



Review

Common food colorants and allergic reactions in children: Myth or reality?

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ARTICLE INFO

Article history:

Received 26 October 2016

Received in revised form 7 March 2017

Accepted 8 March 2017

Available online 16 March 2017

Chemical compounds reviewed in this article:

Allura Red AC Dye (PubChem CID: 6093299)

Erythrosine Extra Bluish (PubChem CID: 27872)

Tartrazine (PubChem CID: 164825)

Sunset Yellow (PubChem CID: 6850717)

Fast Green (PubChem CID: 16887)

Brilliant Blue (PubChem CID: 123671)

Indigotine (PubChem CID: 5353682)

Orange B (PubChem CID: 5835026)

Ponceau 4R (PubChem CID: 9570119)

Keywords:

Allergy

Allergic reactions in children

Food additives

Food colorants

Food dyes

ABSTRACT

Various additives, including food colorants (FCs), are used in the food industry to make food appealing to consumers and to add variety. Despite the widespread usage of FCs, adverse reactions related to their consumption, including reactions triggered by immune (immediate and delayed-type hypersensitivity) and non-immune (intolerance) mechanisms, are considered rare. There is a discrepancy between the perception of patients and parents (7.4%) and the reported prevalence of adverse reactions to additives (0.01–0.23%), which is higher in atopic individuals (2–7%). Documented reactions are mild, involving mainly the skin, and, rarely, anaphylaxis. A major problem in diagnosing reactions to FCs is identification of the offending agent(s), which is based on careful dietary history taking. Allergy testing is usually unrevealing, except for reaction to some natural colorants. Treatment consists of avoidance of the offending colorant as no successful desensitization procedures have been reported.

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1. Introduction

Food colorants (FCs), a functional category of food additives, are used in the food industry for coloring. It is widely believed that the consumption of FCs by children can induce food intolerance (non-immune mediated) and allergic reactions (immune mediated, ranging from urticaria and/or angioedema and asthma to anaphylaxis). Literature on FCs and their impact on adult health is continuously increasing, but to date no clear evidence on possible adverse effects in children has been documented. The objective of this review is to discuss in detail, from the childhood allergy perspective, the most common FCs approved for consumption in the European Union (EU) and the United States (US). Common colorants including Allura Red, Brilliant Blue, Tartrazine and Sunset Yellow account for 90% of all color additives used in products marketed for consumption by children (Batada & Jacobson, 2016). Other frequently used FCs are Amaranth, Erythrosine, Ponceau 4R, Indigotine, Patent Blue, Carmine, Annatto, Saffron, Turmeric, β -carotene, Anthocyanins and Paprika.

1.1. Literature review strategy and methods

A systemic literature search was conducted in PubMed and Scholar for relevant papers in English published between 1959 and 5th March 2017 using combinations of the key words “allergy”, “allergic reactions in children” and “food additives”, “food colorants”, “food dyes”.

2. Definitions

According to the Codex Alimentarius, the first international collection of food standards and guidelines, “food additive” means “any substance not normally consumed as a food by itself and not normally used as a typical ingredient of the food; the term does not include ‘contaminants’ or substances added to food for maintaining or improving nutritional qualities”. Food additives can be classified as preservatives, antioxidants, emulsifiers, stabilisers, flavors, sweeteners and coloring agents (colorants). The Food and Drug Administration (FDA – www.fda.gov) describes “food colorants” as “any dye, pigment or substance which when added or applied to a food, drug or cosmetic, or to the human body, is capable (alone or through reactions with other substances) of imparting color”. The European Food Safety Authority (EFSA – www.efsa.europa.eu) defines “food colors” as “food additives which are added to food aiming to make up for color losses following expo-

sure to light, air, moisture and variation in temperature, to enhance naturally occurring colors and to add color to foods that would otherwise be colorless or colored differently” (<http://www.efsa.europa.eu/en/topics/topic/foodcolours>). “Acceptable Daily Intake” (ADI) as described in the “Codex General Standard for Food Additives” is the amount of a food additive, expressed on body weight basis, that can be ingested daily over a lifetime without appreciable health risk (www.fao.org). ADI “Not Specified” (NS) is applicable in the case of very low toxicity which does not represent to date a hazard to health (www.fao.org). In most countries, the current regulations specify, for each permitted colorant, the source and purity, to which foods the colorant can be added, and the maximum daily intake limits.

