



ANNOTATION

Intolerance to food additives – does it exist?

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Abstract: 'Food intolerance' is often confused with a range of adverse symptoms which may be coincidental to ingestion of food. 'Food intolerance' is defined as a reaction in which symptoms must be objectively reproducible and not known to involve an immunological mechanism. A more precise term is non-allergic food hypersensitivity, which contrasts with food allergies which are due to an immunological mechanism. Some children will experience food reactions to food additives. Reported symptoms range from urticaria/angioedema to hyperactive behaviours. While parents/carers report that over one fifth of children experience of food reaction, only 1 in 20 of these are confirmed to have a non-allergic food hypersensitivity on testing.

Key words: food additive; food allergy; food intolerance; non-allergic food hypersensitivity.

Issues of 'food intolerance' are common in paediatric practice, but the term is used imprecisely. 'Food intolerance' might describe *any* reaction to food, ranging from food toxicity to reproducible symptoms consistent with an immunoglobulin E (IgE)-mediated reaction to non-reproducible symptoms such as headache or diarrhoea. Reported triggers include both naturally derived and artificial (i.e. chemically synthesized) food additives (including colourings, flavourings and preservatives) as well as other ingredients such as lactose and artificial sweeteners. In order to provide parents with clear and appropriate advice, it is vital for paediatricians to use correct terminology.

In 1995, the European Academy for Allergy and Clinical Immunology (EAACI) specified the requirements for a reaction to be termed 'food intolerance', including:¹

- Symptoms must be objectively reproducible
- Not known to involve an immunological mechanism, that is not food allergy
- Not because of food toxicity.

Key Points

- 1 The true incidence of non-allergic food hypersensitivity reactions is 1–2%; although, parents report that over 20% of children have food intolerance.
- 2 Food additives may trigger symptoms in some children with chronic urticaria and angioedema.
- 3 Dietary manipulation with appropriate dietetic involvement may be a reasonable management strategy in some cases.

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Accepted for publication 25 April 2010.

Historically, 'food intolerance' has been used ambiguously in the medical literature – food allergy was originally called 'IgE-mediated food intolerance' in the 1980s. To clarify matters, the EAACI proposed using the term 'non-allergic food hypersensitivity', a decision later adopted by the World Allergy Organisation in 2003.² However, a number of other terminologies – including 'food idiosyncrasy' and 'pseudo-allergy' – continue to exist, particularly in relation to food additives.

Patient-reported rates of 'food intolerance' range from 7% to over 20%.^{3–6} One consistent finding is that the reported rate is about 10 times greater than true prevalence established through double-blind, placebo-controlled (DBPC) food challenges. Using these methods, approximately 1.5% of children may have a non-allergic food hypersensitivity.^{3–6}

Non-immune reactions to food can occur by many mechanisms. These can be summarized as:

- 1 *Enzyme deficiencies.* Malabsorption may present as 'food intolerance' due to an inability to metabolize excess substrate, for example aldehyde dehydrogenase deficiency causing intolerance to alcohol, phenylketonuria, lactose intolerance. The latter entity tends to present in children as a transient phenomenon after an episode of gastroenteritis. Unfortunately, it is frequently confused with cow's milk protein allergy by both parents and health professionals (lactose-free milk contains the same amount of cow's milk protein as normal milk). Excessive consumption of fruit juices (fructose) and sugar-free foods (sorbitol) can promote an osmotic diarrhoea, which may mistakenly be diagnosed as a 'food intolerance'. In adults, some patients presenting with symptoms of Irritable bowel syndrome improve with a reduction in fermentable carbohydrates, and this may be partially attributable to malabsorption.⁷
- 2 *Pharmacological effects.* It has been suggested that foods rich in vasoactive amines (e.g. tyramine and histamine in cheese and preserved foods) can induce symptoms, either by direct action or by causing the release of histamine *in vivo*

(presumably, through non-IgE-mediated mast cell activation). While histamine and other amines can induce gastrointestinal discomfort when instilled directly into the stomach,⁸ there is little peer-reviewed data to support the theory that foods containing these compounds can cause reproducible symptoms. One systematic review assessed 10 eligible studies, concluding 'no relation between oral ingestion of biogenic amines and food intolerance reactions.'⁹

