

Adverse reactions to food additives in children with atopic symptoms

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In a multicenter study conducted at four Danish hospital pediatric departments, the parents of 472 consecutive children were informed of this project to determine the incidence of intolerance of food additives among children referred to an allergy clinic with symptoms of asthma, atopic dermatitis, rhinitis, or urticaria. After a 2-week period on an additive-free diet, the children were challenged with the eliminated additives. The food additives investigated were coloring agents, preservatives, citric acid, and flavoring agents. Carbonated "lemonade" containing the dissolved additives was used for the open challenge. Two doses were used: a low dose and a 10-fold higher dose. Gelatin capsules were used for a double-blind challenge. The children were 4–15 years old, and they were attending an outpatient pediatric clinic for the first time. Of the 379 patients who entered the study, 44 were excluded and 335 were subjected to open challenge. A total of 23 children developed positive reactions after the open challenge. Sixteen of these patients accepted the double-blind challenge, and six showed a positive reaction to preservatives (atopic dermatitis, asthma, rhinitis), coloring agents (atopic dermatitis, asthma, urticaria, gastrointestinal symptoms), and citric acid (atopic dermatitis, gastrointestinal symptoms). The incidence of intolerance of food additives was 2% (6/335), as based on the double-blind challenge, and 7% (23/335), as based on the open challenge with lemonade. Children with atopic skin symptoms had a statistically increased risk of a positive reaction. This may have consequences for the future clinical investigation of children with atopic cutaneous symptoms.

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In recent years, adverse reactions to food additives have been a subject of public debate and concern. The problem has been investigated by the scientific community in studies involving adults and children. Investigation of the incidence of adverse reactions to food additives is difficult because of the large number of additives under suspicion and because of the requirement of extensive patient compliance. The accepted approach is elimination of the suspected food additive, followed by challenge tests (12).

Only a few clinical investigations have attempted to estimate the incidence of intolerance of food additives in selected groups of children with atopic symptoms, and only with small groups of children (6). In an EC report from 1982 based on a review of the literature (4), the prevalence of intolerance of food additives was estimated to be 0.03–0.15%. Young et al. (22) found a prevalence of 0.026% in a clinical trial of 1987.

The aim of this study was to determine the inci-

dence of intolerance of a selected group of food additives among children with various atopic symptoms referred for allergologic examination.

Material and methods

Patients

Criteria for inclusion. The subjects were children aged 4–15 years, referred for the first time for allergologic examination as outpatients in the pediatric departments at the four county hospitals in, respectively, Aalborg, Kolding, Odense, and Viborg, Denmark. The children had all been referred to one of these clinics by a general practitioner, and, according to usual practice, they had neither been previously evaluated nor treated for atopic symptoms. The included children had symptoms of asthma, atopic dermatitis, rhinitis, or urticaria. The study period was 12 months.

Criteria for exclusion. The criteria were the following: poor compliance; in need of the following medication less than 2 weeks before the diet period – oral antihistamine, systemic steroids, nasal inhalation of sodium cromoglycate and steroids; in need of topical steroids less than 1 week before the diet period. For treatment of asthma, only β_2 -agonist as needed was allowed during the study, and not later than 6 h before challenge.

The study was approved by the local Human Research Ethics Committee. Informed consent was given by the parents before their children entered the study.

Design

At the first visit to the outpatient clinic, the children were examined for their symptoms by the department's usual routine; i.e., clinical examination, skin prick test, and, for most patients, total IgE and eosinophilic counts. The lung function of children with asthma was measured on a Vitalograph® or – for the youngest – with a Mini-Wright® peak-flow meter. Children and parents were informed about the food additive project. If parents were willing to participate, they were instructed by a dietitian on how to follow a food-additive-free diet. Furthermore, they were asked whether they suspected food additives of causing problems in relation to the child's symptoms. Finally, the families were instructed to inform the clinic if the diet could not be maintained or if the child needed additional medication during the diet period.

After a diet period of 2 weeks, a challenge with the eliminated food additives was performed at the clinic. Before the challenge, the child was examined and the parents were questioned about the diet period. The challenge was performed if the condition of the child permitted it and if it was judged possible to observe an aggravation of symptoms.

The primary challenge was an open oral challenge with green and red "lemonade", i.e., a solution of food additives in carbonated water. The first lemonades given contained additives in a low concentration. Symptoms were recorded every 30 min. If no reaction had occurred after 3 h, the challenge was repeated with "lemonade" containing the additives in a 10 times higher concentration. Reactions were recorded up to 3 h after the second challenge in the clinic.

