

Delayed- and immediate-type reactions in the atopy patch test with food allergens in young children with atopic dermatitis

Devillers ACA, de Waard-van der Spek FB, Mulder PGH, Oranje AP. Delayed- and immediate-type reactions in the atopy patch test with food allergens in young children with atopic dermatitis.

Pediatr Allergy Immunol 2008.

© 2008 The Authors

Journal compilation © 2008 Blackwell Munksgaard

In recent years, the atopy patch test (APT) has been suggested as an addition in the allergological work-up of children with atopic dermatitis (AD) and suspected food allergy. We initiated a prospective clinical study in children with AD younger than 3 yr, to evaluate the additional clinical value of the APT next to our own standardized allergological work-up in case of a suspected food allergy. One hundred and thirty-five children were included in the study. They were tested using the skin application food test (SAFT), the APT and measurement of specific IgE. The allergens used in the skin tests were freshly prepared food stuffs and included commercially available cow's milk (CM), the egg white of a hard boiled hen's egg and mashed peanuts in a saline solution. Allergy was defined using a flowchart incorporating the results from the SAFT, oral challenges (OCs) and elimination and (re)introduction periods. To determine the additional value of the APT next to the SAFT, we analyzed the SAFT negative patients per allergen and used an exact binary logistic analysis to evaluate the simultaneous effects of the APT and measurement of specific IgE, calculating mutually adjusted odds ratios (ORs) for positive APTs and specific IgE levels above 0.70 U/l. We found clinically relevant food allergies in 23% (egg white) to 28% (CM and peanut) of our study population. Positive SAFT reactions were observed in 14% (peanut), 16% (egg white) and 21% (CM) of our patient population. Next to the SAFT, we did not observe a significant additional value of the APT for the diagnosis of CM or egg white allergy, but we did find a significant additional value for the diagnosis of peanut allergy (OR = 11.56; $p < 0.005$, 2-sided). In clinical practice this statistically significant value does not exclude the need for OC and controlled elimination and (re)introduction periods due to the presence of false-negative as well as false-positive results in the APT. In conclusion, we could not find enough support for the current addition of the APT to our standardized allergological work-up in young children below the age of 3 yr with AD and suspected food allergy. At the moment the additional value of the classical delayed-type APT next to the SAFT seems to be very limited at best in this study population and does not justify the time-consuming nature of the skin test.

A. C. A. Devillers^{1,2}, F. B. de Waard-van der Spek², P. G. H. Mulder³ and A. P. Oranje²

¹Department of Dermatology, Medical Center Rijnmond-Zuid, Rotterdam, The Netherlands,

²Department of Dermatology and Venereology, Pediatric Dermatology unit, Erasmus MC, Rotterdam, The Netherlands, ³Department of Epidemiology and Biostatistics, Erasmus MC, Rotterdam, The Netherlands

Key words: atopy patch test; contact urticaria; food allergy; atopic dermatitis

A.C.A. Devillers, dermatologist, Medical Center Rijnmond-Zuid, Groene Hilledijk 315, 3075 EA Rotterdam, The Netherlands
Tel.: +31-(0)10-290 3960
Fax: +31-(0)10-463 6707
E-mail: devillersa@mcrz.nl

Accepted 2 May 2008

Atopic dermatitis (AD) is a chronic multifactor inflammatory skin disease with a genetic background. It is part of the so-called atopic

syndrome and may be associated with a sensitization for food allergens, especially in childhood. Although the clinical relevance of this

sensibilization is not always clear, there is a small sub-population of children with AD who do develop clinically relevant reactions to different food allergens. This group may benefit from dietary measurements and needs to be separated from the majority of children with AD in whom diets are not beneficial.

The allergological work-up in children with AD and suspected food allergy starts with a careful history and clinical examination. Additional tests usually include the skin prick test (SPT) and/or measurement of serum-specific IgE, both aimed at revealing the immediate-type sensibilization against the allergens tested. The skin application food test (SAFT) has been described as a reliable and child-friendly alternative to the SPT in children with AD below the age of 3 yr (1). The gold standard for the diagnosis of a food allergy is still an oral challenge (OC), preferably double-blind placebo controlled and followed by a supervised reintroduction period (2). Although OC are time-consuming and carry a certain risk, they may be necessary in cases where serology, skin tests and history do not reveal a conclusive result.

