

Compositae dermatitis from airborne parthenolide

E. Paulsen, L.P. Christensen* and K.E. Andersen

Department of Dermatology, Odense University Hospital, Sdr. Boulevard 29, DK-5000 Odense C, Denmark

*Department of Food Science, Danish Institute of Agricultural Sciences, Research Centre Aarslev, Kirstinebjergvej 10, DK-5792 Aarslev, Denmark

Summary

Correspondence

Evy Paulsen

E-mail: evy.paulsen@ouh.fyns-amt.dk

Accepted for publication

10 September 2006

Key words

airborne, allergic contact dermatitis, Compositae, parthenolide, plants, *Tanacetum parthenium*

Conflicts of interest

None declared.

The studies were carried out at the Department of Food Science, Danish Institute of Agricultural Sciences, Research Centre Aarslev and the Department of Dermatology, Odense University Hospital.

Background Compositae dermatitis confined to exposed skin has often been considered on clinical grounds to be airborne. Although anecdotal clinical and plant chemical reports suggest true airborne allergy, no proof has been procured. Feverfew (*Tanacetum parthenium*) is a European Compositae plant suspected of causing airborne contact allergy, and its most important allergen is the sesquiterpene lactone (SQL) parthenolide (PHL).

Objectives The aims of this study were to (i) assess the allergenicity of feverfew-derived monoterpenes and sesquiterpenes and their oxidized products in feverfew-allergic patients and (ii) re-assess the role of PHL and other SQLs in airborne contact allergy.

Patients and methods Feverfew-allergic patients were patch tested with extracts and fractions containing volatile monoterpenes and sesquiterpenes as well as extracts of airborne particles from flowering feverfew plants, obtained by fractionation of ether extracts, dynamic headspace and high-volume air sampler (HIVAS) technique, respectively.

Results Among 12 feverfew-allergic patients, eight had positive patch-test reactions to a HIVAS filter extract, while two tested positive to a headspace extract. Subsequent analysis of the HIVAS extract by gas chromatography and mass spectrometry detected PHL in a concentration of 510 ng mL^{-1} in the HIVAS extract. Testing with a dilution series of PHL showed positive reactions down to 8.1 ng in selected patients. None of the 12 patients tested positive to monoterpenes or sesquiterpenes, whether they were oxidized or not.

Conclusions The clinical results have proved that some feverfew-allergic patients are sensitive to airborne particles released from the plant, and isolation of PHL from the particle-containing HIVAS extract in allergenic amounts is strong evidence of PHL as the responsible allergen.

The classical form of Compositae dermatitis is an airborne pattern eczema, first described in the U.S.A. as weed dermatitis in the 1930s, and 30–40 years later in India as *Parthenium* dermatitis and in Australia as Australian bush dermatitis.^{1–3}

The hypothesis of airborne allergens has been much debated since then, and although the clinical features, the allergenicity of dried plant parts and positive patch-test reactions to a filter from a high-volume air sampler (HIVAS) as well as to air-dried clothing are suggestive of true airborne contact allergy, no definite proof has been established.^{1–7} Furthermore, a European equivalent to airborne Compositae dermatitis has been questioned because of the humid, colder, climatic conditions.⁸

Feverfew [*Tanacetum parthenium* (L.) Schultz-Bip.] is a frequent sensitizer in European Compositae-allergic patients.^{9,10} On the basis of case reports, this plant, which is native to south east

Europe and partly naturalized from gardens in Northern Europe, has been considered to be a cause of airborne contact dermatitis (ABCD).^{11,12} Its main allergenic sesquiterpene lactone (SQL) is parthenolide (PHL, Fig. 1),¹¹ which may constitute up to 0.9% of dry weight in aerial parts of the plant.^{13,14} However, experimental studies using HIVAS and dynamic headspace (DHE) techniques around feverfew plants failed to detect both particle-bound and volatile PHL.¹⁴ The volatiles emitted from feverfew plants were mainly monoterpenes, but as only a minority of feverfew-allergic patients tested positive to these, their contribution to airborne Compositae dermatitis seemed to be of small significance.¹⁵

