

Do ‘cinnamon-sensitive’ patients react to cinnamate UV filters?

STEFANIE E. PENTINGA¹, DIRK J. KUIK², DERK P. BRUYNZEEL¹ AND THOMAS RUSTEMEYER¹

¹Department of Dermatology, and ²Department of Epidemiology and Biostatistics, VU University Medical Center, Amsterdam, The Netherlands

Background: Use of sunscreens has increased dramatically worldwide, and some sunscreen chemicals may be allergens. Ultraviolet (UV) filters are added to various cosmetic products. Cinnamate UV filters are structurally related to cinnamon-related fragrances.

Objective: The purpose of this study was to determine if ‘cinnamon-sensitive’ patients show positive photopatch tests to cinnamate UV filters and, therefore, should avoid these UV filters.

Method: We photopatch tested cinnamon-sensitive patients ($n = 18$) with cinnamon, cinnamon-related fragrances, *Myroxylon pereirae*, and two cinnamate UV filters.

Results: No positive photopatch test to cinnamate UV filters was found (95% confidence interval 0–13%).

Discussion: The risk of developing unwanted allergic contact dermatitis because of cinnamate UV filters in cinnamon-sensitive patients seems to be low, but our study population was small. Therefore, we recommend cinnamon-sensitive patients to perform a use test, for example the repeated open application test, before using cosmetic products containing cinnamate UV filters. In addition, physicians and patients should be aware that many sunscreens contain (cinnamon-related) fragrances and could, therefore, elicit allergic contact dermatitis in cinnamon-sensitive patients, independently from other potential sensitizing components of the sunscreen.

Key words: allergic contact dermatitis; cinnamate; cinnamon; cosmetics; fragrances; photopatch test; sunscreen; UV filter. © Blackwell Munksgaard, 2009.

Conflicts of interest: The authors have declared no conflicts.

Accepted for publication 7 January 2009

The use of sunscreens has increased worldwide to prevent sun damage of the skin. Nowadays, ultraviolet (UV) filters are regularly added to cosmetic products. The class of cinnamon-related UV filters with an absorption maximum within the UVB spectrum called ‘cinnamates’ are frequently used for this purpose (1).

Cinnamon (*Cinnamomum zeylanicum*) and cassia (*Cinnamomum aromaticum*) contain fragrance chemicals such as cinnamal, eugenol, and coumarin (2, 3). These have a strong aroma and are therefore added to cosmetics (including sunscreens), perfumes, cleaning agents, food, and more (2, 4–9). Other cinnamon-related fragrances are cinnamyl alcohol, amyl cinnamal, hexyl cinnamal, benzyl cinnamate, and isoeugenol. The marker of fragrance allergy *Myroxylon pereirae* contains

cinnamon-related fragrances (7). There are structural similarities between cinnamate UV filters and cinnamon-related fragrances (10, 11). Therefore, we wondered whether cross-reactivity, based on these similarities, might occur.

The purpose of this study was to determine if ‘cinnamon-sensitive’ patients show positive photopatch tests to cinnamate UV filters and, therefore, should avoid these UV filters.

Patients and Methods

Our patients with suspected contact dermatitis are routinely patch tested with the European baseline series that includes *M. pereirae* and fragrance mixes I and II. If needed, subsequent testing with individual fragrances or spices is performed.

A prospective study was conducted, with approval from the local medical ethical committee and after informed consent, in cinnamon-sensitive patients selected on the basis of previous patch test results ($n = 18$). Patients with a previously positive patch test ($\geq +$) to fragrance mix I and/or II in combination with a positive patch test to *M. pereirae* ($n = 10$) were defined cinnamon sensitive. Patients who did not meet these criteria were also defined cinnamon sensitive when cinnamon-related fragrances had caused positive patch tests in subsequent testing with individual fragrances ($n = 8$). In addition, four of the participating patients had previously been tested with spices, of whom three had a positive patch test to cinnamon. All patients had a history of skin complaints related to application of cosmetic products, seven patients also to application of sunscreens, and two patients to consumption of cinnamon (including complaints affecting the oral mucosa).