Food allergy is defined as an adverse reaction to food mediated by an immune mechanism, involving specific immunoglobulin E (sIgE) (IgE-mediated), or cell-mediated (non-IgE-mediated) or both IgE and cell-mediated mechanisms (mixed IgE- and non-IgE-mediated) (Muraro et al., 2014). Typically, food sensitization under IgE-mediated conditions can be demonstrated based on the detection of specific IgE to the incriminated food, by laboratory testing or the skin prick test (SPT). As some subjects may be sensitized to food allergens but present no clinical symptoms after exposure, demonstration of sensitization alone is not sufficient to diagnose food allergy (Sampson et al., 2014). Food intolerance is defined as a non-immune reaction to food ingestion. Non-immune adverse reactions, which sometimes mimic reactions typical of an immune response, include metabolic, pharmacological, toxic and/or undefined mechanisms (Sampson, 2014; Sampson et al., 2014). An allergen is any substance stimulating the production of immunoglobulin IgE or a cellular immune response. Allergens are usually proteins, but sometimes haptens are allergenic (Boyce et al., 2010; Muraro et al., 2014). Haptens are small molecules that elicit an immune response only when covalently bound to a large carrier, typically a protein antigen (Chinthrajah, Hernandez, Boyd, Galli, & Nadeau, 2016).

Despite the tendency of certain foods to initiate allergic reactions more frequently, theoretically any food protein is capable of producing an allergic, or even anaphylactic, reaction.

3. Classification

In the EU, FCs are divided into two major classes based on their origin: natural and artificial colorants (Table 1). In the US, FCs are divided into two groups, “exempt from certification” (usually

Table 1

Classification of food colorants in processed foods, with their Acceptable Daily Intake.

Colorant name Code (EU/US)	Colorant	ADI (EU/US) mg/kgbw	Products
Synthetic colorants			
<i>AZO DYES</i>			
AlluraRed E129/FD&C Red No40	Red	7/7	Baked goods and desserts, donuts, gelatine (jelly, Jell-o), snacks, salad dressing, candies
Amaranth E123/FD&C Red No2	Red	0.8/–	Baked goods, tortillas, crackers, porridge, sauces, soups, jellies, confections
Ponceau 4R E124/–	Red	4/–	Sweets, jellies, desserts, tinned and canned fruits and foods, cakes, pastries, soups, soft drinks, canned beverages
Tartrazine E102/FD&C Yellow No5	Yellow	7.5/5	Baked goods and desserts, donuts, gelatine (jelly, Jell-o), snacks, salad dressing, candies
Sunset Yellow E110/FD&C Yellow No6	Yellow	2.5/3.75	Baked goods and desserts, donuts, gelatine (jelly, Jell-o), snacks, salad dressing, candies
<i>Non azo dyes</i>			
Erythrosine E127/ FD&C Red No3	Red	0.1/2.5	Baked goods and desserts, candies, dairy products, snacks
Brilliant Blue E133/ FD&C Blue No1	Blue	10/12	Baked goods and desserts, donuts, gelatine (jelly, Jell-o), snacks, salad dressing, candies, beverages, dairy, ice cream,
Indigotin E132/FD&C Blue No2	Blue	5/2.5	Baked goods and desserts, candies, breakfast cereals, ice cream, snacks
Patent Blue E131/–	Blue	15/–	Scotch eggs, certain jelly sweets, blue caracao, certain jelly varieties (though not in actual Jell-O brand products), among others
FastGreen-/FD&C Green No 3	Green	25/2.5	Baked goods, candies, beverages, dairy, ice cream, puddings
Natural colorants			
Carmines E120	Red	5	Baked products, dairy products and yogurt, cake icing, hard candies, ice cream, gelatine desserts, fruit syrups, jams,
Annatto E160b	Orange-Yellow	NS	Baked goods, dairy products and yogurt, popcorn oil, butter, ice cream, icings, snack, salad dressing
Saffron E164	Yellow	NS	Risotto, paella, baked goods, pastry and plain biscuits
Turmeric E100	Orange-yellow	1	Baked goods, dairy products and yogurt, ice cream, cakes, cookies, popcorn, candies, cake icings, cereals, sauces, gelatine
B-carotene E160a		NS	Margarine, non-dairy creamers
Anthocyanins E163	Red, purple,	2.5 (grape skin extract)	Non beverage drinks, ice cream, yogurt, fruit fillings, candies
Paprika E160c	Red	NS	Baked goods, sausage, cheese sauces, condiments, salad dressings, snacks, icings, cereals

After: (Greenhawt & Baldwin, 2009; John, 2001) (modified), Food and Drug Administration, 2011.