On the other hand, it has been established, notably in fragrance research, that oxidized monoterpenes are often stronger allergens than the nonoxidized substances.¹⁶ Therefore, the aims

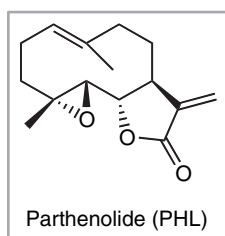


Fig 1. Chemical structure of the sesquiterpene lactone parthenolide (PHL) present in the aerial parts of *Tanacetum parthenium* (feverfew).

of this study on airborne Compositae dermatitis were to (i) assess the allergenicity of feverfew-derived monoterpenes and sesquiterpenes and their oxidized products in feverfew-allergic patients and (ii) re-assess the possible role of PHL and other SQLs in view of more accurate and sensitive gas chromatography–mass spectrometry (GC-MS) methods available with lower detection and quantification thresholds compared with GC-MS techniques used previously for detection of airborne SQLs.¹⁴

Patients, materials and methods

Patients

Adults, who by previous patch testing in our clinic had had at least 2+ reactions to feverfew extract 1% petrolatum (pet.) and PHL 0.1% pet., were invited to participate in the study. Exclusion criteria were pregnancy, treatment with systemic steroid or other immunosuppressive or -modulating drugs as well as recent ultraviolet (UV) radiation therapy.

Patch-test materials were applied to the patient's back for 48 h using Finn Chambers® (Epitest Ltd, Helsinki, Finland) on Scanpor® (Scanpor Alpha AS, Oslo, Norway), and readings were taken on day 3 according to the criteria of the International Contact Dermatitis Research Group.¹⁷

All participants gave their written, informed consent, and in general the study followed the Declaration of Helsinki protocols and was approved by the local ethics committee (case no. 20040123).

Plant material and parthenolide content

Twelve specimens of *T. parthenium* (L.) Schulz Bip. were grown in a greenhouse at 17–23 °C in 20-L pots and watered daily. Plants were grown under natural light conditions. The concentration of PHL (Fig. 1) in the aerial parts of the feverfew plants was $\approx 0.2\%$ of dry weight as determined by analytical reversed-phase high performance liquid chromatography using acetonitrile–water as mobile phase.^{13,14}

Analysis for parthenolide in high-volume air sampler filters

A HIVAS (Air sampler #15000, The Science Source, Waldo-boro, ME, U.S.A.) was placed in a closed chamber of

1.5 × 1.5 × 1.5 m in a greenhouse together with eight flowering feverfew plants at a distance of 15–20 cm from the plants. The sampler was mounted with filter disks capturing plant particles down to 4 µm in size, and equipped with a cap protecting the filter from direct contact with the plants so only airborne particles released from the plants were collected. The air sampler collected airborne particles 8 h a day over a 16-h time period (from 06:00 to 22:00) with a 30-min pause each hour in order to avoid overheating. The sampling of airborne particles was performed at 18–20 °C over a 6-day period. The average flow rate through the air sampler was measured to 215 L min⁻¹. The HIVAS filter was changed once a day and kept in a 250-mL blue-cap flask at –24 °C until analysis. In total six HIVAS filters were obtained, which were randomly divided into two groups with four (group I) and two (group II) HIVAS filters, respectively.

