Is *p-tert*-butylphenol-formaldehyde resin (PTBP-FR) in TRUE Test® (Mekos test) sensitizing the tested patients?

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doi:10.1111/cod.12401

Summary

Background. In a population study using TRUE Test®, we noted late reactions to *p-tert*-butylphenol-formaldehyde resin (PTBP-FR) in 0.5% of subjects tested.
Objectives. In order to explore possible test sensitization, differences in the contents of sensitizers within PTBP-FR in test preparations for TRUE Test® and Finn Chambers® were analysed. Subjects allergic to PTBP-FR and subjects with late reactions to PTBP-FR were retested in order to explore whether these groups reacted to different PTBP-FR sensitizers.
Patients/materials/methods. Four individuals with late reactions and 5 subjects with established allergy to PTBP-FR were retested with defined PTBP-FR sensitizers. PTBP-FR constituents in patches from TRUE Test® were analysed with high-performance liquid chromatography. Previously analysed samples of PTBP-FR constituents served as a reference.
Results. The pattern of reaction to PTBP-FR sensitizers was similar in both groups. Subjects with suspected sensitization had somewhat stronger reactions than controls. The concentrations of monomers, dimers and trimers were generally higher in the TRUE Test® resin than in reference substances.
Conclusions. Retesting did not add information regarding causes of possible sensitization. Analysis showed that the resin used in TRUE Test® has a lower degree of polymerization or condensation, which may enhance its sensitizing properties. A follow-up of late reactions to PTBP-FR in TRUE Test® should be carried out.

Key words: active sensitization; late reactions; retesting.

This is a report on a possible side-effect of patch testing a normal population. The focus of the project in which the tests were performed was to study the association between nickel allergy and orthodontic appliance treatment. Patch testing with the TRUE Test® baseline series was part of the project. A number of healthy subjects may have been sensitized to *p-tert*-butylphenol-formaldehyde resin (PTBP-FR) by the test. When ~1000 subjects were tested in the project, 5 people reported late reactions to PTBP-FR, and this allergen was omitted from further testing.

The resin is a well-known allergen that has been included in standard patch testing since the early 1970s. The test consists of a large number of substances with various sensitizing and eliciting capacities. Several medium and strong allergens have been isolated from the resin and identified. Their elicitation capacities have been studied by patch testing of serial dilutions on PTBP-FR-allergic patients, and their sensitization capacities and cross-reactivity patterns have been studied in animal experiments (1–6).

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Funding: Mekos Laboratories A/S, Hillerød, Denmark provided test material for analysis.
Conflicts of interests: No additional conflicts of interest are declared.

Accepted for publication 21 March 2015

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Sensitization from patch testing with standardized haptens is a rare event (7, 8). We have found a few reports of possible active sensitization from testing with PTBP-FR. In a compilation of late reactions among 7619 patients tested with TRUE Test®, 2 patients reported reactions to PTBP-FR on days 9 and 20 respectively. The second patient was retested, and showed a positive reaction within a few days. In this test population, patients were not specifically encouraged to report late reactions (7). In another summary of late reactions in 884 patients tested with the Finn Chambers® test system, patients were advised to report late reactions after the second reading. One patient reported a late reaction to PTBP-FR on day 14, and experienced a strong reaction within a week on retesting. However, as a doubtful reaction was recorded at the original test reading, it was concluded that primary sensitization to PTBP-FR was unlikely (8). A case report of a very late reaction (5 weeks) to PTBP-FR with a positive reaction on day 2 on retesting was also found (9).

The aims of this study were (i) to analyse differences in the contents of known sensitizers within the PTBP-FR test substance used in TRUE Test® from the same batch as the one used in the project and in test preparations for Finn Chambers®, and (ii) to retest subjects with established allergy to PTBP-FR and subjects with late reactions to PTBP-FR to determine whether these two groups reacted to different PTBP-FR sensitizers.

Subjects and Methods

The focus of a project, of which the present study forms an unplanned part, was to examine the association between nickel allergy and orthodontic appliance treatment and lifestyle factors. The outline of the project has been described in detail in a previous publication (10).