Skin reactions were drawn on stencils. Asthmatic symptoms and a fall in peak flow greater than 20% from the base-line value were registered as a positive reaction if the child had asthma after the challenge. The parents were instructed to record any reactions occurring up to 24 h after the last challenge and to inform the investigators thereof.

If the response to the open challenge was positive, the child was maintained on the additive-free diet in order to permit a double-blind, placebo-controlled challenge with the eliminated food additives in gelatin capsules, as well as an open challenge using solutions of flavoring agents. The double-blind, placebo-controlled challenge was performed at the patient's home. A symptom score form was completed by the parents during the challenge period, and positive reactions were reported to the clinic. In the case of a positive response, the challenge was discontinued until the symptoms had disappeared. If equivocal, the trial was repeated with the capsules in a new randomization. If there were reasons to expect serious or uncertain reactions, the patient was hospitalized during the double-blind challenge.

Only children having 1) symptoms after challenge with capsules containing additives and 2) no symptoms after challenge with placebo were registered as positive.

Food additives

The open challenge was performed with two low-concentration and two high-concentration solutions of additives. The solutions were prepared as a concentrate and were made up in carbonated water to a final volume of 100 ml. Table 1 shows the content of the high-concentration green and red "lemonade". The low concentration was 10% of the high. The sugar contents of the final low- and high-concentration solutions were 1 and 8%, respectively. The color intensity of the beet coloring was 0.62%, which gave a betanine concentration of 0.03 mg. The total amount of additives employed in the challenge with high-concentration green and red solution was

Table 1. Content of the open challenge doses "lemonade", high dose

	Green lemonade	mg/100 ml	Red lemonade	mg/100 ml
Preservatives	Sulfites	12	Benzoic acid	45
	Sorbic acid	100	Propionic acid	100
Synthetic colorings (Coloring I)	Tartrazine	18	Ponceau 4R	1.5
	Quinoline yellow	2.5	Azorubine	7.5
	Patent blue	2.0		
	Sunset yellow	2.5		
Natural colorings (Coloring II)	Turmeric	2.5	β -carotene	6.0
	Annatto	1.6	Chantaxantine	1.0
			Beet coloring	5.5
Flavorings	Anethole (I)	10	Orange oil (II)	10
	Ethylvanillin (I)	10	Lemon oil (II)	10
Acids	Citric acid	40	Citric acid	60

A low-dose concentration (10% of the high) was given 3 h before the high-dose challenge.

equivalent to the additive content of approximately 500 g of (medium-colored) candy, 1 l of soft drink, and 30 g of rye bread.

For the double-blind, placebo-controlled challenge, the same additives were used in the same amounts. The substances were masked in opaque, ferric-oxide-colored gelatin capsules, with one group of additives in each capsule. Preservatives (two capsules because of the amount), synthetic colorings (coloring I), natural colorings (coloring II), and citric acid were given on separate days, randomly interrupted by 2 placebo days. In cases of equivocal results, the trial was repeated with a number of placebo capsules equal to or higher than the number of capsules with additives. As it was impossible to mask the flavorings in gelatin capsules, the challenge with flavorings was performed as an open challenge using two solutions. One solution contained anethole and ethylvanillin (flavoring I), and the other solution contained orange and lemon oil (flavoring II).

The amount of preservatives and colorings to be used for the high-challenge dose was estimated from results taken from the investigation entitled "Dietary habits in Denmark" (7) and the Danish National Food Agency list of approved food additives (11). The amounts were calculated as the median consumption of the food additives in adults (mg/kg body weight) extrapolated to a body weight of 30 kg. The amounts of flavorings to be employed were determined on the basis of palatability. Citric acid and sugar were added to improve the taste of the lemonades. Challenge lemonades and flavoring solutions were prepared by the Danish National Food Agency. The capsules were manufactured by ALK A/S, Denmark.

Diet

The families were instructed thoroughly by a dietitian on how to maintain an additive-free diet. Lists of additives and foods which should be avoided, and suggestions for menus and recipes were given to the families. For some naturally occurring substances, it is virtually impossible to design an elimination diet; in such cases, fruit and vegetables with a very high content of the substances in question, e.g., beet (betanin); carrot, spinach, etc. (β -carotene); cowberry (benzoic acid); and citrus fruits (citric acid, flavorings) were not allowed.