ADI; Acceptable Daily Intake, EU; European Union, US; United States, bw; body weight.

referred to as natural colorants) and “certified colorants” (typically referred to as synthetic colorants).

Different legislation on the use of FCs and subsequent labeling applies in the EU and the US, as well as in other countries around the world, and is enforced by specific agencies (e.g., in the UK by the Food Standards Agency – www.food.gov.uk). Certain FCs are banned in some countries, but not others.

4. Epidemiology

To date, no studies have been published regarding the prevalence of intolerance or allergic reactions to FCs alone, even in the adult population. Although additives, including FCs, have been used since antiquity, allergic reactions to additives have been reported in very few population-based studies and case reports. The prevalence of reactions to food additives is estimated at 1–2% in unselected populations of healthy children, and higher in atopic children, ranging from 7% (after open challenge) to 2% (on double-blind challenge) (Fuglsang, Madsen, Saval, & Osterballe, 1993; Fuglsang et al., 1994).

Early studies in both children and adults have shown a discrepancy between the perception of patients and parents and the reported prevalence of adverse reactions to additives as proven by challenge test (7.4% vs. 0.01–0.23%) (Young, Patel, Stoneham, Rona, & Wilkinson, 1987). In a German adult population, the prevalence of pseudoallergic reactions to food additives, detected by a double blind challenge test, was 0.18% (Zuberbier et al., 2004).

A recent study of 100 patients with chronic idiopathic urticaria (CIU), ranging in age from 14 to 67 years, showed that only 2 had a positive urticarial response on single-blind challenge to 11 common additives, including Tartrazine and Sunset Yellow. On double-blind placebo-controlled food challenge (DBPCFC) neither patient reacted; thus, the prevalence of food additive sensitivity in adult patients with CIU was estimated to be less than 1% (Rajan, Simon, & Bosso, 2014). Earlier studies reported “false-positive” reactions resulting from prior interruption of medication and use of single-blind protocols (Simon, 2003).

The prevalence of allergic reactions to FCs is thus not known, but it is considered to be low. It is apparent that additives (including FCs) are more likely to elicit an allergic reaction in patients with atopic disease than in healthy children.

5. Sources of food colorants in the diet

Consumer attitudes regarding food colorants are directed towards the use of natural colorants, while the food industry prefers artificial colorants because of their stability, strength and price. The consumer tendency to avoid synthetic colorants dictates the trend of the food industry to replace them with fruit and vegetable extracts. These alternatives are slowly being approved in both the EU and the US. The food products containing colorants that are consumed most often by children are soft drinks (beverages) and sugar-based confectionery (Saltmarsh, 2015). Detailed information regarding the most important categories of processed foods utilizing FCs are listed in Table 1.

The quantity of FCs consumed daily by children influences the occurrence of adverse reactions. Recent studies showed wide variation in colorant concentrations in specific foods, with ranges of 0.2–52.3 mg/240 ml in beverages (Stevens, Burgess, Stochelski, & Kuczek, 2014), and 0.3–33 mg in candies, 9.4–41.3 mg in breakfast cereals, 1.9–6 mg in ice cream and 2.8–14.4 mg in snack foods, all per serving size (Stevens, Burgess, Stochelski, & Kuczek, 2015). A dose response effect was observed in the incidence of behavioral change in children (i.e., irritability, restlessness and sleep disturbance) after Tartrazine ingestion (Rowe & Rowe, 1994). In this study, placebo or one of six dose levels of Tartrazine (1, 2, 5, 10, 20, 50 mg), was administrated randomly each morning, and at the end of every day behavioral ratings were recorded. To our knowledge, no studies on dose – response effects of FCs regarding allergic reactions or intolerance have been published.

Full labeling information should be provided on FCs that have been identified as possible triggers of allergic reactions in sensitive patients. Depending on the quantity and the variety of the foods eaten it is possible for a child to consume from different sources accumulative amount of colorants far above the ADI levels published by EFSA and FDA.