The study was based on a cross-sectional survey conducted among all upper secondary schools in Umeå, Sweden and in two upper secondary schools in Örebro, Sweden, from September 2000 to May 2004 in Umeå, and from October 2003 to April 2004 in Örebro.

Following a briefing session, a questionnaire on lifestyle, medical issues and orthodontic treatment was administered to all pupils present. Patch tests with nickel and 23 other common contact allergens were performed on consenting adolescents.

Of the 6364 individuals present at briefings, 70% (4439/6364) consented to patch testing (3013 girls and 1426 boys). TRUE Test® panels I and II (Mekos Laboratories A/S, Hillerød, Denmark) were used, containing 24 of the most common contact allergens. The test was applied for 2 days. On day 4, the patch tests were read once, either by a trained school nurse or by a dermatologist.

After nearly 1000 tests (67% girls and 33% boys), five occurrences of possible active sensitization to PTBP-FR (late reactions) were reported, and 9 subjects (0.9%) showed positive reactions to PTBP-FR at the scheduled reading on day 4. All 14 subjects were girls; no positive reactions were found among boys. Owing to the suspected sensitization, PTBP-FR was removed from further testing in the project. In summary, 0.5% of pupils tested reported late reactions to PTBP-FR. These 5 subjects are described below.

When reading the tests on day 4, the pupils were asked to report any late reactions to the test. Of 4439 subjects tested in the project, late reactions were reported to PTBP-FR exclusively.

Hypothesis

Our hypothesis was that TRUE Test® might have a different composition of PTBP-FR sensitizers from test preparations for Finn Chambers®, and that a higher content of sensitizers with stronger sensitizing capacity within TRUE Test® might explain the unexpectedly high number of late reactions found in our project. This hypothesis could be further supported if subjects with late reactions reacted to different PTBP-FR sensitizers from those with established allergies to PTBP-FR.

Subjects

No. 1, female, aged 17 years. This subject had atopic dermatitis as a child, and had suffered from polymorphous light eruptions (eczema) for 5 years. There was no history indicating previous contact allergy to PTBP-FR. The subject was tested with TRUE Test® in the project in October 2000; a reading on day 4 was negative. Approximately 1 week later, she reported to the research nurse with a late reaction to PTBP-FR. She was retested at the Department of Dermatology with PTBP-FR from TRUE Test®, and she had a positive test reaction (++) on day 7 (for practical reasons, she could not attend for reading on days 3–4). When a new history was taken for assessment of relevance, she reported that she had bought a new watch strap ~6 months before the original test in October 2000. After this test, she had begun to react in the form of eczema to the watch strap. The strap was sent to the Department of Occupational and Environmental Dermatology in Malmö, Sweden for chemical analysis regarding the presence of PTBP-FR. It was concluded that the results possibly indicated active sensitization to PTBP-FR from the test.

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No. 2, female, aged 18 years. This subject had no history of atopic disease. There was no history indicating previous contact allergy to PTBP-FR. The subject was tested with TRUE Test® in the project in November 2000; a reading on day 4 was negative. One month after the reading, she noticed a red square on her back. She reported this to the research nurse. The nurse concluded that the reaction was at the site for panel II of TRUE Test®. She was retested at the Department of Dermatology with panels I and II from TRUE Test®, and she had a positive reaction (+) only to PTBP-FR on day 3 and on day 7. It was concluded that the results indicated active sensitization to PTBP-FR from the test.

No. 3, female, aged 19 years. This subject had flexural eczema on her arms as a child. She remembered having skin reactions to plasters as a child. There was no history indicating previous contact allergy to PTBP-FR. She was tested with TRUE Test® in the project in January 2001; a reading on day 4 was negative. One month after the reading, she noticed an eczematous red square on her back. She reported this to the research nurse. The nurse concluded that the reaction was at the site for no. 13 (PTBP-FR) or no. 19 [mercaptobenzothiazole (MBT)] of panel II of TRUE Test®. The subject was retested at the Department of Dermatology with PTBP-FR and MBT from TRUE Test®, and she had a doubtful (+?) reaction to PTBP-FR on day 3 and a strong reaction (++) on day 7. She had no reaction to MBT. It was concluded that the results indicated active sensitization to PTBP-FR from the test.