In recent years, the atopy patch test (APT) has been suggested as an addition in the allergological work-up of children with AD and suspected food allergy (3–5). The APT is aimed at detecting delayed-type, eczematous, allergic reactions to allergens commonly associated with direct type, IgE mediated, allergic reactions. Its addition is advocated as a means to reduce the number of OC necessary in order to reach a conclusive result (6, 7). Although in theory, the combination of a skin test aimed at immediate-type allergic reactions (SPT or SAFT) and a skin test aimed at delayed-type allergic reactions (APT) seems promising, there have been conflicting results published regarding the clinical value of the APT in daily practice (3–10).

We initiated a prospective clinical study in children with AD younger than 3 yr, to evaluate the additional clinical value of the APT next to our own standardized allergological work-up in case of a suspected food allergy.

Materials and methods

The study was performed on the paediatric dermatology out-patient clinic of the Erasmus MC-Sophia Children's Hospital. Children aged 0–3 yr with AD and an indication for an allergological work-up, were eligible for inclusion. AD was defined by the criteria of Williams et al. (11). Indications for an allergological work-up

consisted of suspected food allergies due to reported reactions, pre-existing diets or refractory skin disease. The inclusion period lasted 2 yr and 10 months.

Patients were subjected to our standardized work-up consisting of a careful history, focusing on clinical signs of food-allergy, combined with the SAFT and measurement of specific IgE. The allergens used in the skin test were freshly prepared food stuffs and included commercially available cow's milk (CM), the egg white of a hard boiled hen's egg and mashed peanuts in a saline solution. There was no further dilution of the allergens and the foodstuffs were tested in the form in which they would be eaten. In addition, the APT was performed, using the same allergens as were used in the SAFT.

Skin application food test

Skin application food tests were performed on the unabraded volar aspects of the lower and if necessary upper arm, using medium (8 mm) Finn-chambers on scanpor. A saline solution was used as a negative control. They were read after 10, 20 and 30 min. The skin test was removed after 30 min or earlier if an urticarial weal and flare response occurred during the prior reading times. Evaluation took place using a scale from 0–3 with 0 indicating no reaction, 1+ erythema only, 2+ urticarial weals within the test area and 3+ urticarial weals spreading beyond the test area. Only 2+ and 3+ reactions were regarded as positive (1).

Atopy patch tests

Atopy patch tests were performed on the unabraded skin of the back using large (12 mm) Finn-chambers on scanpor. A saline solution was tested as a negative control. If the above mentioned SAFT test was positive the APT was removed. After 20–30 min, the remaining test areas were examined as well, to make sure that there was no urticarial weal and flare reaction, in which case the skin test would also be removed. Subsequently the Finn chambers were covered with fixomull, to prevent them from shifting. The skin tests were removed after 24 h, because we feared possible putrefaction of the fresh foods might lead to false-positive results. The APT was evaluated after 48 and 72 h, using the guidelines described by the European Taskforce on Atopic Dermatitis (ETFAD) (12). Only clear-cut reactions of 2+ or more were regarded as positive.

Specific IgE

Blood was drawn from each patient. Allergen-specific IgE was measured in serum with the CAP system (Pharmacia, Woerden, The Netherlands) according to the manufacturer's instructions. Only levels of 0.70 U/l or more were regarded as positive.

Definition of allergy for this study

Figure 1 shows the flowchart used to identify a relevant allergy for any of the three food stuffs. The first step in this chart is based on the results from the SAFT, which has shown a positive predictive value of 100%, as our study group reported previously (1).

Oral challenges

Oral challenges were performed in our day-care unit. Below the age of 2 yr, we generally performed the OC open. When specific IgE levels were above 0.70 U/l, they were performed giving the suspected food stuffs in five steps with a slowly increasing dose and 1 h between each step. The total duration of the OC was 8 h. Safety measures included a capped off infusion needle inserted in an arm vein before the start of the OC. Adequately dosed clemastine, epinephrine and hydrocortison infusion fluids were prepared based on the weight of the patient. When specific IgE values were below 0.70 U/l the total duration of the OC was shortened and the suspected food stuff was given in three steps with a more rapidly increasing dosage and 15 min between each step (bulk provocation). Adequately dosed medication as described earlier was prepared but the infusion needle was not inserted. A qualified paediatric nurse was present during the entire duration of the challenges. After a negative oral

challenge, a monitored introduction period of 4–6 wk was initiated (see next).