Food additives

A food additive is a substance added to a food usually to preserve or improve its quality. A number of food additives, both natural and artificial, are reported to cause physiological symptoms. Almost invariably, these reactions are not IgE-mediated. However, it is important to consider the possibility of an allergic mechanism, though these are very uncommon. Carmine, a natural red colourant (also known as cochineal or 120) is a rare cause of allergy and even anaphylaxis in a few individuals, all of whom had evidence of IgE sensitization on skin or blood tests.¹⁰ Naturally occurring spices generally cause symptoms through pharmacological effects (many spices contain capsaicin which acts upon sensory nerves). However, in a very small number of people, these can occur via an IgE-mediated process. These subjects are generally sensitive to birch pollen or mugwort, and sensitization is due to cross-reactivity to the pollen. Spices implicated include coriander, caraway, fennel, parsley, garlic, onion and chives.¹¹

Tartrazine (102, Yellow no. 5) is the most studied additive, and is an artificial food colourant. It has been reported to provoke urticaria, eczema, vasculitis, asthma and even anaphylaxis. However, data supporting this are very limited. The largest study of DBPC challenges using tartrazine, involving 125 adults with aspirin-sensitive asthma, failed to demonstrate any positive challenges.¹² There are no studies reporting acute bronchoconstriction in children exposed to tartrazine on DBPC challenge. A Cochrane review concluded that it is 'not possible to provide firm conclusions as to effects of tartrazine on asthma control . . . exclusion may not benefit most patients, except those very few individuals with proven sensitivity'.¹³ Tartrazine was found to consistently cause a flare in eczema in 1 of 12 children studied using DBPC challenges, despite all 12 children having a parental history of eczema exacerbation on exposure to this colouring.¹⁴ Tartrazine can trigger symptoms in some children with chronic urticaria.^{15,16} However, in a sample of 18 children with chronic urticaria triggered by tartrazine who subsequently eliminated this additive from their diet, reintroduction of the colouring 1–5 years later did not cause symptoms.¹⁶ Reassuringly, a DBPC study in 26 atopic adults (presenting with allergic rhinitis, asthma, urticaria or symptoms of aspirin sensitivity) found tartrazine did not precipitate any kind of significant cutaneous, respiratory or cardiovascular reactions when compared with placebo.¹⁷

Natural food colourings can also cause symptoms in patients with chronic urticaria. Annatto (a yellow-orange dye found in hard cheese, soft spreads, ice cream and drinks) caused symptoms in one quarter of patients challenged using a single-blinded protocol – more frequent than reported reactions to other artificial colourings in the same study.¹⁸

Sulphites, a preserving agent found in dried fruits, fruit juice (grape, lemon, lime), wine and pickled foods, can cause clinically detectable bronchoconstriction in both adults and children with asthma.¹⁹ While this might be confused as an allergic reaction, the effects on airway calibre are almost certainly because of the release of sulphur dioxide, an airway irritant, from the action of gastric acid on the preservative; while metabisulphite solution caused a decreased in forced expiratory volume in children, consumption of the additive in a capsule form (thus limiting release of sulphur dioxide into the airways) did not cause symptoms in the same subjects.²⁰ Topical sulphite exposure can trigger dermatitis in adults (reviewed by Valley *et al.*)²¹ presumably via a type IV allergic reaction, but there is minimal data in children. With regard to non-allergic food hypersensitivity, a DBPC study found no evidence for sulphites causing symptoms in children at doses normally found in food,²² although a study with poor methodology (open challenges) demonstrated a weak effect in a mixed population adults and children.²³

Benzoic acid (benzoate) is a preservative in (mainly alcoholic) drinks, pickled foods and honey. Benzoates are frequently found in liquid formulations of common paediatric medicines, including paracetamol and ibuprofen. There are limited case reports of an effect on airway patency in adults with asthma. A DBPC study found 8% of adults with non-allergic rhinitis had symptoms triggered by benzoates.²⁴ Children with chronic urticaria may have symptoms triggered by benzoates, one trial of 43 children reporting up to 8% of subjects reacting to benzoate on DBPC challenge.¹⁵

Monosodium glutamate (MSG) was originally extracted from seaweed but is now obtained synthetically and used as a flavour enhancer in many foods. It is reported to trigger a range of reactions including bronchospasm and a set of symptoms known as 'Chinese Restaurant Syndrome' which include paraesthesia, palpitations, headache and flushing.¹ However, although 50% of adults who report a sensitivity to MSG experienced symptoms in a DBPC study, one half of them also reported symptoms to placebo, and the symptoms reported were not reproducible on subsequent challenge.²⁵ A DBPC study found no effect of MSG on adults with asthma who reported previous sensitivity to MSG.²⁶

Although controversy surrounds the role of salicylates in non-allergic food hypersensitivity, there is minimal peer-reviewed data implicating salicylates in food reactions. Salicylates can either be acetylated (e.g. aspirin) and non-acetylated. Naturally occurring salicylates are generally non-acetylated (e.g. methyl-salicylate and other salicylate salts) and are found in a wide variety of plant foods and bacteria.