The HIVAS filters in groups I and II were extracted with 50 mL 96% ethanol, filtered, and the eluates combined and concentrated in vacuo (30 °C) to 50 mL each for testing as is on Compositae-sensitive patients and/or analysis. Only the HIVAS extract obtained from the group I filters was tested on patients and after testing, both the group I and II filter extracts were analysed by GC-MS for PHL and other SQLs. GC-MS analysis was performed on a Trace DSQ single quadrupole mass spectrometer operated at 70 eV and directly coupled to a Trace GC Ultra gas chromatograph (both, Thermo Finnigan, Austin, TX, U.S.A.) equipped with a split/splitless PTV injector (split flow 10 mL min⁻¹, 200 °C) and a Zebtron capillary column (30 m × 0.25 mm internal diameter, film thickness d_f = 0.25 µm, ZB-1, Phenomenex, Torrance, CA, U.S.A.). Helium was the carrier gas at a constant column head pressure of 10 psi. The temperature of the column and transfer line was 200 °C. GC-MS was performed on 2 µL HIVAS extract. Compounds in the HIVAS extract were separated by the following oven temperature gradient: 32 °C for 1 min, programmed to 260 °C at 10 °C min⁻¹ followed by constant temperature for 20 min. The mass spectrometer was operated in full scan mode over a mass range from 39 to 650 amu (1 scan g⁻¹) and analysed for PHL and other SQLs. PHL was the only SQL detected in the HIVAS extracts, and in order to improve the sensitivity for detection of PHL by GC-MS a selected ion monitoring (SIM) acquisition method was developed. PHL was detected by GC-MS SIM by setting the mass selective detector to repeatedly scan for the following ions m/z 145, 190 and 248 (molecular ion). PHL was repeatedly identified in the HIVAS extracts in full and SIM scan modes by comparison with an authentic standard of PHL (Sigma-Aldrich, Steinheim, Germany).

Quantification of PHL in the HIVAS extracts was performed in SIM mode using PHL as external standard. The calibration curve was determined to be linear in the concentration range 50–1000 ng mL⁻¹ (r^2 = 0.988). The detection limit of PHL was determined from the calibration curve to be ≈ 20 ng mL⁻¹ [Signal to noise (S/N) = 10] in SIM scan mode and the quantification limit to be 50 ng mL⁻¹ (S/N = 3).

Isolation of volatiles from feverfew

Volatiles were isolated from aerial parts of feverfew plants by DHE and column chromatography (CC), respectively, for testing. Volatiles emitted from feverfew were collected from the closed chamber mentioned above by DHE technique as described previously with a few alterations.¹⁴ Volatiles were collected directly from the chamber in a 100-mL pipette equipped with 50 g Porapak Q 50–80 mesh (Waters, Milford, MA, U.S.A.), and eluted with diethyl ether, concentrated to a final volume of 300 μ L¹⁴ and dissolved in 5 mL 96% ethanol. Four DHE collections were made and the extracts combined to one headspace extract (20 mL), which was used for testing and for oxidation experiments. The combined headspace extract was analysed by GC and GC-MS as described previously.¹⁴ The total concentration of the volatiles in the ethanol headspace extract was > 1% and used for testing as is.

Volatiles were extracted with 2 L of diethyl ether from 800 g aerial parts of feverfew plants for 60 min. The diethyl ether extract was concentrated *in vacuo* (30 °C) to 10 mL. Volatiles were isolated from the extract by silica gel CC using an *n*-hexane-diethyl ether gradient. Fractions containing volatiles only and no PHL were combined, the solvent removed *in vacuo* (30 °C), and the residue dissolved in 40 mL 96% ethanol for testing and oxidation.

Oxidation by ultraviolet radiation of volatiles isolated by dynamic headspace and column chromatography

The combined DHE extract and the extract obtained by CC were purged with O₂ and oxidized for 30 min using a UV-immersion lamp reactor (Sigma-Aldrich) equipped with a

400-mL reaction vessel made of borosilicate glass. The photon source was provided with a TQ 150 high-pressure Hg lamp with linkage and condenser made of silica (Sigma-Aldrich). Analysis of the oxidized extracts by GC-MS revealed quantitative, but no qualitative, differences in the volatile profile compared with the nonoxidized extracts.