Food elimination and (re)introduction

Elimination and/or introduction periods for a single food allergen lasted 4–6 wk. Before and after each episode an evaluation by a research physician took place. Parents were educated and monitored by a qualified dietician with experience in paediatric patients with food allergies.

Ethical aspects and statistical analysis

The study was approved by the Medical Ethics Committee of the Erasmus MC. The parents of all patients signed informed consent. The statistical analysis was performed using SPSS version 11.0 and LogXact version 4.1.

Results

One hundred and forty-eight children were eligible for inclusion. We experienced 13 dropouts due to active skin disease on the test areas ($n = 8$), very strong positive demography ($n = 1$), multiple positive APT reactions, including the negative control (angry back, $n = 3$) and one child who developed fever based on an airway infection during the test week. The remaining 135 children included 33 children below the age of 1 yr and 102 children between 1 and 3 yr of age.

We were unable to collect complete data concerning the presence of allergy in 34 patients representing 50 APT tests. This was mainly caused by failure to complete the process of OC and/or elimination and (re)introduction in a timely manner because of parents refusing an OC ($n = 14$) or loss during follow up ($n = 17$). Reasons for refusing an OC consisted of anxiety

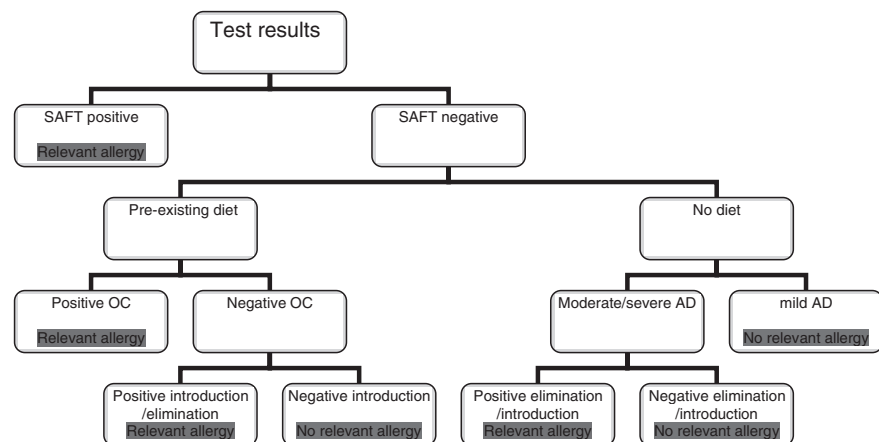


Fig. 1. Flowchart used to identify a relevant allergy in our study population. SAFT = skin application food test; APT = atopy patch test; AD = atopic dermatitis; OC = oral challenge.

concerning the OC procedure, especially placement of the infusion needle or the wish to continue the diet anyway due to believed preventive properties of the diet or the presence of family members with an allergy already making a 'family diet' necessary. One patient suffered from a concomitant gastro-intestinal disorder other than food allergy and needed continuation of hypoallergenic milk substitution and two patients had their OC cancelled due to the failed insertion of an infusion needle and an exacerbation of AD prior to the OC, respectively.

Cow's milk

In 10 patients, the data concerning allergy were incomplete. The remaining 125 patients included 26 patients (21%) with a positive SAFT reaction. Nine additional patients (7%) were later diagnosed with food allergy and 90 patients (72%) were diagnosed as having no food allergy (Table 1). Using Fisher's exact test, there seemed to be a significant additional value of the APT in proving the diagnosis CM allergy in the SAFT negative patient group ($p = 0.015$, 2-sided). Similarly, the presence of specific IgE also showed a significant additional value ($p = 0.014$, 2-sided). We used exact binary logistic regression analysis to evaluate the simultaneous effects of the APT and specific IgE (Table 2). The mutually adjusted odds ratios (ORs) for a positive APT and specific IgE above 0.70 U/l are 9.61 and 5.58, respectively. However, the OR of the APT, adjusted for specific IgE, is not significant ($p = 0.051$, 2-sided) and the OR of specific IgE, adjusted for the APT, is only borderline significant ($p = 0.047$, 2-sided).