Acetylated salicylates can trigger varying symptoms in children on challenge. However, these reactions are probably better termed an adverse drug reaction rather than a non-allergic hypersensitivity to a food additive. Approximately 10–30% of children with moderate-severe chronic asthma (receiving daily preventer medication) are sensitive to aspirin on airway provocation testing,²⁰ but in children with mild-moderate asthma, only 2% develop clinically relevant aspirin-induced bronchospasm.²⁷ Aspirin can trigger symptoms in a minority of children with chronic urticaria in DBPC trials.²⁸ The mechanism of action probably involves transfer of the aspirin acetyl group to other

Table 1 Summary of trials investigating role of food additives in children with chronic urticaria and angioedema

Study	n	Food challenge	Summary of findings
Park <i>et al.</i> (2008) ²²	21	DBPC	Using an additive mix (colourings, sulphite, benzoate and monosodium glutamate), three subjects developed skin symptoms to the mix, two to placebo and two to both.
Ehlers <i>et al.</i> (1998) ³⁴	16	DBPC	Twelve children had reactions to either preservatives and/or colourings.
De Martino <i>et al.</i> (1992) ³⁵	120	SBPC	Fifty-six subjects developed symptoms. 65% of reactions were to colourings, 57% to benzoate, 50% to aspartame and 12% to aspirin.
Supramaniam & Warner (1986) ¹⁵	43	DBPC	Twenty-four subjects developed symptoms: 25% to tartrazine, 21% to sunset yellow, 8% to benzoate, 4% to aspirin
Kemp & Schembri (1985) ²⁸	18	DBPC	39% of children improved with an additive free diet. Of 14 children who underwent food challenges, five reacted to aspirin.

DBPC, double blind placebo controlled; SBPC, single blind placebo controlled.

proteins, and/or inhibition of the enzyme cyclo-oxygenase causing a shift towards proinflammatory mediators.²⁹

Although there are very few reports of children experiencing symptoms after consuming foods rich in naturally occurring salicylates, some authors recommend an exclusion diet in children experiencing food reactions.³⁰ However, the evidence for this is weak, and there are no DBPC studies to support this assertion. For example, Dahl demonstrated no effect on airway patency after ingestion of 2 g of sodium salicylate in 12 patients with aspirin-sensitive asthma.³¹ Children are probably able to tolerate high levels of dietary salicylate because these are mostly non-acetylated.³² A DBPC study found no evidence for reactions to naturally occurring salicylates in children with chronic urticaria,³³ but interestingly found that many foods rich in salicylates also contain aromatic compounds which might trigger symptoms, that is salicylates may merely be a marker for the presence of these other compounds.³³ We are unable to identify any other DBPC studies concerning reactions to natural salicylates, and we therefore conclude that there is no basis for the suggestion that children sensitive to acetylated salicylate (aspirin) should avoid foods containing naturally occurring, non-acetylated salicylates.

Therefore, in most children, there is very limited evidence for any role of food additives in causing non-allergic food hypersensitivity. Reactions may be more common in children with chronic urticaria and angioedema, and the available evidence is summarized in Table 1. While other symptoms including migraine, gastrointestinal disturbances and arthralgia have been attributed to food additives, there are no reproducible and consistent data from DBPC studies to support this.¹

Food additives and hyperactivity

Feingold proposed in 1975 that 30–50% of children with attention deficit hyperactivity disorder (ADHD) respond to an additive-free diet.³⁶ Unfortunately, his research (describing an elimination regimen known as the Feingold diet) was never published in a peer-reviewed journal. A systematic review published by the EAACI in 1999 was 'unable to show a significant effect (of food additives) on behaviour in children with true

hyperkinesis'.¹ However, a subsequent meta-analysis found 'results strongly suggest an association between artificial food colourings and hyperactivity' in children with ADHD; although, the clinical relevance continues to be controversial.³⁷

In 2007, the Lancet published the 'Southampton Study'.³⁸ This DBPC crossover trial assessed whether children from the general population without ADHD developed hyperactive behaviours with consumption of food colourings and benzoic acid. In total, 154 3-year-olds and 144 8/9-year-olds were put on an additive-free diet and given one of two mixtures of food colourings and benzoate or fruit juice as placebo over a 6-week period. The colourings used were sunset yellow FCF (110); quinoline yellow (104); carmoisine (122); allura red (129); tartrazine (102); ponceau 4R (124), in quantities equivalent to 112 g of sweets per day. The study found a small but statistically significant increase in hyperactivity levels with additives compared with placebo, but the effect was not consistent across both age groups and the overall effect did not therefore reach statistical significance.