No. 4, female, aged 19 years. This subject had flexural eczema as a child. There was no history indicating previous contact allergy to PTBP-FR. She was tested with TRUE Test® in the project in January 2001; a reading on day 4 was negative. Two weeks later, she noticed a red square on her back, which she showed to the nurse 1 month after the first reading. The nurse concluded that the reaction was at the site for no. 13 (PTBP-FR) or no. 19 (MBT) of panel II of TRUE Test®. The subject was retested at the Department of Dermatology with panel II from TRUE Test®, and she had a positive reaction (+) only to PTBP-FR on day 3 and on day 7. It was concluded that the reported late reaction could be a normal but late reaction to PTBP-FR, but that active sensitization was equally possible.

No. 5, female, aged 19 years. This subject had a history of atopic rhinitis but not of atopic dermatitis. There was no history indicating previous contact allergy to PTBP-FR. She was tested with TRUE Test® in the project in April 2001; a reading on day 4 was negative. One month after this reading, she visited the nurse and had a positive reaction to what was considered to be patch no. 13 (PTBP-FR). She reported that the reaction had occurred 'weeks' after the first reading. She was retested at the Department of Dermatology with PTBP-FR from TRUE Test®, and she had a positive reaction (++) to PTBP-FR on day 3. It was concluded that the results indicated active sensitization to PTBP-FR from the test.

Retesting the patients

All subjects with possible sensitization to PTBP-FR (n = 5) and all subjects with positive reactions to PTBP-FR at normal readings in the project (control group, n = 9) were asked to take part in retesting of six chemically defined PTBP-FR sensitizers, which were either synthesized or isolated from the resin at the Department of Occupational and Environmental Dermatology, Malmö (Table 1 and Fig. 1). The substances were patch tested in equimolar concentrations. The test substances were applied to the upper back in Finn Chambers® for 2 days, and readings, classified according to ICDRG guidelines (11), were carried out on days 3–4 and 7. All readings were performed by the same investigator (B.S.). These tests were performed in 2005–2006, 4–5 years after the tests performed in the original study.

As this examination was carried out in order to assess possible sensitization from PTBP-FR, it was regarded as an extension of the original project and a clinical examination in patients (for insurance purposes) and control subjects. The testing within the original project was approved by the Ethics Committee of the Faculty of Medicine and Odontology, Umeå University. All subjects were informed about the reason for retesting, and they all gave their informed consent and were managed in agreement with the Helsinki Declaration. Four individuals from the first group (subjects 2–5) and 5 from the control group agreed to participate.

Analysis of the watch strap

The watch strap belonging to subject no. 1 was analysed for PTBP-FR with gas chromatography–mass spectrometry (GCMS).

Analysis of patch test preparation and corresponding PTBP-FR

Ten patches (0.80 cm^2 each) containing PTBP-FR were cut from Mekos patch test panel II. The patches were extracted with 5 ml of methanol in a test tube, and the resulting solution was filtered. The solution was evaporated under vacuum (30°C), and adjusted to a

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Table 1. Patch test results from patch testing with 4-*tert*-butyl-2,6-bis-hydroxymethyl-phenol (**1**), 4-*tert*-butyl-2-(5-*tert*-butyl-2-hydroxy-3-hydroxymethyl-benzyloxymethyl)-6-hydroxymethyl-phenol (**2**), 4-*tert*-butyl-2-(5-*tert*-butyl-2-hydroxy-benzyloxymethyl)-6-hydroxymethyl-phenol (**3**), 4-*tert*-butyl-2-(5-*tert*-butyl-2-hydroxybenzyl)-phenol (**4**), 4-*tert*-butyl-2,6-bis-(5-*tert*-butyl-2-hydroxy-3-hydroxymethyl-benzyl oxymethyl)-phenol (**5**) and 4-*tert*-butyl-2-(5-*tert*-butyl-2-hydroxy-benzyloxymethyl)-6-(5-*tert*-butyl-2-hydroxy-3-hydroxymethyl-benzyl oxymethyl)-phenol (**6**) in patients with suspected sensitization and in a comparison group of previously sensitized individuals