Egg white

In 15 patients, the data concerning allergy were incomplete. The remaining 120 patients included 19 patients (16%) with a positive SAFT reaction. Seven additional patients (6%) were later diagnosed with food allergy and 94 patients (78%) were diagnosed as having no food allergy (Table 1). Using Fisher's exact test, we found no significant additional value of the APT in

Table 2. Exact binary logistic regression model listing the odd ratios for allergy in case of a positive atopy patch test or specific IgE value in patients with a SAFT negative, given the combination of both the tests

		95% CI		
	Odds ratio	Lower	Upper	p-Value (2-sided)
Cow's milk				
APT	9.61	0.99	95.52	0.051
IgE	5.58	1.02	39.06	0.047
Egg white				
APT	1.05	0.02	11.60	1.000
IgE	10.37	1.49	∞	0.014
Peanut				
APT	11.56	2.10	87.75	<0.005
IgE	32.86	4.94	∞	<0.005

CI = confidence interval; APT = atopy patch test.

proving the diagnosis egg white allergy in the SAFT negative patient group ($p = 0.566$, 2-sided). However, the presence of specific IgE did show a significant additional value ($p = 0.013$, 2-sided). In the exact binary logistic regression analysis, the respective ORs are 1.05 and 10.37 (Table 2). The OR of the APT, adjusted for specific IgE, is very near to 1 and off course not significant ($p = 1.000$, 2-sided). The OR of specific IgE, adjusted for the APT, equals 10.37 and is significant (0.014, 2-sided).

Peanut

In 25 patients, the data concerning allergy were incomplete. The remaining 110 patients included 15 patients (14%) with a positive SAFT reaction. 15 additional patients (14%) were later diagnosed with food allergy and 80 patients (72%) were diagnosed as having no food allergy (Table 1). Using Fisher's exact test, we found an additional value for both the APT and specific IgE in proving the diagnosis peanut allergy in the SAFT negative patient group (both $p < 0.005$, 2-sided). In the exact binary logistic regression analysis the respective mutually adjusted ORs are 11.56 and 32.86, both significant (Table 2; $p < 0.005$, 2-sided).

Discussion

The APT could form a relevant and important addition to our allergological work-up of

Table 1. Number of positive and negative skin application food tests (SAFT), atopy patch tests (APT) and additionally diagnosed allergy

	SAFT		APT		Additionally diagnosed allergy	
	Positive	Negative	Positive	Negative	Positive	Negative
Cow's milk	26 (n = 125)	99 (n = 125)	7 (n = 99)	92 (n = 99)	9 (n = 99)	90 (n = 99)
Egg white	19 (n = 120)	101 (n = 120)	11 (n = 101)	90 (n = 101)	7 (n = 101)	94 (n = 101)
Peanut	15 (n = 110)	95 (n = 110)	18 (n = 95)	77 (n = 95)	15 (n = 95)	80 (n = 95)

APTs were only performed in SAFT negative patients. The additional diagnosis of food allergy was made in SAFT negative patients using oral challenges and elimination/reintroduction periods as defined in the flowchart in Fig. 1.

patients with AD and a suspected food allergy. We know from the previous research that the delayed-type skin reaction in a positive APT is allergen-specific, correlates with the presence of food allergy, is predominantly if not only observed in patients with AD and forms an *in vivo* model of the skin lesions in AD (10). Combining skin tests aimed at immediate-type allergic reactions, like the SPT or SAFT, with a skin test like the APT could be very beneficial. However, previously reported results regarding the additional value of the APT in the diagnosis of food allergy in children with AD are very variable. Reported sensitivity ranges from 18% to 93%, specificity from 41% to 97% and positive predictive values from 40% to 96% (3–10). Some authors claim a reduced need for OC, especially when APT and SPT or specific IgE values are combined (6, 7). Others are less enthusiastic about the value of the APT in daily clinical practice (8, 9). Comparing the data from these studies is difficult due to varying patient populations, differences in methodology and interpretation of skin testing and differences in methodology and interpretation of OC, including the presence of subdivisions in early and late allergic reactions. The first steps towards standardization have been made, but further work is still needed (10, 13–15).