Statistical analyses

A stratified chi-square analysis (Cochrane-Mantel-HaenszelTM, using SAS/STAT release 6.03), was performed to determine whether there was a statistically significant difference between the prevalence of challenge-positive children with and without a

given diagnosis; that is, asthma does not increase the risk of a positive result upon lemonade challenge, the examiner checking for rhinitis, atopic dermatitis, and urticaria. Similar analyses were performed for rhinitis, atopic dermatitis, and urticaria. An analysis stratifying also for the presence or absence of the diagnosis "other" did not alter the results (the diagnosis "other" was the only diagnosis in 15 children, and they were therefore excluded to minimize the number of strata). Suspicion/nonsuspicion of food additives was compared by chi-square and Fisher's exact test (SAS/STAT).

Results

The parents of 472 patients were informed about the project. Of these, the parents of 93 children (59 boys) did not wish their children to participate: the parents of 63 declined because of lack of motivation, and the parents of 30 declined because they did not feel they could cope with the conditions laid down for the study. A total of 379 patients (237 boys) entered the study; 335 followed the diet and were subjected to open challenge with lemonade. Forty-four patients (30 boys) were excluded: of these, 35 were excluded because they needed medication not allowed during the diet period, and nine were excluded because they were unable to follow the diet.

The mean age of the children who entered the study was 9 years. This was also the mean age of the children whose participation was declined, of the excluded group, and of the group of children with positive reactions after the double-blind challenge.

The diagnoses after the general clinical examination for atopic disease were distributed as follows. Of the 335 children who completed the study, 62% had asthma, 43% rhinitis, 29% atopic dermatitis, 10% urticaria, and 7% other symptoms. In the group of excluded children, 73% had asthma, 23% had rhinitis, 18% atopic dermatitis, 2% urticaria, and 2% other symptoms. In the group whose participation was declined, 76% had asthma, 37% had rhinitis, 17% atopic dermatitis, 3% urticaria, and 8% other symptoms. The mean number of symptoms per child was 1.5.

A total of 335 children underwent the open challenge. Twenty-three had positive reactions to low- or high-dose lemonade challenge. In addition, there were 25 equivocal positive reactions to the lemonade challenge. Fifteen of these were rechallenged and found to be negative. Ten did not wish to be subjected to rechallenge, and, upon interview, the parents of these 10 children stated that they did not suspect food additives of aggravating their child's symptoms; the 10 doubtful positive reactions were therefore classified as negative reactions.

Sixteen patients participated in the double-blind,

placebo-controlled challenge, and six of these had positive reactions after the double-blind, placebo-controlled challenge with preservatives, colorings, and citric acid capsules. Six patients had positive reactions after the open challenge with flavoring solutions (Table 2). All patients except one were challenged twice with capsules/flavorings. The results of the double-blind challenges were recorded at home, and although we did not see the patients at the moment of onset of symptoms, there was no difference in delay of onset of symptoms, as compared with the open challenge.

We wished to rechallenge with lemonade 14 of the 23 patients with positive reactions after the lemonade challenge; that is, those seven of the 14 patients that were negative after the double-blind challenge and those seven patients who had never been subjected to the double-blind challenge. Only four (two from each group) were willing to repeat the trial. All four had positive reactions to the open rechallenge. When asked, the parents of the remaining children stated that their children had symptoms after ingestion of food containing additives and they therefore did not want to bother with the elimination diet and challenge. On the basis of the above, we have assessed all 14 patients as having positive, adverse reactions to a mixture of additives.

Cutaneous symptoms were the most common findings among the children with positive reactions. Sixteen patients had skin reactions after the lemonade challenge. Seven of these also reacted with skin symptoms after capsule/flavoring challenge. Only

two children had asthma after the double-blind challenge. Gastrointestinal symptoms were found in three children after capsule/flavoring challenge.

The group of lemonade-positive children had 1.8 symptoms per child (range 1–3). The distribution of diagnoses, symptoms, and additives involved is shown in Tables 2 and 3. There were 11 children with urticaria, and 10 with atopic dermatitis; of these, four had both urticaria and atopic dermatitis. Six had gastrointestinal symptoms, three had hay fever, and two had asthma. The lemonade-positive children were not evenly distributed among the diagnostic groups. There was a statistically significant association between positive lemonade challenge and atopic dermatitis or urticaria ($P < 0.001$). A chi-square analysis of association between diagnostic group and positive capsule and flavoring challenge also showed a statistically significant association between positive capsule/flavoring and atopic dermatitis ($P < 0.011$) or urticaria ($P = 0.000$). Because of the small number of patients, this test was not performed as stratified.