Results

Clinical studies

Twelve people (11 female, one male, mean age 54 years) with contact sensitization from feverfew and PHL were recalled for patch testing with extracts and fractions containing volatile monoterpenes and sesquiterpenes as well as HIVAS filter extracts of airborne particles from feverfew plants. The results of the initial patch testing, including repeated testing with the crude feverfew extract and PHL, are summarized in Table 1. Contrary to former results, the subjects were mainly positive to airborne fractions: eight of 12 tested positive to an extract from HIVAS filters, and two of 12 had positive reactions to an extract collected by the DHE technique. On the other hand, no one tested positive to the monoterpene and sesquiterpene fraction. Ten consecutive eczema patients tested negative to the HIVAS filter extract as well as to the oxidized and nonoxidized headspace extracts. After PHL had been detected in the extract from the HIVAS filters in minute amounts, it was decided to retest some of the eight people with positive reactions to the crude extract in order to determine the threshold elicitation concentration of PHL. Two dilution series of PHL, incorporated in a dry film using the TRUE Test[®] technology, were kindly provided by Mekos Laboratories AS (Hillerød,

Table 1 Results of patch testing with oxidized and nonoxidized extracts from feverfew, collected by HIVAS, DHE or direct extraction, in 12 feverfew-allergic patients

Patient no.	1	2	3	4	5	6	7	8	9	10	11	12
Sex/age (years)	F/48	F/55	F/42	F/59	F/53	F/48	M/79	F/47	F/61	F/55	F/52	F/59
Allergen												
Feverfew 1% pet.	++	++	++	+++	++	+++	++	++	++	+++	++	++
PHL 0.1% pet.	+++	++	++	+++	+++	+++	++	+++	++	+++	+++	+++
l-Carvone 1% pet.	–	–	–	–	–	–	0	+	–	0 foll.	–	0 foll.
l-Carvone 5% pet.	0 foll.	0	0	–	–	–	0	0	–	++	0	0
Nonoxidized monoterpenes and sesquiterpenes	–	–	0	–	–	–	–	–	0	–	–	–
Oxidized monoterpenes and sesquiterpenes	–	–	0	–	–	–	0	–	0	0 foll.	–	–
HIVAS filter extract	++	+	++	–	–	+	++	–	++	++	0	++
Nonoxidized DHE extract	–	–	0 foll.	–	–	–	++	–	–	+	–	–
Oxidized DHE extract	–	–	0 foll.	–	–	–	+	0	–	–	–	0 foll.
HIVAS filter under Scanpor [®]	–	–	–	–	–	–	–	–	–	–	–	–
HIVAS filter in FC under Scanpor [®]	0	–	–	–	–	–	–	–	–	–	–	–
Colophonium 1500 μ g cm ⁻²	+	–	–	–	–	–	++	+	–	–	–	–
FM I 450 μ g cm ⁻²	++	–	–	++	++	++	+	–	–	++	++	–
Feverfew p.s.	No	No	No	Yes	Yes	No	Yes	?	No	Yes	No	Yes
ABCD suspected by patient	No	Yes	No	No	Yes	No	Yes	No	Yes	Yes	Yes	Yes

F, female; M, male; PHL, parthenolide; HIVAS, high-volume air sampler; DHE, dynamic headspace; FC, Finn Chamber; FM I, fragrance mix I; p.s., primary sensitizer; ABCD, airborne contact dermatitis; foll., follicular reaction; 0, doubtful positive reaction.

Table 2 Results of patch testing with two dilution series of parthenolide

Patient no.	2	3	7	9	12
Sex/age (years)	F/55	F/42	M/79	F/61	F/59
PHL concentration					
0.010 mg cm ⁻²	NT	NT	NT	NT	+++
0.0033 mg cm ⁻²	++	++	NT	++	++
0.0011 mg cm ⁻²	++	++	NT	++	+++
0.00037 mg cm ⁻²	0 foll.	+ foll.	NT	++	++
0.00012 mg cm ⁻²	0 foll.	–	NT	++	++
0.060 µg cm ⁻²	–	–	+ foll.	++	++
0.030 µg cm ⁻²	–	0 foll.	0	+	++
0.010 µg cm ⁻²	–	–	–	0	+
0.0030 µg cm ⁻²	–	–	–	–	0 foll.
0.0010 µg cm ⁻²	–	–	–	–	–

PHL, parthenolide; F, female; M, male; 0, doubtful positive reaction; foll., follicular reaction; NT, not tested.