The results have generated much controversy. In the UK, the Food Standards Authority (FSA), which funded the study, now recommends parents to avoid giving their children the six artificial colourings used if their child demonstrates hyperactive behaviours. Furthermore, the FSA has introduced a 'voluntary ban' with the aim of phasing out these six colouring agents during 2010.³⁹ The European Food Safety Authority (EFSA) conducted a re-analysis of the same data and concluded 'in view of the considerable uncertainties, such as the lack of consistency and relative weakness of the effect and the absence of information on the clinical significance of the behavioural changes observed, the findings of the study cannot be used as a basis for altering the acceptable daily intake of the respective food colours or sodium benzoate'.⁴⁰ Despite this, the European Parliament passed legislation in July 2008 requiring foods containing these colourings to be labelled 'may have an adverse effect on activity and attention in children'.

Food Standards Australia and New Zealand (FSANZ) also examined the Southampton study and concurred with the findings of the EFSA, also quoting data that Australian food manufacturers use these colours at much lower levels than those used

Table 2 Summary of evidence for food additives and colourings in the causation of non-allergic food hypersensitivity reactions

Antioxidants	×	Few case reports of urticaria to BHA/BHT but not replicated with DBPC challenges
Stabilizers	×	Few case reports to gums only
Flavouring/enhancers	×	Hypothesis that monosodium glutamate causes 'chinese restaurant syndrome' not replicated with DBPC challenges
Artificial Sweeteners	×	Few case reports of urticaria to aspartame but not replicated with most studies using DBPC challenges.
Preservatives	(✓)	Benzoates & acetylated salicylates (aspirin) may be a trigger in chronic urticaria Sulfites can trigger asthma, probably through release of sulphur dioxide. ?Benzoates may trigger in hyperactivity in some
Colourings	(✓)	Colourings may trigger symptoms in some with chronic urticaria Tartrazine may trigger bronchospasm in a limited number of individuals with asthma. ?Role in hyperactivity

BHA/BHT, butylated hydroxyanisole/butylated hydroxytoluene; DBPC, double blind placebo controlled.

in the UK study.⁴¹ One conclusion is that there is not enough consistent data to support or oppose a role for food colouring in hyperactive behaviours, although there have been active campaigns by some advocacy groups to introduce a ban. Some manufacturers are phasing out the additives in question, and at least one major supermarket chain has imposed a voluntary ban.⁴²

We have previously suggested that, 'in view of the relatively harmless intervention of eliminating colourings and preservatives . . . it might be proposed that an appropriately supervised and evaluated trial (of elimination of food additives) should be part of standard treatment' in children with hyperactive behaviour.⁴³ Such a trial should take place over a 4-week period (not a long time in the context of hyperactive behaviours), thus limiting issues of confounding variables including too short a wash-out period. Perhaps the only certainty is that as the additives are phased out in the UK, the controversy is likely to continue.

Summary

While some individuals exhibit food reactions that are perceived as food intolerance, the true incidence of non-allergic food hypersensitivity reactions is low. The available evidence is poor and inconsistent, partly because of significant person-to-person variation seen even in well-designed trials with positive results (see Table 2). In the absence of new data, the only conclusions which can be drawn are that for the vast majority of individuals, there is no evidence that food additives cause clinical symptoms in a reproducible manner. It will certainly be interesting to

assess whether the voluntary ban on six food colourings affects the clinical burden of ADHD in the UK over the next decade. Where there is diagnostic uncertainty, a trial of an elimination diet over 4 weeks followed by DBPC challenges may be indicated in certain cases (shorter trials may be confounded by the presence of intercurrent viral infections among other issues which can precipitate urticaria). We would recommend assistance from an accredited dietician where significant dietary manipulation is considered. In the absence of positive findings, the diet should be normalized.

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