6. Possible mechanisms

Food hypersensitivity is an adverse or abnormal reaction to a food or a food additive, including FCs, and can be differentiated into allergic reactions (food allergy), which involve an immune mechanism, and non-allergic reactions. Based on the underlying pathophysiological mechanism, allergic adverse reactions to additives can be classified as IgE-mediated, non-IgE-mediated (cell-mediated) and mixed IgE/non-IgE-mediated reactions (Sampson, 2014) (Fig. 1).

It is likely that multiple mechanisms are involved, but most reactions are not IgE mediated (Wilson & Bahna, 2005). Clinically relevant specific IgE production has been demonstrated with some natural additives, although most synthetic additives are simple chemicals that most likely act as haptens, binding with protein to induce an IgE-mediated response (Stevens et al., 2013). Both responses involve activation of specific components of the immune system, leading to histamine release and increased leukotriene production. Leukotrienes play an important role in allergy and inflammatory disease. Compared with histamine, which causes constriction of the airways and edema formation, the leukotrienes,

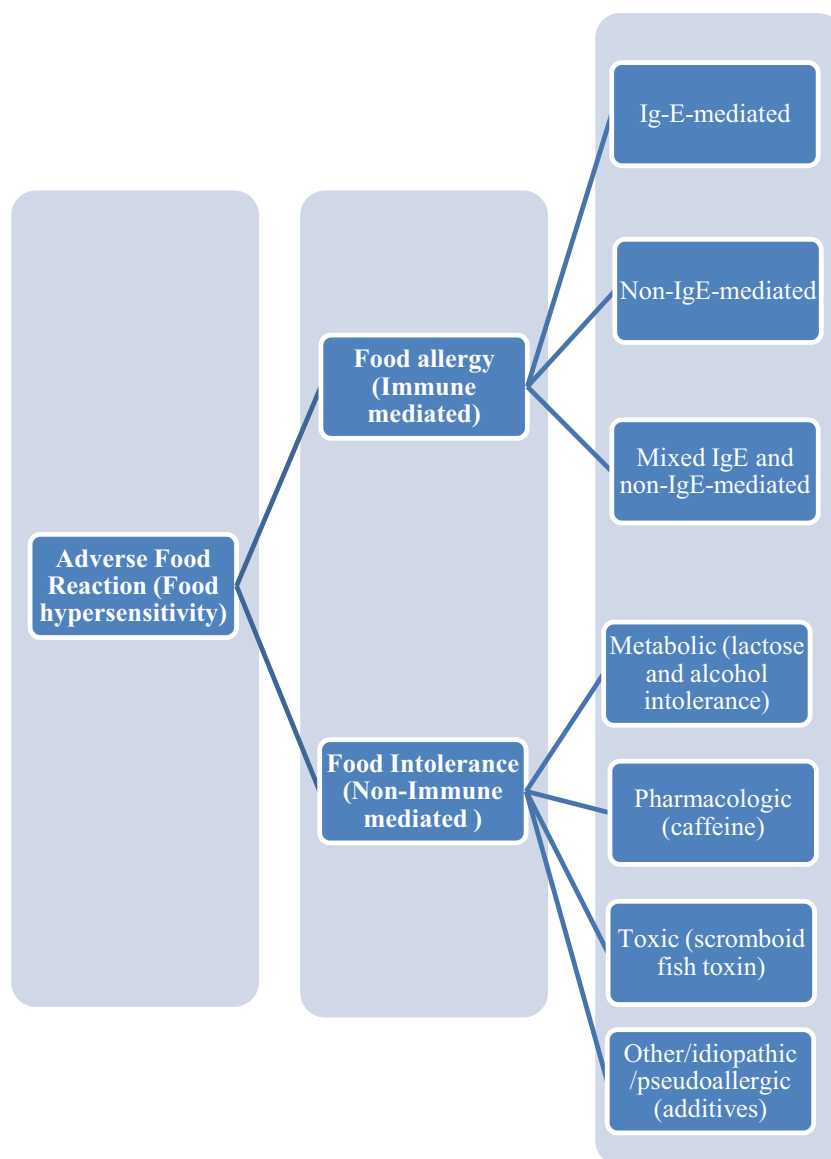


Fig. 1. Classification of food reactions, (modified from Sampson (2014)).

a family of biologically active molecules, are three to four orders of magnitude more potent, and the effects have longer duration (Hammarstrom, 1983). FCs can be classified as haptens because of their low molecular weight. Haptens can elicit an immune response only when they are attached covalently to a large carrier molecule, such as a protein, in the gastrointestinal tract (Wilson & Bahna, 2005). Sensitization to the hapten carrier results in activation of T cells and release of granules and cytokines by mast cells, which trigger typical symptoms of allergy and an increase in IgE levels (Stevens et al., 2013).