		Patient number								
Substance	Concentration (% wt/vol)*	1-p	2-p	3-p	4-p	5-c	6-c	7-c	8-c	9-c
1	0.52	++	+?	+++	+?	+	+	+?	++	+
	0.052	++	+?	+++	+?	+?	+?	+?	+	+
	0.0052	+?	–	++	–	–	–	–	+?	+
	0.00052	–	–	–	–	–	–	–	–	–
2	1.0	+++	+++	+++	++	++	++	+	++	++
	0.1	++	++	+++	+?	++	++	+	++	+?
	0.01	++	++	+++	+?	+?	++	+?	+	+?
	0.001	+?	–	+++	+?	–	+?	+?	+?	+?
	0.001	–	–	++	–	–	–	–	–	–
3	0.93	+++	+++	+++	++	+?	++	+	+++	++
	0.093	++	++	+++	++	+?	++	+	++	++
	0.0093	++	–	+++	+	–	+?	+	++	+
	0.00093	+?	–	+++	+?	–	–	+?	+	+?
	0.000093	–	–	+	–	–	–	–	–	–
4	0.85	–	++	+++	–	–	–	–	+	–
	0.085	–	–	+?	–	–	–	–	+?	–
	0.0085	–	–	–	–	–	–	–	–	–
5	1.5	++	++	+++	++	++	++	+	+	+
	0.15	++	++	+++	+	+?	++	+	+	+
	0.015	+?	–	++	–	–	+?	+?	+?	–
	0.0015	+?	–	+?	–	–	–	–	–	–
	0.00015	–	–	–	–	–	–	–	–	–
6	1.4	++	++	++	+	+	++	+	+	+
	0.14	+	–	–	–	+	+?	+?	+	+
	0.014	+?	–	–	–	–	–	+?	–	–
	0.0014	–	–	–	–	–	–		–	–
	0.00014	–	–	–	–	–	–	–	–	–
STS		**28**	**21**	**49**	**14**	**11.5**	**19.5**	**12**	**23**	**16**

c, reference person previously sensitized; p, patient with suspected active sensitization; STS, summarized test score.
Readings obtained on days 3–4 are given.
*The concentrations are equimolar, and the vehicle is acetone.

final volume of 0.50 ml. This sample was analysed with high-pressure liquid chromatography (HPLC) with a diode array detector according to analytical HPLC methods described earlier, for monomers (12) and for larger substances (5). A 0.10% wt/vol methanol solution of PTBP-FR (Mekos Laboratories A/S) was analysed in the same manner. This resin came from the same batch that had been used for preparation of the analysed patches, and served as a reference for determination of the amount of PRBP-FR in the patches. Previously isolated and identified samples of the different low molecular weight PTBP-FR constituents, substances **1**, **2**, **4**, and **5** (Fig. 1), served as reference substances for determination of the amounts of these substances in PTBP-FR (3, 5, 6, 13). No reference was available for substance **3** at the time.

Statistics

For comparison of the strengths of test reactions of a possibly allergic nature (irritant reactions excluded), the scores were transformed to numerical values: $-=0$, $+?=0.5$, $+=1$, $++=2$, and $+++=3$. The mean values of the summarized test scores (STSs) (14) were compared between the two groups of subjects (possibly sensitized and control) by use of the Mann–Whitney *U*-test.