Most of the children reacted to more than one group of additives in the capsule/flavoring challenge. Four children reacted to synthetic colorings and two to natural colorings. Two reacted to preservatives. Six reacted to flavorings; three to anethole and ethylvanillin, and three to orange and lemon oil. Three reacted to citric acid. The distribution of symptoms in the additive groups is shown in Table 2.

There were no correlations between the results of allergy tests, i.e., positive skin prick test, total IgE, eosinophilic counts, and reaction to additives, either for the open challenge or for the double-blind-challenge-positive children (data not shown).

Table 2. Patients with positive reactions after double-blind challenge with preservatives and colorings and after open challenge with flavorings

Patient No.	Sex	Age (years)	Diagnosis	Symptoms after challenge	Challenge additives
1	F	15	AD	AD	Coloring II H Flavoring II H Preservatives H
2	M	5	U	U	Coloring I L Coloring II L Flavoring I H
3	M	8	U	U	Citric acid (C)
4	M	10	AD	U, AD, C	Flavoring II L (C) +H (C, Di)
5	M	7	A, R, U	C, Di	Coloring I H (A, AD) Citric acid (AD)
6	F	4	A, AD	A, AD	Preservatives H (A, R) Flavoring I H (AD) Citric acid (C)
7	M	5	A, AD, R	A, AD, R, C	Coloring I H Flavoring I H Flavoring II H
8	M	6	AD	C, V	
9	F	5	A, U, AD	U, AD	

AD: atopic dermatitis; U: urticaria; A: asthma; R: rhinitis; C: colic; Di: diarrhea; V: vomiting; H: high dose; L: low dose.

Table 3. Patients with positive reactions to open "lemonade" challenge

Patient No.	Sex	Age (years)	Diagnosis	Symptoms after challenge	Lemonade	
					Low	High
10	F	6	AD, U	U	+	+
11	M	7	A	U	+	+
12	M	9	A, R, U	U, C, Di	+	+
13	M	4	A, R, AD	AD	-	+
14	M	5	A, R, AD	U, AD	+	+
15	M	11	A, AD	AD	+	ND
16	F	8	A, R	V	-	+
17	F	7	A	U	-	+
18	F	15	R	U, AD	+	+
19	F	4	AD	AD	-	+
20	F	8	A	C	+	+
21	M	14	A, R	R	-	+
22	M	5	A, R	R	-	+
23	F	9	U	U	+	+

AD: atopic dermatitis; U: urticaria; A: asthma; R: rhinitis; C: colic; Di: diarrhea; V: vomiting; ND: not done.

Before entering the trial, 22.7% of the parents of the 335 children suspected that food additives caused symptoms in their child. In the excluded group (44 children), the number was 20.2%. In the group that did not wish to participate (93 children), only 6.5% suspected that food additives caused symptoms.

Of the 23 children who were positive to lemonade challenge, the parents of 14 of these suspected that food additives caused symptoms in their child. In the group of positive capsule/flavoring challenges, the parents of 8/9 had suspected food additives. Thus, 8–14 children out of a total of 76 children with suspected allergy to food additives reacted to food additives (11–18%). Of the 259 without suspected food-additive allergy, from one to nine children were positive upon challenge (0.4–3%). The difference in the number of children with positive challenge and suspected allergy to food additives, as compared with positive challenge without suspicion of allergy to food additives, was statistically significant for both lemonade challenge (chi-square; $P < 0.001$) and capsule/flavoring challenge (Fisher's exact test; $P < 0.001$).

Discussion

All patients were newly referred to a hospital outpatient allergy clinic. The children entering the present study had various symptoms of hypersensitivity. We did not find any severe or anaphylactic reactions.

Most of the patients had asthma. This is not typical of the distribution of atopic symptoms in the population as a whole, but is typical of hospital outpatient allergy clinics where the children with the most severe symptoms are treated. The children with severe asthma were excluded either because of need of medication or because their participation was declined. As a result, we cannot tell whether patients with serious asthmatic symptoms would show reactions to food additives if the design was changed to include the latter category of children.

Neither of the two asthmatic children who were positive in the open challenge reacted with severe symptoms. Both were confirmed by the double-blind challenge, according to which one child reacted to synthetic coloring, while the other child reacted to preservatives. Both children had associated atopic dermatitis and positive skin reactions to other additives (flavorings and citric acid), and one of them also had rhinoconjunctivitis and gastrointestinal symptoms after challenge.