Denmark). The results are shown in Table 2: two of five persons tested positive to 30 and 10 ng PHL, corresponding to 24.3 and 8.1 ng per patch as a TRUE Test[®] allergen occupies 0.81 cm².

Six patients were sensitized by gardening, and three of these reported feverfew to be one of the primary sensitizers, whereas four were occupationally sensitized as gardeners/greenhouse workers or sandwich makers. The last two pati-

ents were both privately and occupationally sensitized by gardening.

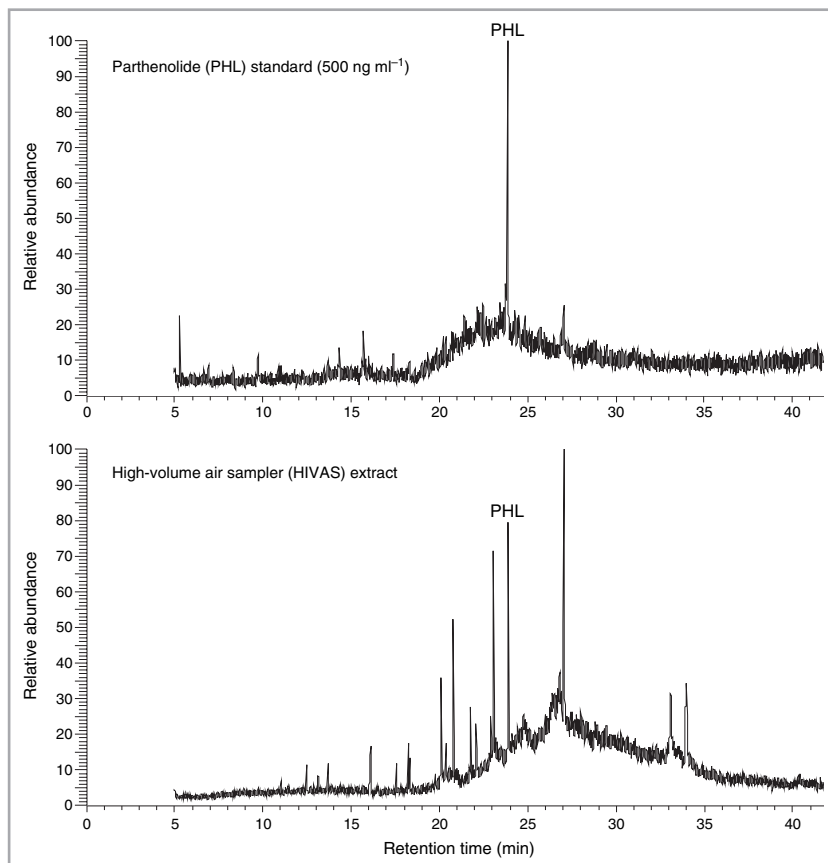
Chemical studies

The particles and volatiles collected by HIVAS and DHE techniques, respectively, were derived from several feverfew plants in a greenhouse instead of single specimens to imitate the natural outdoor conditions and ensure a sufficient amount of any volatile allergen for patch testing.

PHL was detected using GC-MS SIM by repeatedly scanning for the following ions *m/z* 145, 190 and 248 (molecular ion), which are some of the characteristic and/or major ions in the mass spectrum of PHL. The retention time for PHL was 23.9 min and was repeatedly identified in the combined HIVAS extracts in full and SIM scan mode by comparison with an authentic standard of PHL as illustrated in Figure 2.

PHL in the combined HIVAS extracts used for testing (group I) was determined to be 510 ng mL⁻¹ HIVAS extract corresponding to an average release of ≈800 ng PHL h⁻¹ or 100 ng PHL h⁻¹ per feverfew plant. The presence of PHL was also detected in the group II HIVAS extracts that were not used for testing. The concentration of PHL in this combined HIVAS extract corresponded to an average release of ≈310 ng PHL h⁻¹ or 40 ng PHL h⁻¹ per feverfew plant, thus confirming that PHL was released over the whole collection period, but, as expected, not released uniformly.