All 18 patients were photopatch tested with cinnamon, cinnamon-related fragrances (amyl cinnamal, benzyl cinnamate, cinnamal, cinnamyl alcohol, coumarin, eugenol, hexyl cinnamal, and isoeugenol), *M. pereirae*, and two cinnamate UV filters (ethylhexyl methoxycinnamate and isoamyl-*p*-methoxycinnamate). Test substances were obtained in petrolatum from Hermal (Reinbeck, Germany) or Chemotechnique Diagnostics (Malmö, Sweden). Test concentrations are shown in Table 1. Chemical structure of investigated sub-

stances (except cinnamon and *M. pereirae* because these contain numerous components) is shown in Fig. 1.

Finn Chambers[®] (Epitest Ltd Oy, Tuusula, Finland) on Scanpor[®] tape (Epitest Ltd Oy, Tuusula, Finland) were applied in duplicate on the left and right side of the mid-upper back (avoiding the paravertebral groove) and removed after 2 days. The left side was covered with a light-impermeable MoliNea plus D[®] dressing (Paul Hartmann BV, Nijmegen, the Netherlands). The right side was first exposed to 5 J/cm² UVA (Psoralen UVA 800 Unit; Waldmann, FRG) and then covered with MoliNea plus D dressing. Photopatch test readings were scheduled according to the recommendations of the European Taskforce for Photopatch Testing at D0 (2 days after application) before and 15 min after irradiation, D1, and D2, and patch test and photopatch test results were graded according to the scoring system of the International Contact Dermatitis Research Group (12).

A positive photopatch test was defined as a negative patch test (–) at the non-irradiated side (left) at all readings in combination with a positive patch test ($\geq +$) at the irradiated side (right) for at least one reading.

An 'inverse photopatch test' was defined as a negative patch test (–) at the irradiated side (right) at all readings in combination with a positive patch test ($\geq +$) at the non-irradiated side (left) for at least one reading.

Table 1. Results of patch test and photopatch tests in 18 patients

Category	Substances ^a	Maximum patch test scores ^b					Total positive patch tests	Percentage positive patch tests (%)	Total positive photopatch tests	Percentage positive photopatch tests (%)	Upper limit percentage, positive photopatch test, 95% CI ^c
		–	?+	+	++	+++					
Cinnamon	Cinnamon (30%)	11	1	2	3	1	6	33	1	6	
Cinnamon-related fragrances	Amyl cinnamal (2%)	16	0	1	1	0	2	11	0	0	
	Benzyl cinnamate (5%)	17	1	0	0	0	1	6	0	0	
	Cinnamal (2%)	14	0	0	2	2	4	22	0	0	
	Cinnamyl alcohol (2%)	12	1	1	3	1	5	28	2	11	
	Coumarin (5%)	17	0	0	0	1	1	6	1	6	
	Eugenol (2%)	14	1	1	0	2	3	17	1	6	
	Hexyl cinnamal (10%)	16	1	0	1	0	1	6	0	0	
	Isoeugenol (2%)	13	2	0	2	1	3	17	1	6	
Fragrance marker	<i>Myroxylon pereirae</i> (25%)	9	1	2	3	3	8	44	1	6	
Cinnamate UV filters	Ethylhexyl methoxycinnamate (10%)	18	0	0	0	0	0	0	0	0	13.1
	Isoamyl- <i>p</i> -methoxycinnamate (10%)	18	0	0	0	0	0	0	0	0	13.1

CI, confidence interval; UV, ultraviolet.

^aVehicle: petrolatum.

^b–, negative; ?+, doubtful (or follicular); +, weak positive; ++, strong positive; +++, extreme positive.

^cOnly computed for cinnamate UV filters.