It was remarkable that we found positive reactions from another organ than expected according to the diagnosis, but the results were confirmed by re-challenges.

Only a very few studies describe asthmatic symp-

toms in children after challenge with colorings and preservatives. In a Danish, placebo-controlled study, Østerballe et al. (13) found mild asthmatic reactions in 2 out of 46 asthmatic children challenged with colorings and benzoic acid.

Tartrazine and sulfites are the most investigated additives. In a review article (3), Collins-Williams concluded that tartrazine is important in precipitating attacks of asthma, but he could not confirm this conclusion in his own studies. Stevenson et al. (17) and Robinson (16) concluded after reviewing the literature that tartrazine can provoke urticaria but not asthma. Towns et al. (19), on the other hand, found positive reactions to sulfites in a group of asthmatic children. Busch et al. (2) have concluded in a review article that the incidence of sulfite sensitivity in non-steroid-dependent asthmatic patients is 0.8%.

In the present study, 16 of the 23 children who had positive reactions after the open challenge had skin symptoms in the form of either atopic dermatitis or urticaria. Urticaria is a well-described symptom in the literature concerning food additives. One of the central studies is that of Juhlin, who found that one-third of 330 adult patients had positive reactions in provocation tests with various food additives (9).

Very few studies describe skin reactions to food additives in children. Østergaard (14) and Bever et al. (1) performed placebo-controlled studies with children with atopic dermatitis. Østergaard found that 8% of 62 children with atopic dermatitis had itching of the skin or eczema and urticaria after provocation with food colorings. Bever et al. found positive reactions after challenge of six children with severe atopic dermatitis. The only coloring they used was tartrazine in a low dose, i.e., 0.1 mg, which produced reactions in two of six children.

Supramaniam et al. (18), Ibero et al. (8), and Kemp & Schembri (10) have challenged children suffering from urticaria; they all found positive reactions to colorings and preservatives.

Two children had skin reactions after challenge with citrus flavoring. It is known that citrus fruits can exacerbate atopic dermatitis, but it is not known whether the flavorings are responsible for this.

The aim of our study was to estimate the incidence of adverse reactions to food additives. We therefore chose to mimic the natural situation by challenging with a mixture of additives. Furthermore, this approach had the advantage that the first challenge involving all the additives could be completed in one day, and that we did not have to persuade several hundred children to swallow a large number of capsules. Although the challenge lemonades did not taste like commercial soft drinks, they were consumed without too much effort.

We do not know whether the total amounts of

additives given in the form of solution, as compared with the small amounts of additives given in the form of capsules, may influence the reactions after the blind challenge. The negative reactions to blind challenge after a positive reaction following open challenge may reflect the difference in dose and the manner of administration. If so, the lemonade challenge is possibly the challenge which most precisely reflects the "natural" situation.

We made no attempt to prepare a lemonade for the double-blind provocation test, because of the content of flavorings. Wilson & Scott (21) tried to perform a double-blind study with a drink colored with synthetic β -carotene to mask differences in appearance. They ran into difficulties because they found positive reactions to the control drink.

The number of reactions to preservatives and to natural and artificial colorings after double-blind challenge was evenly distributed. The three observed positive reactions to citric acid were unexpected, although two of the reactions might have been due to local gastrointestinal irritation. Citric acid is a common additive, and challenge studies with patients having suspected intolerance to this additive would be interesting.

Six of the nine children who were positive in the capsule/flavoring challenge reacted to flavorings. The flavoring challenge was (owing to the technical problem of masking the taste) not double-blind. The positive reactions can therefore be taken only as indicative, and should be followed up by further studies.

The higher number of reactions to the lemonade challenge than the double-blind challenge could be due to the difference in the amount of additives given as a mixture; this might give an additive effect, as compared with the capsules with separated additives. Parents of children with symptoms of hypersensitivity tend to experiment with diets in the hope of reducing or eliminating symptoms in their children (5, 20). In our study, the parents of 22.7% of the included patients suspected food additives of causing adverse reactions. This could be confirmed in only 7% of the cases. Thus, if these children were more frequently investigated for intolerance of additives, or if the parents knew more about the incidence of intolerance of food additives, much unnecessary worry could be avoided.

The role of food additives in affecting children's behavior has been investigated by various authors and in various types of studies. Pollock (15) concludes in his review that there is no impressive evidence that either food additives or any other dietary factor is a major cause of childhood hyperactivity. Our study was not designed to elucidate this problem, and we did not see any hyperactivity reactions.