Exposure to colorants can, theoretically, be through ingestion, inhalation or skin contact, but in children, ingestion is the main route. The involvement of an immune mediated mechanism has been demonstrated for certain FCs. Carmine for example, contains components both with high and low molecular weight (carminic acid). Hence, the allergens may act through an immune IgE mediated mechanism or as haptens (Lucas, Hallagan, & Taylor, 2001). Case reports suggest that adverse reactions to Carmine are the result of an IgE mediated mechanism (Beaudouin, Kanny, Lambert, Fremont, & Moneret-Vautrin, 1995; DiCello, Myc, Baker, & Baldwin, 1999). Identification of the Carmine allergens responsible has not been widely documented, although Lizaso and colleagues identified three proteins with molecular weights of 17, 28 and 50Kd, respectively, implicated in occupational asthma (Lizaso et al., 2000). Carmine was demonstrated in three patients as the allergen responsible for food allergy (Chung, Baker, Baldwin, & Chou, 2001), but it is unclear whether the culpable allergens are simple proteins or a protein-carminic acid complex.

Annatto has been related to IgE-mediated reactions (Lucas et al., 2001). Nish and colleagues identified specific IgE to Annatto protein (50 kD) in an adult who developed anaphylaxis after ingestion of food containing Annatto (Nish, Whisman, Goetz, & Ramirez, 1991). In an adult with a reaction to Annatto highly indicative of IgE mediation, the assumption was reinforced by positive SPT, basophil activation test (BAT) and IgE-immunoblot to Annatto (Ebo, Ingelbrecht, Bridts, & Stevens, 2009).

Spices, including these with coloring properties (e.g., saffron, turmeric, paprika), may produce symptoms through pharmacological effects (from capsaicin). Symptoms may also follow an IgE-mediated process in patients initially sensitized to mugwort and birch pollen, who react to spice due to cross-reactivity to the pollen (Turner & Kemp, 2012). Leitner and colleagues identified a 23-kDa allergen in paprika which binds IgE present in the serum of patients with the mugwort-birch-celery-spice syndrome. In this case, the cross-reactivity did not occur on the basis of pan-allergens, such as profilins or Bet v 1 (Leitner et al., 1998).

Saffron produces IgE-mediated reactions, even severe anaphylaxis (Fiocchi, Dahdah, Martelli, Mazzina, & Manzotti, 2014). Immunoblotting showed five IgE-binding bands to a high-molecular-weight protein (40–90 kDa) in saffron extract (Wuthrich, Schmid-Grendelmeyer, & Lundberg, 1997). Immunoblotting of the in-house Pru p 3 extract revealed a band of approximately 9 kDa, indicating the presence of lipid transfer protein (LTP) in the saffron extract (Gomez-Gomez et al., 2010); thus a cross-sensitization to the other LTP plant allergens may be possible.

Artificial FCs may cause adverse reactions, but, as they do not contain protein, true allergies are fortunately very rare. An immune mechanism has not been identified, and reactions to the FCs are classified as intolerances or sensitivities (Burks et al., 2012). Symptoms due to, or exacerbated by artificial FCs usually involve a non-IgE-mediated mechanism (i.e., pseudo-allergic reaction) and are typically less severe rather than those induced by food allergy (Cardinale et al., 2008). Several mechanisms for pseudo-allergic reaction have been proposed over the years. An early study showed an increase in the plasma histamine level after ingestion of 200 mg

Tartrazine, suggesting a pharmacological mechanism (Murdoch, Pollock, & Naeem, 1987). A decrease in the cyclooxygenase metabolism, and consequently of prostaglandin production, has also been suggested (Supramaniam & Warner, 1986).

