The prevalence of reaction to food additives in a survey population

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The self-diagnosis of food additive intolerance has become commonplace but it is not clear how often perceived problems of this kind tally with more objective clinical assessments. It is sometimes implied that such reactions are allergic, but it is not known whether those who perceive themselves to be intolerant to food additives experience reactions that are characteristic of allergy or have an unduly high prevalence of atopic conditions such as hayfever, asthma or eczema.

Most of the past estimates of the prevalence of food additive reactions have been based on selected populations [1–6] and the challenge dose used has varied. The combined effects of different additives have not been sufficiently studied [6], and the assessment of prevalence is further complicated by a frequent inability to reproduce symptoms by means of rechallenge, even in patients with apparently good evidence of urticaria induced by food additives on previous occasions [7,8].

Most epidemiological studies of food additive intolerance have been carried out on selected groups of patients with asthma, rhinitis or urticaria who have attended respiratory, allergy or dermatology clinics [2, 9–12]. Juhlin [10] calculated the prevalence of food additive intolerance in the Swedish population by first estimating the number of those suffering from urticaria and angio-oedema, asthma, and hayfever (the most commonly identified reactions) and then estimating the percentage of food additive-intolerant subjects within each of these groups. For the selected types of reaction studied, Juhlin calculated a prevalence of 0.4 per cent for aspirin intolerance, 0.6 per cent for tartrazine reactions and 0.5 per cent for benzoate intolerance. These figures might represent an underestimate if, for example, childhood behavioural and mood changes were provoked by food additives unaccompanied by any of the symptoms listed by Juhlin, but there is no evidence that this is so. When Poulsen used Juhlin's method in Denmark [4], he concluded that 0.01 to 0.1 per cent, of the population were sensitive, respectively to tartrazine and benzoates. The Commission of the European Communities, reviewing the available evidence in 1981, suggested a prevalence of food additive intolerance of 0.03 to 0.15, which compares with the somewhat higher estimated prevalence of aspirin intolerance of 0.3 to 0.4 per cent [9,10] and of cow's milk protein intolerance of between 0.2 and 7.5 per cent of young children [13].

The 1984 joint Report of the Royal College of Physicians and the British Nutrition Foundation on food intolerance and food aversion [14] recommended that further work on the epidemiology of adverse reactions to food additives was needed. The Ministry of Agriculture, Fisheries and Food (MAFF) subsequently commissioned this study, a part of which has been the survey of the Wycombe Health Authority population. Our aim has been to assess the prevalence of perceived food additive intolerance as judged by the response to a questionnaire and to compare this with the number which could be confirmed by means of double-blind challenge with selected food additives. We have also enquired about any possible association between food additive intolerance and atopic disease, food intolerance and aspirin intolerance.

Materials and methods

A questionnaire was designed in collaboration with all centres involved in the study and with the help of the British Market Research Bureau. This questionnaire consisted of a front page and separate questionnaire sheet for each member of the household. Ethical Committee approval was given for all stages of the study and

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questionnaires were sent to 10 per cent of the Wycombe Health Authority population. The electoral register was used as a sampling frame, and 11,388 households, comprising an estimated 30,000 people, were contacted. This sample included people from commuter towns, village and rural communities and the town of High Wycombe with 14 per cent of the population estimated to have been born abroad [15].

The questionnaire was designed to ascertain perceived reactions to food and drink, food additives and aspirin and symptoms of atopic disease. The key question was: 'Have you personally ever had any problems which you felt were caused by an allergy or sensitivity to food additives such as colourings, flavours or preservatives?' and 'if so, has this problem occurred more than once?' and 'how sure are you about the cause?' Positive replies were classified as 'definitely', 'probably' and 'not sure'.