Our study was initiated to determine the additional value of the APT in our standardized allergological work-up of young children below the age of 3 yr with AD and suspected food allergy. Our usual work-up in this age group consists of the SAFT and measurement of specific IgE with additional OC and elimination and (re)introduction periods if necessary. We wanted to know whether the APT could identify children with a false-negative SAFT, thus reducing our need for oral challenges and/or elimination and (re)introduction periods. To determine the additional value of the APT next to the SAFT, we analyzed the SAFT negative patients per allergen and used an exact binary logistic analysis to evaluate the simultaneous effects of the APT and measurement of specific IgE, calculating mutually adjusted ORs for positive APTs and specific IgE levels above 0.70 U/l. The results showed clinically relevant food allergies in 23% (egg white) to 28% (CM and peanut) of our study population. Next to the SAFT, we did not observe a significant additional value of the APT for the diagnosis of CM or egg white allergy, but we did find a significant additional value for the diagnosis of peanut allergy (OR = 11.56; $p < 0.005$, 2-sided). In clinical practice, this statistically significant value does not exclude

the need for OC and controlled elimination and (re)introduction periods due to the presence of false-negative as well as false-positive results in the APT. This concurs with the conclusions of Mehl et al., who found that in daily clinical practice the APT adds only a small predictive value to the standard SPT and sIgE measurement in the diagnostic work-up of suspected food allergy in children (16).

When we looked at the presence of specific IgE concentrations above 0.70 U/l, there was a significant additional value for this measurement next to the SAFT for diagnosing an allergy for peanut (OR = 32.86), egg white (OR = 10.37) and CM (OR = 5.58). However, there were false-negative and especially false-positive values present, resulting in the need for continued OC and controlled elimination and (re)introduction periods. This is in concordance with what we know from the literature regarding the use of elevated levels of food-specific IgE as a test for clinically relevant food allergy (12). Especially, the presence of false-positive values but also the presence of false-negative values warrants caution in the interpretation of this test. The group from Sampson was the first to report improved results by using food-specific IgE concentrations that could predict clinically relevant food allergy with more than 95% certainty in their study population (17, 18). Although others have reported similar results, we have not been able to determine comparable 95% predictive values in our own setting due to a wide variation in specific IgE levels in patients with and without a clinically relevant allergy [Novak J and Oranje AP, abstract ESPD congress 2005].

Because the methodology of the SAFT and APT basically only differ with regard to occlusion and reading time, we would expect a substantial number of urticarial reactions during an APT with food allergens. We also know from experience that a strong positive SAFT can be followed by a positive delayed-type eczematous reaction after 2–3 days, even if the allergen is removed after 20–30 min [ACAD, FBWS, APO]. We found positive SAFT reactions in 14% (peanut), 16% (egg white) and 21% (CM) of our patient population. However, data on the occurrence of urticarial APT reactions to food allergens are almost non-existent and if reported seems to consist of relatively low percentages (3–9, 15, 16). We suspect urticarial APT reactions are relatively underreported. This might be caused by a lack of inspection of the test site after 20–30 min. Differences in study populations may also play a part, as we know that contact urticaria to food allergens are predominantly

found in younger children (19). In our own study population, the question remains whether some or all positive SAFT reactions in our study would have turned out as positive APT reactions if they had not been removed. For future use, we would like to propose to change the name of the SAFT into the immediate-type APT reaction. With this name change, we hope to prompt increased interest in the urticarial immediate-type reactions which can be found next to the classical delayed-type APT reaction, especially in young children with AD and food allergy.

Our study took place in a clinical setting and is based on a large number of young children with AD. The drop-outs during inclusion ($n = 13$) and the incomplete data on allergy ($n = 34$ representing 50 APT tests) could in theory encompass a bias for the presence of allergy. However, based on the reasons why the data were not available and the fact that patient characteristics between patients included and excluded for statistical analysis are very similar, such a bias is not to be expected.

In conclusion, we could not find enough support for the current addition of the APT to our standardized allergological work-up in young children below the age of 3 yr with AD and suspected food allergy. At the moment, the additional value of the classical delayed-type APT next to the immediate-type APT (or SAFT) seems to be very limited at best in this study population and does not justify the time-consuming nature of the skin test. This conclusion is supported by a recent publication from Mehl et al. (16). Further studies aimed at standardization, reproducibility and clinical validation are needed before the APT with food allergens can be used in routine daily clinical practice as a diagnostic test. Despite our current findings, we believe that these studies are worthwhile to undertake because a positive APT with food allergens does function as an allergen-specific delayed-type hypersensitivity reaction, which still seems promising for further use as a diagnostic test.