Results

The results from patch testing with serial dilutions are given in Table 1. Substance **4** gave a positive reaction in 3 of 9 subjects, substance **1** in 6 subjects, and substance **3** in 8 subjects, whereas substances **2**, **5** and **6** gave positive reactions in all 9 subjects. The patients with suspected

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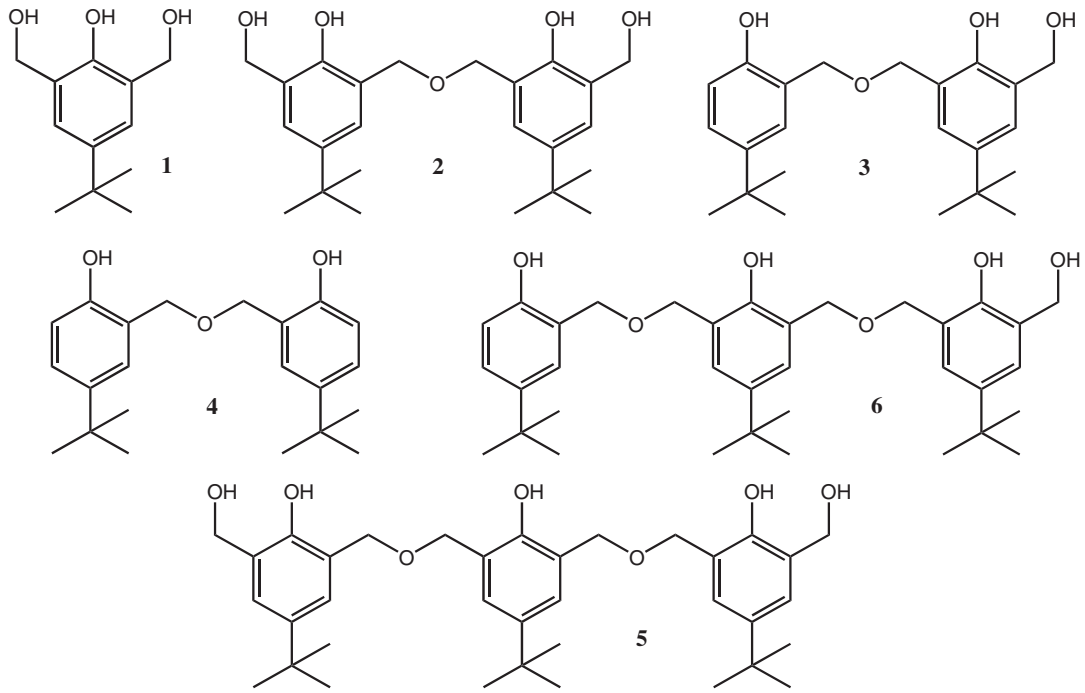

Fig. 1. Chemical structures of the patch tested allergens: 4-*tert*-butyl-2,6-bis-hydroxymethyl-phenol (**1**), 4-*tert*-butyl-2-(5-*tert*-butyl-2-hydroxy-3-hydroxymethyl-benzyloxymethyl)-6-hydroxymethyl-phenol (**2**), 4-*tert*-butyl-2-(5-*tert*-butyl-2-hydroxy-benzyl oxymethyl)-6-hydroxymethyl-phenol (**3**), 4-*tert*-butyl-2-(5-*tert*-butyl-2-hydroxybenzyl)-phenol (**4**), 4-*tert*-butyl-2,6-bis-(5-*tert*-butyl-2-hydroxy-3-hydroxymethyl-benzyloxymethyl)-phenol (**5**), and 4-*tert*-butyl-2-(5-*tert*-butyl-2-hydroxy-benzyloxymethyl)-6-(5-*tert*-butyl-2-hydroxy-3-hydroxymethyl-benzyloxymethyl)-phenol (**6**).

sensitization showed a tendency (non-significant) to have stronger reactions (higher STS) than the controls with previous sensitization, but no obvious difference could be seen between the groups regarding elicitation thresholds for these substances.

The GCMS analysis of the watch strap showed the presence of PTBP-FR monomers. By comparison with our reference PTBP-FR, we estimated the total amount of resin in the watch strap to be 80 mg.

Analysis of the TRUE Test® patches showed that each patch contained ~ 0.039 mg PTBP-FR.