Fig 2. Gas chromatography–mass spectrometry (GC-MS) selected ion monitoring (SIM) chromatogram of a standard sample of parthenolide (PHL) in a concentration of 500 ng mL⁻¹ and the combined high-volume air sampler (HIVAS) extract, respectively. PHL was detected at 23.9 min in SIM and full scan mode (*m/z* 39–650) in both samples. The selected ions in the GC-MS SIM acquisition method were *m/z* 145, 190 and 248 [molecular ion (M)⁺].



Analysis of the combined headspace extract by GC-MS revealed the monoterpenes camphene, *p*-cymene, camphor, *trans*-chrysanthanol and *trans*-chrysanthenyl acetate as the major volatiles, and no PHL was detected in the extracts in accordance with previous investigations.¹⁴

The major terpenes in the monoterpene and sesquiterpene extract were camphor and *trans*-chrysanthenyl acetate as shown by GC-MS,¹⁴ although the concentrations of oxygenated monoterpenes such as bornyl acetate were higher in this extract compared with the headspace extract. The total concentration of the volatiles in this ethanol extract was > 2% and tested as is.

Discussion

Although Hjorth *et al.*,⁴ in their frequently quoted paper on Compositae dermatitis in Danish patients, emphasized the airborne pattern, later studies have shown a greater diversity of clinical features in European Compositae-allergic patients, which is probably why the existence of airborne Compositae dermatitis in Europe has been doubted.^{8,18,19}

Concerning feverfew, anecdotal reports have been suggestive of the plant as a cause of ABCD based on clinical features and information on exposure.^{11,20}

However, this is the first study where several feverfew-allergic patients consistently showed positive patch-test reactions to airborne fractions that were subsequently proved to contain PHL. This allergen is not volatile, so its presence must be due to plant particles containing traces of PHL.¹⁴ PHL is probably synthesized in glandular trichomes on the leaf surface as it has been reported in other allergenic Compositae species.²¹ The concentration of PHL in the HIVAS extract of 510 ng mL⁻¹ would allow an amount of ≈ 8 ng per Finn Chamber[®], providing that the chamber contained 15 μ L. However, the particle-bound PHL was probably unevenly distributed, and furthermore, the extract was not applied by a micropipette, but by capillary tubes, which would lead to a higher concentration of PHL in the Finn Chamber[®].

The fact that some of the subjects were very sensitive to the allergen, reacting positively down to 8.1 ng, is strong evidence of PHL as the allergen causing the reactions to the HIVAS extract. The average amount of PHL released from a single test plant in this study was 100 ng h⁻¹, meaning that a border of feverfew plants may release milligrams of the allergen, which would be sufficient to elicit reactions in moderately sensitive persons: among the five subjects tested with the PHL dilution series, the least sensitive tested positive to 0.0011 mg cm⁻² corresponding to < 1 μ g per test area. Furthermore, the feverfew plants used in this study contained 0.2% PHL of dry weight in the aerial parts, but concentrations of up to 0.9% PHL of dry weight in leaves has been reported previously as well as concentrations exceeding 1.2% PHL of dry weight in leaves of post-flowering feverfew plants.¹³ So the release of PHL under real-life conditions may be even higher as those reported in the present study.

The fact that PHL elicits patch-test reaction on normal skin on the back of some PHL-sensitive patients in a dose of 10 ng in a TRUE Test[®] patch makes it one of the most powerful contact allergens in the environment.²² Dermatitis on exposed areas may be even more sensitive. PHL has been isolated from a number of other Compositae plants such as, e.g. tansy (*T. vulgare*), *Anthemis cretica*, *Inula aschersoniana*, *Ambrosia* and *Arctotis* spp. as well as members of the Magnoliaceae family,²³ and furthermore there is evidence of true cross-reactivity between PHL and the allergens of the popular *Chrysanthemum indicum* L. [*Dendranthema indicum* (L.) Desm.].²⁴ The implications are that it may be quite difficult to avoid this strong allergen and closely related compounds.