References

- DE WAARD-VAN DER SPEK FB, ELST EF, MULDER PG, MUNTE K, DEVILLERS AC, ORANJE AP. Diagnostic tests in children with atopic dermatitis and food allergy. *Allergy* 1998; 53: 1087–91.
- MURARO MA. Diagnosis of food allergy: the oral provocation test. *Pediatr Allergy Immunol* 2001; 12 (suppl. 14): 31–6.
- NIGGEMAN B, REIBEL S, WAHN U. The atopy patch test (APT) – a useful tool for the diagnosis of food allergy in children with atopic dermatitis. *Allergy* 2000; 55: 281–5.
- MAJAMAA H, MOISIO P, HOLM K, TURJANMAA K. Cow's milk allergy: diagnostic accuracy of skin prick and patch tests and specific IgE. *Allergy* 1999; 54: 346–51.
- STROMBERG L. Diagnostic accuracy of the atopy patch test and the skin-prick test for the diagnosis of food allergy in young children with atopic eczema/dermatitis syndrome. *Acta Paediatr* 2002; 91: 1044–9.
- ROEHR CC, REIBEL S, ZIEGERT M, SOMMERFELD C, WAHN U, NIGGEMANN B. Atopy patch tests, together with determination of specific IgE levels, reduce the need for oral food challenges in children with atopic dermatitis. *J Allergy Clin Immunol* 2001; 107: 548–53.
- ISOLAURI E, TURJANMAA K. Combined skin prick and patch testing enhances identification of food allergy in infants with atopic dermatitis. *J Allergy Clin Immunol* 1996; 97: 9–15.
- BREUER K, HERATIZADEH A, WULF A, et al. Late eczematous reactions to food in children with atopic dermatitis. *Clin Exp Allergy* 2004; 34: 817–24.
- VANTO T, JUNTUNEN-BACKMAN K, KALIMO K, et al. The patch test, skin prick test and serum milk-specific IgE as diagnostic tools in cow's milk allergy in infants. *Allergy* 1999; 54: 837–42.
- TURJANMAA K, DARSOW U, NIGGEMAN B, RANCÉ F, VANTO T, WERFEL T. EAACI/GA2LEN position paper: present status of the atopy patch test. *Allergy* 2006; 61: 1377–84.
- WILLIAMS HC, BURNEY PGJ, HAY RJ, et al. The U.K. working party's diagnostic criteria for atopic dermatitis. *Br J Dermatol* 1994; 131: 383–416.
- DARSOW U, RING J. Airborne and dietary allergens in atopic eczema: a comprehensive review of diagnostic tests. *Clin Exp Dermatol* 2000; 25: 544–51.
- DARSOW U, LAIFAOU J, KERSCHENLOHR K, et al. The prevalence of positive reactions in the atopy patch test with aeroallergens and food allergens in subjects with atopic eczema: a European multicenter study. *Allergy* 2004; 59: 1318–25.
- BINDSLEV-JENSEN C, BALLMER-WEBER BK, BENGTSSON U, et al. Standardization of food challenges in patients with immediate type reactions to foods – position paper from the European Academy of Allergology and Clinical Immunology. *Allergy* 2004; 59: 690–7.
- HEINE RG, VERSTEGE A, MEHL A, STADEN U, ROLINCK-WERNINGHAUS C, NIGGEMANN B. Proposal for a standardized interpretation of the atopy patch test in children with atopic dermatitis and suspected food allergy. *Pediatr Allergy Immunol* 2006; 17: 213–7.
- MEHL A, ROLINCK-WERNINGHAUS C, STADEN U, et al. The atopy patch test in the diagnostic work-up of suspected food-related symptoms in children. *J Allergy Clin Immunol* 2006; 118: 923–9.
- SAMPSON H. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. *J Allergy Clin Immunol* 2001; 107: 891–6.
- SAMPSON HA, HO D. Relationship between food-specific IgE concentration and the risk of positive food challenges in children and adolescents. *J Allergy Clin Immunol* 1997; 100: 444–51.
- ORANJE AP, VAN GYSEL D, MULDER PGH, DIEGES PH. Food-induced contact urticaria syndrome (CUS) in atopic dermatitis: reproducibility of repeated and duplicate testing with a skin provocation test, the skin application food test (SAFT). *Contact Dermatitis* 1994; 31: 314–8.