Analysis of the TRUE Test® PTBP-FR (Mekos) used in these patches gave the concentrations of specific substances in the resin shown in Table 2. Previously determined and published concentrations of these substances in two other PTBP-FRs are given for comparison (2, 5, 13). The concentrations of monomers, dimers and trimers were generally higher in the TRUE Test® resin.

Discussion

On the basis of clinical criteria, our report suggests that testing with PTBP-FR has caused active sensitization in a number of subjects. Chemical analysis of the watch strap that had been used by subject no. 1 verified that the glue in the strap contained PTBP-FR. It was concluded that the first reported late reaction (subject no. 1) could be a normal late reaction, but that the history of reactions to the watch strap supported the assumption that active sensitization to PTBP-FR from testing had taken place. Our observations outnumber previously reported cases of active sensitization in clinical settings.

Late test reactions are not exclusively caused by active sensitization. Reactivation of a previous allergy can result in very late reactions, as shown in a study by Paulsen et al. (15). None of our subjects with possible sensitization had any history of previous reactions to PTBP-FR, and it is unlikely that reactivation would occur for only one of 24 tested allergens.

One possible characteristic of a PTBP-FR that can favour sensitization is that it contains high concentrations of the most sensitizing substances. The sensitizing substances are relatively small substances with molecular weights usually lower than 700, for example monomers, dimers, and trimers. We know from other studies that the concentration of one of the main sensitizers (substance **2**) can vary more than 10-fold in different PTBP-FRs (16). When comparing the concentrations of some monomers,

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Table 2. Concentrations of individual sensitizers in the *p-tert*-butylphenol-formaldehyde resin (PTBP-FR) used in TRUE Test®

Substance	Concentration (% w/w)	
	PTBP-FR in TRUE Test®	PTBP-FR 1–PTBP-FR 2
Monomers		
1	2.04	0.23–0.73
Dimers		
2	2.23	1.0–1.7
3	ND	0.75–0.90
4	0.65	ND
Trimers		
5	2.55	0.09–0.65

Corresponding values published previously for two other PTBP-FRs (PTBP-FR 1 and 2) are given for comparison (2, 5, 13).
1, 4-*tert*-butyl-2,6-bis-hydroxymethyl-phenol; **2**, 4-*tert*-butyl-2-(5-*tert*-butyl-2-hydroxy-3-hydroxymethyl-benzyloxymethyl)-6-hydroxymethyl-phenol; **3**, 4-*tert*-butyl-2-(5-*tert*-butyl-2-hydroxy-benzyloxymethyl)-6-hydroxymethyl-phenol; **4**, 4-*tert*-butyl-2-(5-*tert*-butyl-2-hydroxybenzyl)-phenol; **5**, 4-*tert*-butyl-2,6-bis-(5-*tert*-butyl-2-hydroxy-3-hydroxymethyl-benzyloxymethyl)-phenol.
ND, not determined.
PTBP-FR 1 = Shenectady – Midland SP 134, Chemotechnique, Malmö, Sweden.
PTBP-FR 2 = Alresen PA 103, Vianova Resins GmbH, Frankfurt, Germany.

dimers and trimers in the TRUE Test® resin, and in the resins used for patch testing at the Malmö department, we found higher concentrations of these substances in the TRUE Test® resin, indicating that this resin has a lower degree of polymerization or condensation. This difference alone can hardly explain the increased frequency of PTBP-FR sensitization indicated in this study.

The factor that is described as being most important for active sensitization is the dose of the allergen applied per unit area (mg/cm^2) of the skin; normally, a higher dose will increase the frequency of sensitization (17). The dose applied for patch testing 1% wt/wt PTBP-FR in petrolatum (20 mg) with the Finn Chambers® technique (0.50 cm^2) is 0.40 mg/cm^2. The TRUE Test® (0.80 cm^2) patch contains 0.039 mg of PTBP-FR, according to our analysis. The calculated dose per unit area from our results is 0.049 mg/cm^2, and the dose specified by the manufacturer is 0.050 mg/cm^2. However, this comparison has been made with the recommended dose in Finn Chambers®; under clinical conditions, the applied patch test amount often varies between 15 and 25 mg, which gives a dose per unit area ranging between 0.30 and 0.50 mg/cm^2. These data indicate that differences in dose per unit area cannot explain the suspected sensitization. As the dose per unit area is 6–10 times lower when testing is performed with TRUE Test® than when it is performed with the Finn Chambers® technique, this could even compensate for the observed concentration variations of the main sensitizers in the PTBP-FRs.