The degree of sensitivity to PHL varied in the five subjects tested with the dilution series (Table 2): the most sensitive patient (no. 12), who was diagnosed with Compositae allergy in 2004, reported feverfew as a primary sensitizer and still had problems with summer-exacerbated eczema. On the other hand, the second most sensitive person (patient no. 9) was diagnosed with Compositae allergy in 2003, probably sensitized by gardening, but not feverfew, and her hand eczema was well controlled now.

The relation between the patients' suspicion of ABCD and a positive reaction to the HIVAS extract was not unambiguous, but in five of the eight patients the two parameters were coincident. Feverfew as a primary sensitizer was not associated with positive reactions to the HIVAS extract.

As expected, PHL was not detected in the headspace extracts and neither were other SQLs. The positive reactions to nonoxidized/oxidized extracts in two patients thus could not be explained by their SQL allergy, but patient no. 7 had a colophonium and patient no. 10 a fragrance allergy, and it is possible that their headspace extract reactions are due to cross-reactivity between volatile terpenes from feverfew and terpenes in colophonium and fragrance mix I. Cross-reactivity between fragrance terpenes, colophonium and Compositae plant extracts has been reported before, although it is not invariably seen in all patients as documented in this study.²⁵ Likewise, there was no association between positive reactions to fragrance mix/colophonium and the extract from the HIVAS filters. Also, all people in this study tested negative to the monoterpene and sesquiterpene fraction isolated directly from feverfew plants, whether the fraction was oxidized or not, emphasizing that these are not primary allergens.

Carvone was included in the patch-test series due to a previously reported association between sensitization to this monoterpene and Compositae extracts.²⁶ Two of the 12 subjects tested positive (Table 1), and the allergy was of old relevance in one and unknown relevance in the other, making true cross-reactivity a possibility in the latter.

In conclusion, the clinical part of this study has proved that feverfew-allergic patients are sensitive to airborne and—to a lesser degree—volatile fractions from feverfew, and the subsequent isolation of the SQL PHL from the particle-containing airborne fraction in amounts sufficient to elicit positive patch-test reactions in the same patients is strong

evidence of PHL as the allergen responsible for ABCD in feverfew-allergic patients. In accordance with previous studies, monoterpenes and sesquiterpenes seem to be of minor importance.^{14,15}

Acknowledgments

Kgl. Hofbundtmager Aage Bangs Fond is gratefully acknowledged for financial support and Mekos Laboratories AS, Hilerød, Denmark for providing the parthenolide dilution series.