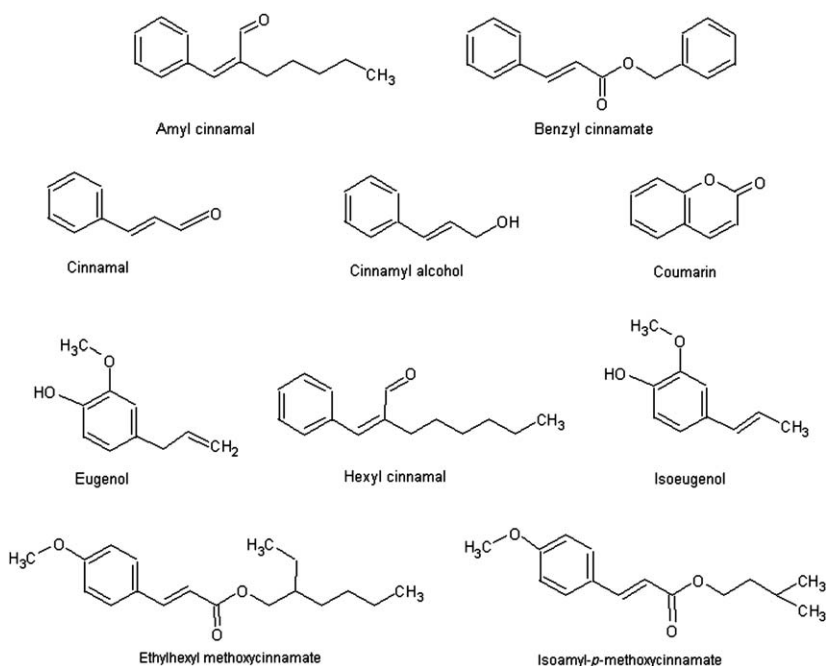


Fig. 1. Illustration of chemical structure of cinnamon-related substances (15).

Maximum patch test scores of cinnamon, cinnamon-related fragrances, and *M. pereirae* were obtained from the non-irradiated patch test side (left).

The 95% confidence interval (95% CI) for the percentage of positive photopatch tests to the cinnamate UV filters was calculated with a local statistical program.

Results

Photopatch tests

All 18 patients had negative photopatch tests to the two cinnamate UV filters. Therefore, the percentage of positive photopatch tests to a cinnamate UV filter of this study was 0% (upper limit of 95% CI: 13.1). Positive photopatch tests were seen to cinnamon ($n = 1$), cinnamyl alcohol ($n = 2$), coumarin ($n = 1$), eugenol ($n = 1$), isoeugenol ($n = 1$), and *M. pereirae* ($n = 1$).

Inverse photopatch tests

A negative patch test (–) at the irradiated side (right) during all readings, in combination with a positive patch test ($\geq +$) at the non-irradiated side (left) during at least one reading, was seen with cinnamon ($n = 2$), amyl cinnamal ($n = 1$), and eugenol ($n = 1$).

Patch tests

Thirteen patients had positive ($\geq +$) patch tests to cinnamon, cinnamon-related fragrances, or

M. pereirae, of whom 5 patients had one positive patch test, 3 patients had two positive patch tests, and 5 patients had three to six positive patch tests. Most positive patch test reactions were found to *M. pereirae* (8/18), cinnamon (6/18), and cinnamyl alcohol (5/18). No positive patch test to the two cinnamate UV filters was seen.

All results are shown in Table 1. Fig. 2 shows a photograph of a negative photopatch test with multiple positive patch test reactions.



Fig. 2. Photograph of negative photopatch test with positive patch test reactions to four cinnamon-related fragrances, *Myroxylon Pereirae* (in picture named Balsam of Peru), and cinnamon.

Discussion

No positive photopatch test to cinnamate UV filters was found. Based on this study, the risk of developing unwanted allergic contact dermatitis because of cinnamate UV filters in cinnamon-sensitive patients appears to be low (a maximum of approximately one of seven cinnamon-sensitive patients as seen from the 95% CI). Hence, it might be concluded that the two tested cinnamate UV filters can be used relatively safely in these patients. Nevertheless, whether this is applicable to other new UV filters of the cinnamate class is unknown. Results from this study should be considered cautiously because of the limited number of participants ($n = 18$) and the absence of later photopatch readings at D3 or D4; confirmation in a larger study population is required, preferably with readings at D3 and D4 (12).

Positive photopatch tests to cinnamyl alcohol, cinnamon, coumarin, eugenol, isoeugenol, and *M. pereirae* are consistent with previous studies in which photoallergy and phototoxicity have been described with fragrances (13, 14).