Those whose replies about themselves or on behalf of their children indicated that they perceived a reaction to food additives were invited to attend for interview at research clinics arranged at Wycombe General Hospital and Amersham General Hospital. Interviews were conducted by members of the medical team using a standard form and according to a rehearsed interview technique. During the interview period of the study (from August 1985 until February 1987) only two doctors conducted clinics at any one time. Questions at interview were directed to the symptomatology related to food additive ingestion and to the duration and frequency of these complaints. A personal and family history of atopy was obtained by asking: 'Have you, or any first-degree relative, ever suffered from hayfever, asthma or eczema?' Interviewees were asked to state how sure they were about the association between symptoms and food additives and to reply in one of four categories: 'definitely', 'probably', 'unsure' or 'none'. Similar questions were asked regarding perceived reactions to foods and aspirin. At the end of the interview a decision was made either to exclude the subject from further study because there were no grounds for suspecting food additive intolerance or to offer further investigation by means of a double-blind trial of food additives and placebos. Criteria for entry were that subjects should be over four years of age at the time of entry into the trial and should have given a history of reproducible clinical symptoms after ingestion of food additives. Those submitted to study were asked to fill in diary cards (Fig. 1) for (a) a seven-day period while on normal diet, (b) a 14-day period while on an additive-free diet (see Fig. 2) and (c) a further period of at least 20 days during which time they remained on an additive-free diet

Fig. 1. *Patient's diary card.*

1. DAY NUMBER		1	2	3	4	etc
2. CAPSULE NUMBER						
3. WHEEZE	score (0–3)					
4. CHANGE IN BEHAVIOUR OR MOOD	(0–3)					
5. RED, SORE OR RUNNY EYES	(0–3)					
6. ECZEMA	(0–3)					
7. FLUSHING	(0–3)					
8.. STOMACH UPSET	(0–3)					
9. HAYFEVER, SNEEZING RUNNY NOSE	(0–3)					
10. HEADACHE	(0–3)					
11. ITCHING	(0–3)					
12. JOINT PROBLEMS	(0–3)					
13. URTICARIA (NETTLE RASH)	(0–3)					
14. OTHER						
15. ANTIHISTAMINE (if taken, one tick for each dose)						
16. COMMENTS						
SCORE: 0 = NONE; 1 = MILD; 2 = MODERATE; 3 = SEVERE						
		CODE NUMBER				

This diet may be helpful and should be used throughout the period recommended by your doctor, including when taking the challenge capsules.

Additives: These are permitted additives widely used by food manufacturers. They are found particularly in brightly coloured soft drinks, sweets, cakes and instant or convenience foods.

The main ones to avoid are:

Tartrazine	E102	Green S	E142
Quinoline Yellow	E104	Annatto	E160(b)
Sunset Yellow	E110	Benzoate preservatives	E210–E219
Carmoisine	E122	BHA	E320
Amaranth	E123	BHT	E321
Indigo Carmine	E132		

NB: Also make sure that you avoid all coloured medicines and use white toothpaste.

If a product states only 'permitted preservatives' it is best to avoid it as it is impossible to know which colouring or preservative has been used.

Fig. 2. *Instructions concerning additive-free diet.*

and followed a trial regime that involved taking five different low dose capsules during the first 10 days, alternating with lactose placebo capsules, and then taking five high dose capsules, alternating with placebo, during the next 10 days.

Additives selected for study were those most commonly reported as causing adverse reactions. The British Industrial Biological Research Association provided the raw materials and monitored quality control of additive chemicals. These were encapsulated at the Brompton Hospital Pharmacy. Aspirin was included in the challenge sequence as was annatto, a natural colour containing bixin and norbixin which has been reported as inducing urticaria [16]. The additives were mixed in combinations which took chemical compatibility into account.

The contents of the low dose capsules were: Capsule 1, amaranth 0.5 mg, sunset yellow 0.5 mg, carmoisine 0.5 mg, and tartrazine 0.5 mg; Capsule 2, green S 0.5 mg, quinoline yellow 1 mg, and indigo carmine 1 mg; Capsule 3, annatto 1 mg; Capsule 4, butylated hydroxyanisole and butylated hydroxytoluene 1 mg of each; Capsule 5, aspirin 50 mg with sodium benzoate 10 mg.

