 12          | 59  | Female | Face, feet                     | Yes     | Benzophenone 4, cocoamidopropyl betaine                                                                                                                |
| 13          | 47  | Female | Face, eyes, axillae            | Yes     | Benzophenone 4, benzophenone 3, phenylbenzimidazol, sulphonic acid, phenyl mercuric acetate                                                            |

MCI, methylchloroisothiazolinone; MI, methylisothiazolinone.

allergen in one study (6). Benzophenone 10 is no longer commonly used in sunscreen manufacture (6). One of our male patients, who presented with a rash on his face, trunk and limbs, patch tested positive to benzophenone 10. This patient gave a history of facial swelling a few days after using a shampoo. There appears to be a general absence of reported positive results to benzophenone 8. As far as we are aware, this allergen is not commercially available for patch testing. Benzophenone 4 has been included in photopatch test series in the USA and several European countries, including the UK, since the late 1990's (6, 9) with few positive patch test results being documented (8, 9).

Despite widespread use over the last few decades, the incidence of PACD to UV filters is considered to be relatively small and not a significant clinical problem in patients who do not have any underlying photodermatoses (6). The potential for these filters to induce sensitization without photostimulation is similarly considered to be low (10).

Most cases of ACD and PACD to chemical UV filters are reported to result from the application of sunscreen products. Multiple sensitivities are often found due to their being used in combinations, in order to produce a product with a high sun protection factor. ACD rather than PACD has, at times, been reported to form the majority of reactions in both sunscreens and cosmetics (9). In patients with healthy skin, ACD and PACD reactions to UV filters are less likely to occur. As well as patients with photodermatoses, who routinely use sunscreens, are potentially at increased risk of sensitization when cosmetics and personal hygiene products are applied onto

damaged skin where barrier function has already been compromised.

Positive patch test results to benzophenone 3 have repeatedly been reported but this has not been the case for benzophenone 4 (8, 9). Occupational ACD from benzophenone 4 in a hair care product was reported in a hairdresser with hand eczema (11). None of our benzophenone positive patients had worked as hairdressers. However, 3 male and 1 female patients were patch tested using the facial/cosmetic series because of our suspicion that skin contact with toiletries was contributing to their hand and other non-facial rashes. In the case report by Alanko et al., their patient had used professional shampoos and hair care products containing benzophenone 4 and benzophenone 3 in the workplace. Our investigations have showed that both of these UV filters are commonly found, usually singularly, as ingredients of popular bath/shower gels as well as shampoos and other hair care products. In practice, it is often not possible to ascertain whether the product that was patch tested was, indeed, the one that produced the primary sensitization. Irritant contact dermatitis of the hands is known to be prevalent in hairdressers with sensitization to frequently used hairdressing chemicals also being a well-recognized occupational risk. Inflammation of the skin is acknowledged as an important factor in the induction and elicitation of ACD. The irritancy of some chemicals that are frequent ingredients in detergents, such as toiletries and hair care products, can also augment such reactions (12, 13). The potential for rinse/wash-off products, such as soaps and shampoos, to produce allergic skin reactions may well have been underestimated in the past. Frequent

applications of some chemicals does appear to increase the likelihood of ACD, even when contact time is relatively short (14). The hairdressing industry may well provide an ideal employment environment for the production of ACD to other less well-documented allergens (15).

2 cases of benzophenone allergy causing facial rash have previously been described: 1 patient with ACD and the other PACD to benzophenone 3 (16). In the second patient, benzophenone 4 was also reported to produce an equivocally positive PACD reaction. Benzophenone 3 was identified as an ingredient in both patients' shampoos. The author points out that most patients are unaware of the presence of UV filters in hair products. Dermatologists also need to be vigilant to such usage. Benzophenone allergy certainly needs to be considered in a differential diagnosis of atypical facial eczema when conditions such as rosacea are being considered. 2 of our male (patient numbers 9 and 10) and 1 female (patient number 4), who patch tested positive to benzophenone 4, were referred to our department with a diagnosis of likely rosacea. 1 atopic female (patient number 3), with a long history of rosacea, was also referred because of a change in the presentation of her rash. Our results indicate that not only does benzophenone 4 produce a cosmetic dermatitis of the face and neck but it also needs to be considered as a cause of sensitization at other sites.

We have identified benzophenone 4 as being a possible important patch test allergen. The sensitizing potential of chemicals may only become apparent with increasing product use and increased frequency of patch testing. It is likely that the use of this UV filter in toiletries and hair care products has increased significantly over recent years and certainly over the last decade or so (9). The constituent allergens used in various patch test series needs to be regularly revised, in order to reflect their frequency of exposure in populations. The need to consider patch and photopatch testing with UV filters, in cases of cosmetic dermatitis, has previously been recommended some years ago (17). Our results would support the inclusion of benzophenone 4 for routine patch testing in a facial/cosmetic series.

### Acknowledgement

We thank deputy sister Jen Patterson for her skillful assistance with the initial collation of these results.

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