The concordance of positive reactions to allergens in TRUE Test® and corresponding allergens tested with Finn Chambers® has been reported to be 63–67% (18, 19). Overall, both test methods detect similar numbers of positive reactions, with some variations between allergens. The numbers of positive reactions to PTBP-FR were similar (19). These results imply that the bioavailability of allergens in TRUE Test® is similar to that in Finn Chambers®, in spite of the lower concentrations. When TRUE Test® panel II was introduced, the concentration of PTBP-FR was 0.040 mg/cm^2 (19, 20). At the time of our study, the concentration of PTBP-FR had been increased to 0.050 mg/cm^2. The pharmaceutical formula is, however, unchanged. Since 2002, a new method of analysis has been implemented that entails a higher value (M. Nielsen, SmartPractice, Denmark, pers. comm. 2014).

Another possible factor influencing the risk of sensitization is the area over which the substance is applied. When small areas (<1 cm^2) have been compared, it has been shown that the risk of sensitization increases with the area when a constant dose per unit area is maintained (21). The proposed explanation for this difference is that the number of exposed, antigen-presenting cells increases with area. The area of the patch is 1.6 times larger in TRUE Test® than in Finn Chambers®, but this difference seems to be too small to serve as a probable explanation for our findings.

We consider each of these known and discussed risk factors to be an insufficient explanation for our findings of active sensitization to PTBP-FR. Active sensitization may be overlooked in the clinical setting, as it is a rare phenomenon and the risk of underreporting is clear. When large populations are tested, as we have done, such events can be detected, especially if subjects are encouraged to report late reactions. A proper action based on our observation would be to systematically look for late reactions when patch testing with PTBP-FR, regardless of the patch test technique used.

Four of five subjects with possible sensitization were 'atopics' (three had a history of atopic eczema; one had allergic rhino-conjunctivitis). As the number of individuals is small, random variation might explain the apparent overrepresentation of 'atopics'. Previous results from sensitization experiments indicate, rather, that persons with atopic eczema have a decreased potential for active sensitization on uninvolved skin (22, 23).

Finally, we noted that all pupils, both those who were actively sensitized and those with an established allergy

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to PTBP-FR, were girls (14/670 versus 0/330; $p = 0.007$, Fisher's exact test, two-sided). The sex distribution in the sensitized group is probably caused by chance. There are no consistent data showing that women are more prone to be sensitized than men (24). The sex difference in subjects with established allergy to PTBP-FR is probably attributable to differences in exposure, and female predominance has also been observed in Swedish clinical patch test data (25).

We contacted all 5 possibly sensitized persons by mail for follow-up, and 4 of these responded. The girl with reactions to a watch strap soon after the final test has not had any new reactions possibly caused by exposure to PTBP-FR. Two of the other girls have, since the final test, noted eczematous reactions, one of them to a watch strap, and the other to some shoes, which they had never experienced before the tests. In this case report, if sensitization has occurred, the consequences are moderate and should not discourage us from patch testing.

Conclusion

Although reactivation of previous allergy cannot be ruled out, the case series reported indicates that active sensitization to PTBP-FR has occurred as a result of testing with TRUE Test® according to normal routines. Retesting with different sensitizers in the resin did not add information that could identify possible causes of this event. Analysis of the patches used gives some support to the hypothesis that the resin used in TRUE Test® has a lower degree of polymerization or condensation, which may enhance its sensitizing properties. A systematic, large-scale follow-up of late reactions to PTBP-FR in TRUE Test® (Mekos test) should be performed.

Acknowledgements

We would like to acknowledge the contribution of Mekos Laboratories A/S, Hillerød, Denmark for providing test material for analysis and for supporting this study.

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