High dose capsules contained: Capsule 1, amaranth 2.5 mg, sunset yellow 2.5 mg, carmoisine 2.5 mg and tartrazine 2.5 mg; Capsule 2, green S 1 mg, quinoline yellow 2.5 mg and indigo carmine 2.5 mg; Capsule 3, annatto 10 mg; Capsule 4, butylated hydroxyanisole and butylated hydroxytoluene 50 mg of each; Capsule 5, aspirin 300 mg with sodium benzoate 100 mg. The capsules were of opaque gelatin tinted with iron oxide and titanium dioxide (neither of which has been reported as causing adverse reactions). Placebo capsules contained lactose powder, lactose intolerance being uncommon in our community. Individual additives were also prepared in capsule form for testing single substances in subjects for whom the 'cocktail' challenge proved positive.

The initial 'low' dose was set at a level which was not expected to cause severe adverse reactions and the 'high' dose equated with the maximum daily intake as estimated from figures provided by MAFF.

Atopy was assessed by total IgE estimation and by skin testing and will be the subject of a future report.

Each subject's general practitioner was informed and a hospital telephone number was available in case of adverse reactions. Medication was discontinued during the study but terfenadine was supplied as an antihistamine in case of need as were the additive-free anti-asthma medications ketotifen and terbutaline. The study subject was asked to discontinue the challenge sequence at any point if severe symptoms occurred, to report the incident, and to take no further capsules until these symptoms had subsided.

The study subjects attended for interview after completing the challenge sequence. Their diary cards were analysed using the Wilcoxon signed rank test [17], com-

Table 1. Distribution of the differences between additive and placebo, for total symptoms on high dose.

Additive minus placebo score	Additive 1	2	3	4	5	At least one additive
−21				1		
−20				—		
−19				—		
−18				—		
−17				—		
−16				—		
−15				—		
−14				—		
−13				—		
−12			1	—		
−11			—	—		
−10			—	—		
−9			—	—		1
−8			—	—		—
−7	1		—	—		1
−6	—		—	1		5
−5	—		—	1	1	3
−4	2		1	2	2	5
−3	5	2	2	3	4	4
−2	3	9	5	4	7	6
−1	11	7	8	9	7	3
0	36	44	46	35	36	19
1	7	5	8	9	10	8
2	7	4	4	6	5	8
3	2	5	4	6	3	2
4	2	1		1	2	9
5	3	—		—	1	3
6		1		1	—	2
7		—			1	1
8		—				1
9		—				
10		—				
11		—				
12		—				
13		—				
14		—				
15		—				
16		1				

Table 2. Respondents, and losses during follow-up.

Stage of assessment	Number	Respondents	Non-respondents
Questionnaire	30,000*	18,582(62%)	11,418(38%)
Called for interview	1,223	649(53%)	574(47%)
Entered into trial	132	81(61%)	51(39%)

*estimated

paring the total symptom scores on each day on which additive and placebo were taken, assuming no time delay or carry-over effect [18]. After the data had been entered, the code was broken, the study subject and general practitioner informed of the result, and appropriate advice given.

Three methods were used to assess the prevalence of reactions to food additives in the community. The first clinical method was simply to ascertain the number of cases in which a reaction to an additive capsule could be confirmed clinically. The second was to assess each individual's diary card score by subtracting the reaction score after placebo from the score after high dose additive capsules. Some positive and negative scores might be expected to occur by chance and to be symmetrically distributed (see Table 1), and a correction for these random variations was therefore made by subtracting the number with a negative score from the number with a positive score. Since only 81 out of 132 suspect cases were studied (Table 2), an appropriate correction was also made on the assumption that this group of 81 was representative of the 132 potentially reactive individuals among our total sample of 18,582. The third method was designed to avoid any possibility of underestimating the prevalence of reactions—in effect, by making *no* correction for negative diary card scores but assuming that every score of 2 or more to any additive capsule indicated an adverse reaction.

