













Very late reactions in the patch test with fragrance mix I and oak moss absolute (*Evernia prunastri*, INCI): Data of the Information Network of Departments of Dermatology (IVDK)

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Patch test reactions that become positive de novo at around day 7 (D7) are called “late” patch test reactions,¹ and are frequently seen after patch testing neomycin, for example.² Reactions beyond D7 (“very late reactions”) may indicate active sensitization.^{1,3} However, very late reactions (2 to 4 weeks after patch testing) without being linked to active sensitization have also been observed.^{4–6} We were interested in very late reactions (beyond D7) in patch testing fragrance mix I (FMI) and oak moss absolute (OM). INCI name: *evernia prunastri*.

arms, respectively, and read as usual on D2 and D3 or D4. Patients without positive reactions were asked to present themselves again if from D4 onward a reaction became visible, or, in case of a negative outcome, to fill in a standardized letter on D28 at the latest. Patients who did not respond were contacted by telephone. Thus patients with positive late reactions were always evaluated in the clinics, whereas the response letter or the phone call aimed at confirming a negative test outcome up to D28.

METHODS

The study was conducted between 2015 and 2018 in 13 units of the IVDK, with 1789 patients participating. Methods of the IVDK (www.ivdk.org) have been described in detail elsewhere.⁷ Patch tests of FMI (8% pet.) and OM (1% pet.) (supplied by SmartPractice Europe, Greven, Germany) were applied on the left and right anterior upper

RESULTS

In 78% of the patients (n = 1393), late readings were documented. On D3/D4, 6.8% [95% confidence interval [CI] 5.63–7.97] had positive reactions to the FMI, and 1.8% [95% CI: 1.23–2.47] to OM (Table 1). Of 131 patch-test positive patients, 24 (18.3%) reacted to both preparations, 98 (74.8%) to FMI only, and 9 (6.9%) to OM and

not to FMI, although OM is a constituent of FMI. Positive reactions to all single FMI constituents without positive reactions to the mix were observed rarely, but most often in OM positives.⁸ One might speculate on different allergen content (eg, atranol) in-between the raw material used. Very late reactions were seen in 20 patients. For only patient No. 11, “perfume, deo, or aftershave” were documented as suspected allergen sources. Eleven patients reacted to FMI, 11 to OM, and (only) 2 of them to both preparations (Table 2). All of these reactions, except one ++ reaction, were rated as weak, with virtually no infiltrate in three cases. In 3 of these 20 patients, four doubtful reactions between D5 and D7 were documented. Very late reactions to each of the preparations were documented in 0.8% of patients

evaluable for late readings. Regarding all positive reactions, 11/136 (8.1%) of FMI-positive patients and 11/45 (24.4%) of OM-positive patients showed very late reactions (Table 1).

DISCUSSION

A relatively high proportion of patients tested showed very late reactions >D7. These results are surprising, as the FMI was usually found to produce “early reactions,” mainly appearing on D3/4.^{2,9} It is recommended to re-test the allergens with very late reactions. If then the patch test reaction occurs within a “normal” time course (positive

TABLE 1 Results of reading fragrance mix I (FMI) and oak moss absolute (OM) in n = 1789 patients at different points of time

	N patients	Positive D3(D4)	% D3(D4)	Late positive D4-D7	Very late positive. (>D7)	Very late pos (%)	n reactions (total)	>D7% of total
FMI	1789	122	6.8	3				
	1304				11	0.8	136	8.1
OM	1789	33	1.8	1				
	1374				11	0.8	45	24.4

Note: For 78% of the patients (n = 1393), late readings were documented, and after corrections for incorrect classification (eg, excluding cases already positive at D3/4 in one allergen but not the other), n_{FMI} = 1304 and n_{OM} = 1374 patients were evaluable for very late readings, respectively. Eleven of 1304 patients (0.8%) reacted very late to FMI, and 11/1374 (0.8%) to OM. Eleven of 136 total positive reactions to FMI (8.1%) and 11 of 45 (24.4%) reactions to OM were very late reactions (>D7). Three questionable reactions ≥D25, one to FMI and two to OM, were included in suspicion for positive reactions.

TABLE 2 Very late reactions (>D7) documented in 20 patients. For each patient, substance, day of very late reading, reactions strength, and reactions until D7 are given. INCI name for oak moss absolute: *evernia prunastri*

Patient No.	Substance	Day of very late reading	Reaction	Reactions until D7
1	Fragrance mix I	25	+	
2	Fragrance mix I	14	+	
3	Oak moss absolute	25	?	
4	Oak moss absolute	25	+	
5	Oak moss absolute	28	?	
6	Fragrance mix I	9	+	D2 (+), D3 (0)
7	Oak moss absolute	25	+	D7 (?)
8	Fragrance mix I	21	+	
	Oak moss absolute	21	+	
9	Oak moss absolute	27	+	D2 (?)
10	Fragrance mix I	25	+	D5 (?)
	Oak moss absolute	25	+	D6 (?)
11	Oak moss absolute	25	+	D3 (?)
12	Fragrance mix I	25	+	D7 (?)
13	Fragrance mix I	25	+	
14	Fragrance mix I	12	+	
15	Fragrance mix I	25	?	D1 & D2 (?)
16	Oak moss absolute	15	+	
17	Oak moss absolute	25	+	D3 (?)
18	Fragrance mix I	25	++	
19	Oak moss absolute	12	+	
20	Fragrance mix I	25	+	D2 (?)

at $\leq D7$), this “late/early reaction pattern” is considered to support the assumption of active sensitization.¹ Unfortunately, none of our patients with very late reactions agreed on being re-tested.