To our knowledge, a negative patch test at the irradiated side at all readings with a positive patch test at the non-irradiated side during at least one reading has not previously been described for cinnamon, amyl cinnamal, and eugenol. These observations may be because of false-positive patch tests at the non-irradiated side or false-negative patch tests at the irradiated side. We speculate that UV-induced immune suppression of the skin may have caused absence of positive patch test reactions at the irradiated side.

In conclusion, the results of our limited study suggest that cinnamate UV filters may be used relatively safely in cinnamon-sensitive patients, but this needs to be confirmed. We recommend that cinnamon-sensitive patients should perform a use test, for example repeated open application test, before use of cosmetic products containing cinnamate UV filters. In addition, physicians and patients should be aware that many sunscreens contain (cinnamon-related) fragrances and could, therefore, elicit allergic contact dermatitis in cinnamon-sensitive patients, independently from other potential sensitizing components of the sunscreen.

Acknowledgements

We thank the 'Huidfonds' and 'Nederlandse Cosmetics Vereniging' for their financial support for reimbursement of the participating patients.

References

1. Maier T, Korting H C. Sunscreens – which and what for? *Skin Pharmacol Physiol* 2005; 18: 253–262.
2. de Groot A C, Frosch P J. Adverse reactions to fragrances. A clinical review. *Contact Dermatitis* 1997; 36: 57–86.
3. Lungarini S, Aureli F, Coni E. Coumarin and cinnamaldehyde in cinnamon marketed in Italy: a natural chemical hazard? *Food Addit Contam* 2008; 25: 1297–1305.
4. Bousquet P J, Guillot B, Guilhou J J, Raison-Peyron N. A stomatitis due to artificial cinnamon-flavored chewing gum. *Arch Dermatol* 2005; 141: 1466–1467.
5. Friedman M, Kozukue N, Harden L A. Cinnamaldehyde content in foods determined by gas chromatography-mass spectrometry. *J Agric Food Chem* 2000; 48: 5702–5709.
6. Garcia-Abujeta J L, de Larramendi C H, Berna J P, Palomino E M. Mud bath dermatitis due to cinnamon oil. *Contact Dermatitis* 2005; 52: 234.
7. Hausen B M. Contact allergy to balsam of Peru. II. Patch test results in 102 patients with selected balsam of Peru constituents. *Am J Contact Dermat* 2001; 12: 93–102.
8. Miller R L, Gould A R, Bernstein M L. Cinnamon-induced stomatitis venenata, clinical and characteristic histopathologic features. *Oral Surg Oral Med Oral Pathol* 1992; 73: 708–716.
9. Rastogi S C, Heydorn S, Johansen J D, Basketter D A. Fragrance chemicals in domestic and occupational products. *Contact Dermatitis* 2001; 45: 221–225.
10. Dromgoole S H, Maibach H I. Sunscreening agent intolerance: contact and photocontact sensitization and contact urticaria. *J Am Acad Dermatol* 1990; 22: 1068–1078.
11. Fisher A A. Sunscreen dermatitis: part II – the cinnamates. *Cutis* 1992; 50: 253–254.
12. Bruynzeel D P, Ferguson J, Andersen K et al. Photopatch testing: a consensus methodology for Europe. *J Eur Acad Dermatol Venereol* 2004; 18: 679–682.
13. Placzek M, Fromel W, Eberlein B, Gilbertz K P, Przybilla B. Evaluation of phototoxic properties of fragrances. *Acta Derm Venereol* 2007; 87: 312–316.
14. Schauder S, Ippen H. Contact and photocontact sensitivity to sunscreens. Review of a 15-year experience and of the literature. *Contact Dermatitis* 1997; 37: 221–232.
15. United States National Library of Medicine. United States National Library of Medicine, 2008. *Toxnet*. Available at: <http://toxnet.nlm.nih.gov/>. Accessed date 1 August 2009.

Address:
 Stefanie E. Pentinga
 Department of Dermatology
 VU University Medical Center
 PO Box 7057
 1007 MB Amsterdam
 The Netherlands
 Tel: +0031 204 442 819
 Fax: +0031 204 442 816
 e-mail: se.pentinga@vumc.nl