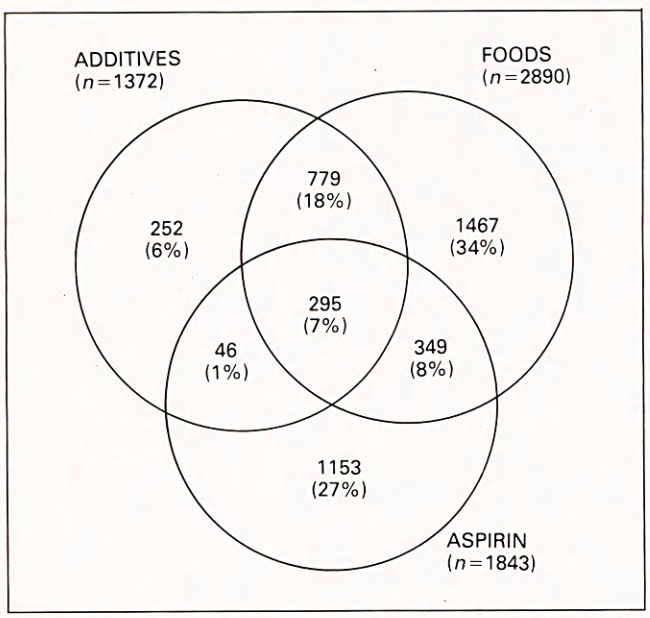

Fig. 3. *Analysis of 4341 respondents to questionnaire who reported problems with foods, food additives and aspirin (in total of 18,582).*

Results

Questionnaire survey

The response to the questionnaire was 61.9 per cent, of which 7.4 per cent of the 18,582 respondents stated that they had a problem with food additives (including 1.4 per cent who cited food additives alone; 15.6 per cent stated they had a problem with foods and 9.9 per cent stated they had symptoms related to aspirin (Fig. 3). Non-responders sometimes refused further cooperation, but a sample (280) of the non-respondent population provided detailed answers when subsequently contacted by house and telephone call and three of these (1.1 per cent) assessed themselves as having a problem caused by additives. Thus, the respondent group would have a higher intolerance rate to food additives than the non-respondent group.

Of the 18,582 people who answered the questionnaire, 28 per cent gave a positive answer to the question relating to personal atopy, and this group included 50 per cent of those with food additive symptoms. Among 2890 people with a food problem, 47.5 per cent gave a history of atopy as compared with a 36 per cent prevalence of atopy in those who thought they had a problem with aspirin. Those who felt they had symptoms related to food additives, foods or aspirin showed a statistically significant higher incidence of atopy than the overall responders ($p < 0.001$).

The age/sex distributions of respondents are shown in Table 3 indicating a preponderance of reactions in the first decade of life (as reported by parents), tailing off in the older age groups. There was a female preponderance in all age groups apart from the first decade of life, where there was a slight preponderance of males. The sex ratio of the respondents matches well with the population figures from the national census in 1981. The figures for atopy showed a slight male preponderance, in accord with previous reports [19,20].

The association between symptoms and the agents causing them is shown in Table 4. All symptomatic groups showed a higher degree of atopy than the overall respondents. Asthma, hayfever, rhinitis, eczema, urticaria and angio-oedema were commonly perceived to be associated with food additives and foods, and so were gastrointestinal symptoms. Aspirin induced symptoms were usually associated with gastrointestinal upset rather than with atopy.