However, alternative explanations for very late reactions were already discussed: low patch test dose,⁶ slow absorption,² low sensitization level,³ and true late reactions (as an individual biologic variation), in particular in those reacting late again on re-testing.¹⁰ The three very late reacting cases with four doubtful reactions on D5-7 (2 to OM and 2 to FMI) as well as two patients with doubtful reactions to OM on D3 (including patient No. 11) may alternatively be considered as cases with a low sensitization level. The cases of very late reactions mentioned above⁴⁻⁶ are very rare, were reported mostly as case reports only, and probably do not explain our findings. In support of active sensitization, fragranced products were not suspected as cause in almost all patients with very late reactions. However, although our categorical system of exposure assessment might be considered as not very specific, the relevance of patch test reactions is rarely assessed in IVDK publications (mainly because of a lack of standardization and poor reliability of detailed exposure data), and there was no follow-up of the patients involved—which all can be considered as limitations of our study. In our opinion, the frequent very late reactions to FMI and OM (each 0.8% of the patients tested and re-evaluated) are suggestive of active sensitization,¹¹ despite the lack of unequivocal evidence. The impact of active sensitization for patients should be studied.¹²

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CONFLICT OF INTEREST

The authors have no personal conflicts of interest to declare. The IVDK, maintained by the IVDK e.V., of which J. Geier and S. Schubert are employees, is sponsored by the cosmetic and fragrance industry (associations) as well as by public funds. A. Schnuch works as an ad hoc consultant for cosmetic industry (associations), partly remunerated. All other authors have no conflicts of interest to declare with regard to this study.

AUTHOR CONTRIBUTIONS

Steffen Schubert: Data curation (equal); formal analysis (equal); project administration (equal); software (equal); writing – original draft (equal); writing – review and editing (equal). **Axel Schnuch:** Conceptualization (lead); project administration (equal); supervision (equal); writing – original draft (equal); writing – review and editing (equal). **Andrea Bauer:** Investigation (equal); methodology (equal); resources (equal); writing – review and editing (equal). **Nicola Wagner:** Investigation (equal); methodology (equal); resources (equal); writing – review and editing (equal). **Claudia Schröder-Kraft:** Investigation (equal); methodology (equal); resources (equal). **Heinrich Dickel:** Investigation (equal); methodology (equal); resources (equal); writing – review and editing (equal). **Elke Weisshaar:** Investigation (equal); methodology

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“Re-testing” suggests that cosensitizations to isobornyl acrylate and sesquiterpene lactones may be due to cross-reactivity

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Patients with allergic contact dermatitis from the glucose sensor FreeStyle Libre (Abbott Diabetes Care, Witney, UK) are often (strongly) sensitized to isobornyl acrylate (IBOA).^{1,2} About 40% to 60% of these patients also have a concomitant positive patch test to the sesquiterpene lactone mix (SLM; 0.1% pet.), an observation for which an explanation is lacking.^{3,4}

CASE REPORT

A 19-year-old male patient with diabetes mellitus type 1 developed severe allergic contact dermatitis from FreeStyle Libre several weeks after starting its use. Patch tests, performed as described elsewhere,⁴ and including the application of IBOA 0.3% pet. (in-house prepared

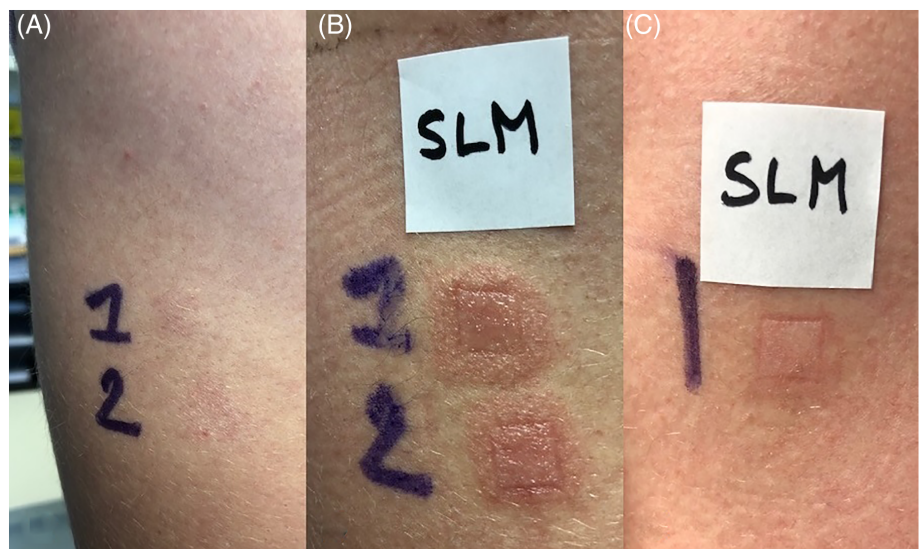


FIGURE 1 (A) Day (D) 0: residual erythema 6 weeks after positive patch tests to isobornyl acrylate (IBOA) 0.1% pet. (no. 1) and 0.3% pet. (no. 2) on the right upper arm. (B) D2: strong positive patch test reactions (++) to sesquiterpene lactone mix (SLM) 0.1% pet. on the previous positive patch tests sites of IBOA (no. 1 = 0.1%, no. 2 = 0.3%) on the right upper arm. (C) D2: doubtful positive patch test reaction (??) to SLM 0.1% pet. on a normal (previously patch test uninvolved) skin site on the left upper arm