References

- Shelmire B. Contact dermatitis from vegetation. Patch testing and treatment with plant oleoresins. *J S Med Assoc* 1940; **33**:337–46.
- Lonkar A, Jog MK. 'Epidemic' contact dermatitis due to *Parthenium hysterophorus* (Compositae family of plants). Report of 350 cases. *Contact Derm Newsl* 1972; **11**:291–2.
- Burry JN, Kuchel R, Reid JG, Kirk J. Australian bush dermatitis: Compositae dermatitis in South Australia. *Med J Aust* 1973; **1**:110–16.
- Hjorth N, Roed-Petersen J, Thomsen K. Airborne contact dermatitis from Compositae oleoresins simulating photodermatitis. *Br J Dermatol* 1976; **95**:613–20.
- Hausen BM. Kompositenallergie. Ein Beitrag zur Identifizierung der Kontaktallergene, ätiologischen Diagnostik und aktuellen Bedeutung. *Allergologie* 1979; **2**:143–7.
- Schumacher MJ, Silvis NG. Airborne contact dermatitis from *Ambrosia deltoidea* (triangle-leaf bursage). *Contact Derm* 2003; **48**:212–16.
- Srinivas CR. Transmission of *Parthenium* dermatitis by clothing. *Arch Dermatol* 2005; **141**:1605.
- Schmidt RJ. Compositae. *Clin Dermatol* 1986; **4**:46–61.
- Geier J, Hausen BM. Epikutantestung mit dem Kompositen-Mix. *Allergologie* 2000; **23**:334–41.
- Paulsen E, Andersen KE, Hausen BM. Sensitization and cross-reaction patterns in Danish Compositae-allergic patients. *Contact Derm* 2001; **45**:197–204.
- Mensing H, Kimmig W, Hausen BM. Airborne contact dermatitis. *Hautarzt* 1985; **36**:398–402.
- Hausen BM, Vieluf IK. Allergiepflanzen/Pflanzenallergene. *Handbuch und Atlas der allergieinduzierenden Wild- und Kulturpflanzen*, 2nd edn. Landsberg/München: Ecomed Verlagsgesellschaft mbH, 1997.
- Awang DVC, Dawson BA, Kindack DG. Parthenolide content of feverfew (*Tanacetum parthenium*) assessed by HPLC and ¹H-NMR spectroscopy. *J Nat Prod* 1991; **54**:1516–21.
- Christensen LP, Jakobsen HB, Paulsen E *et al.* Airborne Compositae dermatitis: monoterpenes and no parthenolide are released from flowering *Tanacetum parthenium* (feverfew) plants. *Arch Dermatol Res* 1999; **291**:425–31.
- Paulsen E, Christensen LP, Andersen KE. Do monoterpenes released from feverfew (*Tanacetum parthenium*) plants cause airborne Compositae dermatitis? *Contact Derm* 2002; **47**:14–18.
- Matura M, Sköld M, Börje A *et al.* Selected oxidized fragrance terpenes are common contact allergens. *Contact Derm* 2005; **52**:320–8.
- Wahlberg JE. Patch testing. In: *Textbook of Contact Dermatitis* (Rycroft RJG, Menné T, Frosch PJ, Lepoittevin J-P, eds), 3rd edn. Berlin and Heidelberg: Springer Verlag, 2001:435–68.
- English J, Norris P, White I, Cronin E. Variability in the clinical patterns of Compositae dermatitis. *Br J Dermatol* 1989; **121** (Suppl. 34): 27.
- Paulsen E, Andersen KE. Compositae dermatitis in a Danish dermatology in 1 year (II). Clinical features in patients with Compositae contact allergy. *Contact Derm* 1993; **29**:195–201.
- Diepgen TL, Häberle M, Bäurle G. Fallstricke in der Berufsdermatologie: Das aerogene Kontaktekzem auf Pflanzen. *Dermatosen* 1989; **37**:23–5.
- Hausen BM, Spring O. Sunflower allergy. On the constituents of the trichomes of *Helianthus annuus* L (Compositae). *Contact Derm* 1989; **20**:326–34.
- Johansen JD, Andersen KE, Svedman C *et al.* Chloroatranol, an extremely potent allergen hidden in perfumes: a dose-response elicitation study. *Contact Derm* 2003; **49**:180–4.
- Fischer NH, Olivier EJ, Fischer HD. The biogenesis and chemistry of sesquiterpene lactones. III. Germacranolides. In: *Progress in the Chemistry of Organic Natural Products* 38 (Herz W, Grisebach H, Kirby GW, eds). Wien: Springer-Verlag, 1979.
- Schulz KH, Hausen BM, Wallhöfer L, Schmidt-Löffler P. Chrysanthemen-Allergie. 2. Experimentelle Untersuchungen zur Identifizierung der Allergene. *Arch Derm Forsch* 1975; **251**:235–44.
- Paulsen E, Andersen KE. Colophonium and Compositae mix as markers of fragrance allergy: cross-reactivity between fragrance terpenes, colophonium and Compositae plant extracts. *Contact Derm* 2005; **53**:285–91.
- Paulsen E, Andersen KE, Carlsen L, Egsgaard H. Carvone: an overlooked contact allergen cross-reacting with sesquiterpene lactones? *Contact Derm* 1993; **29**:138–43.