Abnormal behaviour, as reported on the questionnaire, differed from other symptoms in being perceived mainly as related to additives. Twenty-two per cent of 252 subjects related behavioural/mood changes to food additives *only,* compared with 7 per cent of 1467 who related these changes to foods *only* and 5 per cent of 1153 who related their behavioural symptoms to aspirin *only* (Table 4). Fifty-one per cent of those reporting abnormal behaviour related to food additives noted this as an isolated symptom, 29 per cent had atopic symptoms of rhinitis,

Table 3. Reactions to food additives, foods and aspirin by age and sex.

Age group (years)	Total Female (*n*)	Total Male (*n*)	Total with symptoms Female (*n*)	(%)	Total with symptoms Male (*n*)	(%)	Food additives Female (%)	Food additives Male (%)	Foods Female (%)	Foods Male (%)	Aspirin Female (%)	Aspirin Male (%)
0–4	507	468	117	(23)	107	(23)	13	16	17	19	4	4
5–9	631	647	135	(21)	171	(26)	13	17	17	19	4	6
10–19	1498	1468	289	(19)	223	(15)	7	7	14	12	6	3
20–39	2412	2297	776	(32)	428	(19)	9	9	22	14	14	6
40–59	2395	2346	790	(33)	489	(21)	9	9	22	13	17	10
60 or over	1837	1485	465	(25)	269	(23)	4	4	10	8	13	11
Age unspecified	333	258	52	(16)	32	(12)	5	7	12	9	8	5
TOTAL	9613	8969	2624	(27)	1719	(19)	1372 (7.4%)		2890 (15.6%)		1843 (9.9%)	

Table 4. The association between symptoms and provoking agent as reported by questionnaire respondents (percentages).

Symptoms	Foods only (*n* = 1,467)	Additives only (*n* = 252)	Aspirin only (*n* = 1,153)	Foods and food additives (*n* = 779)	Total responders (*n* = 18,582)
Atopy (of any type)	44.2	37.7	29.5	53.5	27.7
Hayfever	10.9	7.5	5.5	20.0	
Asthma	9.3	7.9	5.2	20.7	
Eczema	13.6	13.9	7.8	24.0	
Rhinitis	11.2	11.5	7.2	24.5	
Conjunctivitis	2.9	2.0	2.3	6.3	
Urticaria	16.1	13.5	8.2	19.4	
Angio-oedema	13.4	9.1	8.5	16.8	
Pruritus	17.7	16.7	12.8	29.0	
Flushing	6.4	5.6	6.3	11.6	
Gastrointestinal symptoms	27.6	19.8	49.5	30.2	
Musculo/skeletal	4.3	7.1	6.7	8.6	
Behavioural/mood changes	6.7	21.8	5.5	27.2	
Headache	26.8	17.1	9.7	26.8	

asthma or eczema and the remaining 20 per cent had a variety of other symptoms. This compares with only 11 per cent reporting isolated behavioural mood changes after foods, 44 per cent declaring other atopic manifestations and the remaining 45 per cent reporting non-atopic symptoms. In those reporting abnormal behaviour related to aspirin ingestion, 33 per cent had no other symptoms, 30 per cent had atopic symptoms and of the remaining 37 per cent, most reported gastrointestinal upset.

Clinical assessment

Of individuals who stated that they had a problem with food additives 89.1 per cent indicated that they were willing to attend for further interview. A total of 649 attended (53%), of whom 10 per cent had clearly misinterpreted their reactions and either had no reactions (but thought that additives were harmful) or had symptoms of mild dyspepsia or other vague symptoms of weakness or lethargy. Of the 44 individuals (7%) who reported symptoms that could be attributed to monosodium glutamate sensitivity, 19 (43%) experienced gastrointestinal pain after ingestion of monosodium glutamate, 13 (30%) experienced headache, 8 (18%) reported behavioural or mood changes, 4 (9%) reported asthma and 3 (7%) reported flushing. These patients were excluded from further investigation but will be the subjects of a separate report. Twenty-six (6%) of those interviewed reported symptoms related to alcohol, of whom 9 (35%) reported exacerbation of asthma, 9 (35%) reported headache, and 5 (19%) reported upper abdominal pain or less clearcut symptoms. These subjects were excluded from further investigation, and although sulphites in alcohol may have contributed to their symptoms, these agents were not included in our challenge study. Headache related to food ingestion was reported in 14 per cent of those interviewed but had not previously been regarded as migrainous in nature.