In the present study the incidence of intolerance

to food additives was 2% (6/335) based on the double-blind challenge, and 7% (23/335) based on the open lemonade challenge. Children with atopic skin symptoms and children whose parents suspected that food additives contribute to symptoms had a statistically significant increased risk of being positive upon challenge with food additives. This finding may have consequences for the future clinical investigation of children with atopic skin symptoms.

The present study was made on a selected group of children. Therefore, the incidence of intolerance of food additives does not reflect the incidence of intolerance of food additives in the child population as a whole, which would be expected to be even lower.

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References

1. BEVER HP, DOCK M, STEVENS WJ. Food and food additives in severe atopic dermatitis. *Allergy* 1986; 44: 588-94.
2. BUSCH RK, TAYLOR SL, BUSSE W. A critical evaluation of clinical trials in reactions to sulfites. *J Allergy Clin Immunol* 1986; 78: 191-202.
3. COLLINS-WILLIAMS C. Clinical spectrum of adverse reactions to tartrazine. *J Asthma* 1985; 22: 139-43.
4. Commission of the European Communities. Food science and techniques. Report of the Scientific Committee for Food. Report of a working group on adverse reactions to ingested additives. Twelfth Series, 1982.
5. FORD RKP, DAWSON KP, MODRIDGE N. Children's diet: what do parents add and avoid? *N Z Med J* 1989; 102: 443-5.
6. HANNUKSELA M, HAAHTELA T. Hypersensitivity reactions to food additives. *Allergy* 1987; 42: 561-75.
7. HARALDSDOTTIR J, HOLM L, JENSEN JH, et al. Dietary habits in Denmark (main results). *Levnedsmiddelstyrelsen* 1986; 136 (in Danish; summary in English).
8. IBERO M, ESEVERRI JL, BARROSO C, et al. Dyes, preservatives and salicylates in the induction of food intolerance and/or hypersensitivity in children. *Allergol Immunopathol* 1982; 10: 263-8.
9. JUHLIN L. Incidence of intolerance to food additives. *Int J Dermatol* 1980; 19: 548-51.
10. KEMP J, SCHEMBRI G. An elimination diet for chronic urticaria of childhood. *Med J Aust* 1985; 148: 234-5.
11. List of approved food additives (the positive list). National Food Agency of Denmark, 1985.
12. METCALFE DD, SAMPSON HA. Workshop on experimental methodology for clinical studies of adverse reactions. *J Allergy Clin Immunol* 1990; 86: 421-42.
13. ØSTERBALLE O, TAUDORF E, HAAHR J. Intolerance to aspirin, food-colouring and food-preservatives in childhood asthma. *Ugeskr Laeger* 1979; 141: 1908-10.
14. ØSTERGAARD PA. The incidence of intolerance to colouring agents in children with eczema. *Ugeskr Laeger* 1986; 148: 711-14.

15. POLLOCK I. Hyperactivity and food additives. In: SOMOGYI JC, MULLER HR, OCKHUIZEN TH, eds. Food allergy and food intolerance. Nutritional aspects and developments. *Bibl Nutr Dieta* 1991; 48: 81–9.
16. ROBINSON G. Tartrazine – the story so far. *Food Chem Toxicol* 1988; 26: 73–8.
17. STEVENSON DD, SIMON RA, LUMRY WR, et al. Adverse reactions to tartrazine. *J Allergy Clin Immunol* 1986; 78: 182–92.
18. SUPRAMANIAM G, WARNER JO. Artificial food additive intolerance in patients with angio-oedema and urticaria. *Lancet* 1986; 18: 907–9.
19. TOWNS SJ, MELLIS CM. Role of acetylsalicylic acid sodium metabisulfite in chronic asthma. *Pediatrics* 1984; 73: 631–7.
20. WEBBER SA, GRAHAM-BROWN RAC, HUCHINSON PE, et al. Dietary manipulation in childhood atopic dermatitis. *Br J Dermatol* 1989; 121: 91–8.
21. WILSON N, SCOTT A. A double-blind assessment of additive intolerance in children using a 12 days challenge period at home. *Clin Exp Allergy* 1989; 19: 267–72.
22. YOUNG E, PATEL S, STONEHAM M, et al. The prevalence of reaction to food additives in a survey population. *J R Coll Physicians Lond* 1987; 21: 241–7.

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