All those who had a history suggesting a possible intolerance to food additives but failing to attend one of our initial clinics were offered another appointment immediately and, at a late date, an attempt was made to contact those who had not attended. Of these 574 people, 63 (11%) were given another appointment at their request, 297 (52%) did not wish to attend, 60 (10%) had moved address, 5 (0.9%) declared their stated problems had resolved and the remainder (26%) could not be contacted.

A hundred and thirty-two subjects were submitted to additive challenge; 81 of these completed the trial, 18 (14%) failed to complete the study because of their inability to keep to an additive-free diet and the remaining 33 subjects (25%) still indicated an interest but, for

various reasons, had been unable to complete the study at the time of this review.

Of the 81 subjects who completed the trial, three showed consistent reactions to low and high dose challenge by our clinical criteria. Of these, one was a 50-year-old atopic male who had reported headaches occurring after ingestion of colourants within a period of 12 hours; these symptoms had been present for five years. He reacted to challenge with annatto, which reproduced his headache at both low and high dose after four and five hours respectively. He also reacted to placebo on one occasion. The second was a 31-year-old non-atopic female who reported upper abdominal pain after ingestion of foodstuffs. She had related this to ingestion of preservatives and antioxidants. Her symptoms were reproduced on challenge with annatto at low and high dose. The third was a five-year-old atopic child with eczema and a family history of hayfever who showed a change in mood one to two hours after azo dye challenge at both low and high dosage but also after placebo on two occasions. During the course of the challenges, he vomited twice during the night, more than 12 hours after a placebo capsule challenge on one occasion and at a similar interval after an antioxidant capsule on the other. At his parents' request, investigation was then stopped and individual azo dyes could therefore not be given. Some doubt persists about his case although the time relationship of reaction after additives challenge was consistent on both occasions. Like the other two reactive individuals who have been contacted again 12 months after challenge, this subject remains well while avoiding the relevant additive but relates an occasional recurrence of symptoms to inadvertent ingestion on social occasions. As three patients out of 81 showed a consistent reaction to low and high dose challenge, we can estimate that 4.9 patients would have reacted out of a total of 132 who were eligible to enter the cross-over trial, so the prevalence of reaction to food additives would be 4.9 out of 18,582, ie 0.026 per cent. (The 95% confidence interval for this prevalence is 0.003–0.049%.)

The results obtained from our diary card data have yielded a similar range of results. Table 1 shows the distribution of symptom scores obtained from the diary cards with our high dose capsules. No evidence for an excess of additive-induced over placebo-induced reactions could be obtained using the Wilcoxon signed rank test for any of the active capsules. A possible prevalence of 0.07 per cent was then estimated, notably in response to capsule 4 (antioxidants), using the method noted in Table 5. Using a less stringent method in which all positive scores of 2 or more were regarded as significant, the highest prevalence of reactions for all additives reached a value of 0.23 per cent. We have since looked at a number of other possible ways of analysing our data and have obtained similar results.

For the additives we have studied it was thus not possible to corroborate the 7.4 per cent prevalence of food intolerance suggested by questionnaire or to reconcile this with the prevalence figures of between 0.01 and 0.23 per cent suggested by clinical assessment and diary card.

Table 5. Prevalence of reaction to food additives (%).

	Additive 1	Additive 2	Additive 3	Additive 4	Additive 5	At least one additive
Lower Limit (95% confidence interval)	0 (0 to 0)	0 (0 to 0)	0.01 (0.004 to 0.024)	0.07 (0.03 to 0.11)	0.01 (0.004 to 0.024)	0.01 (0.004 to 0.024)
Upper Limit (95% confidence interval)	0.12 (0.07 to 0.17)	0.11 (0.06 to 0.16)	0.07 (0.03 to 0.11)	0.17 (0.11 to 0.23)	0.11 (0.06 to 0.16)	0.23 (0.16 to 0.30)

Discussion

We have attempted to assess the prevalence of food additive intolerance in the community by sampling a large population, by interviewing those who responded positively to a questionnaire and by correcting for any bias by sampling non-responders at every stage. Of the 132 whose symptoms were regarded as sufficiently suggestive to warrant investigation, 81 completed the challenge sequence and three were regarded on clinical grounds as having a positive response to double-blind challenge leading respectively to headache, abdominal pain and possibly behavioural change. Although the response to our questionnaire suggested that behavioural and mood changes were the most common adverse effect of food additives—and this association was regarded as 'common knowledge'—we were unable to provide supporting evidence for this except for a single 'probable' case of a child who also had atopic eczema. We were unable to demonstrate behavioural changes in the absence of other evidence of allergy.

Our estimated figure of 0.01–0.23 per cent prevalence of food additive intolerance, using two methods of calculation, corresponds well with calculations already available [2–6]. It suggests that the problem of food additive intolerance in our study population is small. Sampling of non-respondents to our questionnaire indicated that, as a group, they regarded food additives to be a cause of symptoms far less often (1.1% of cases) than respondents (7.4% of cases). It is, therefore, unlikely that the prevalence estimates would have been greatly changed if we had achieved a 100 per cent response to our questionnaire. We may have missed a few cases among those 'non-responders' who subsequently said they suspected a reaction to food additive, but they did not attend the research clinics for a personal interview. There were, however, other potential sources of error—in both directions—which should be borne in mind in interpreting our figures. Symptoms which we considered as possibly related to monosodium glutamate have still to be analysed; and sulphites, which cannot easily be studied by the capsule method [21], were excluded from our study. In addition, a few individuals reported that their food additive intolerance had subsided spontaneously—and we

may therefore have failed to identify some transient reactions. On the other hand, we found a number of people who based their perception of 'food additive problems' on publicised concepts of the harmful nature of 'junk food' and had no food-related symptoms at all. In any future prevalence studies there will be a need to identify and allow for misconceptions of this kind.

Previous work emphasising the frequency of food additive reactions [22] has involved the use of much higher dosages of tartrazine than in our present study. The dosages we have used were based on the probable average daily intake in the UK, although it has been stated that the daily intake of tartrazine in the USA is as high as 100–400 mg [23]. We cannot therefore rule out the possibility that increased doses or cumulative effects might produce a higher reaction rate. However, even if a number of subjects who gave a good clinical history changed from a negative to a positive reaction if challenged more intensively, the prevalence would still fall below many of the claims made in the literature [2,10]. Further studies are nevertheless needed to establish whether more intensive challenge methods can detect further cases of mild or variable intolerance. Further studies are also needed because of the possibility of transient reactions, like the 'strawberry rashes' of childhood, which require a different method of analysis, combining systematic follow-up and rechallenge studies [24].

While evidence of reactions to food additives remains incomplete, action has already been taken by individual manufacturers in respect of the removal of some additives from foods and the substitution of 'natural' substances, in the belief that these are less likely to cause adverse reactions. We found no evidence to support this belief, however, since two of the three reactions that occurred in our subjects appeared to be caused by annatto, a 'natural' colour.

For the small percentage of the population who remain intolerant to food additives, the labelling of foodstuffs, which is now mandatory in the UK, should offer sufficient protection and enable the offending agent to be avoided. As far as prevalence studies are concerned, the figures available from our own and previous work do not appear to indicate that this policy needs revision. However, there may be a need for a surveillance system to provide information on any new developments and to help the future detection of any undesirable effects caused by new or modified additive substances.

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