Ehlers and colleagues confirmed the role of non allergic hypersensitivity to certain food additives, including, azo and non-azo FCs, in children with chronic continuous urticaria (Ehlers, Niggemann, Binder, & Zuberbier, 1998). Of 16 children with moderate to severe chronic continuous urticaria, 13 (81%) entered remission under a stringently controlled low-pseudoallergen diet, and all continued to react with wheals after mistakes or discontinuation of the diet. DBPCFC to various different additives, including Tartrazine, Sunset Yellow, Azorubine, Amaranth, Ponceau, Brilliant Black, Quinoline Yellow and Erythrosine performed in six patients revealed that food additives including FCs caused 83% of reactions (Ehlers et al., 1998).

In spite of the continuous increase in literature on food additives and FCs, no study has been conducted to date to evaluate the possible mechanism in children with adverse reactions.

7. Natural food colorants

Changes in consumer behavior in recent years has led to increased use of natural FCs, as a result of which there has been a rise in the diagnosis of allergic reactions to natural colorants.

Carmine (E120, color index No. 75470) is the most frequently studied common natural FC. It is a naturally derived red color, carminic acid, which is extracted from cochineal, produced by the dried female insect *Dactylopius coccus* Costa, a parasite of the prickly pear cactus. Carmine should not be confused with Indigo Carmine (E133, Blue No 2), or Ponceau 4R (Cochineal Red, E124) (Greenhawt & Baldwin, 2009a).

Annatto (E160b, color index no75120), the second natural FC reported to produce allergic reactions, is prepared from the seeds of the annatto tree (*Bixa orellana* L). Its major color component is considered to be bixin.

Turmeric (curcumin, E100) is obtained from the ground rhizomes of strains of *Curcuma longa* L. The major pigment in turmeric is curcumin or curcuminoids, and there is no convincing evidence of allergic reactions (Lucas et al., 2001).

Saffron (E164) consists of dried stigmas of *Crocus sativus* L., a bulbous perennial plant cultivated in Mediterranean countries. Usually categorized as a spice, it has been used since antiquity also as a FC, although its usage is restricted due to its distinctive spicy flavor. The major component of the saffron extract is crocin (Yuan-Kun & Hwee-Peng, 2001).

Paprika extract (E160c) is obtained by extraction from the ground fruit pods of *Capsicum annum* L.

There have been no case reports to date, of allergy, even in adult subjects, to grape skin extract, grape color extract (Anthocyanins – E163 as the coloring principle), beetroot powder, carrot oil or cottonseed derived color (carotenoids as the coloring principle) when used as FC.

8. Synthetic food colorants

Azo dyes are a large class of synthetic organic dyes, some of which are used as FCs. Even very small doses of azo-dyes absorbed from tattoos have recently been suggested to trigger an immune response (Baumler, 2015). A recent study on products and FC information from 810 items in one grocery store in North Carolina (US) showed that the most frequently encountered synthetic FCs were Allura Red, Brilliant Blue, Tartrazine and Sunset Yellow, present in 28.9%, 24.2%, 20.5% and 19.5% respectively of the products marketed for consumption by children (Batada & Jacobson, 2016).

Allura Red, also named E129 or FD&C Red No40 is a red azo-dye. Other red azo-dye FCs are Amaranth (E123, FD&C Red No2) and Ponceau 4R (E124), both of which are banned in the US and Finland, but permitted in the EU. Tartrazine (E102, FD&C Yellow No5) and Sunset Yellow (E110, FD&C Yellow No6) are both azo-dyes and are the most frequently used FCs for achieving yellow shades.

The non-azo dyes used as FCs include Erythrosine, Brilliant Blue, Indigotin, and Patent Blue. Erythrosine is also known as E127 and Red No3 and belongs to the xanthene group, while Brilliant Blue (E133, FD&C Blue No1) belongs to the triarylmethane group. Indigotine (E132, FD&C Blue No2) belongs to the indigo colorants and was initially extracted from the shrub *Indigofera tinctoria* (Carocho, Barreiro, Morales, & Ferreira, 2014). Patent blue (E131) is a non-azo-dye banned in the US, although permitted in the EU.

9. Clinical manifestations

Tables 2 and 3 show the wide variety of symptoms that have been attributed to FCs. Studies document the association of FCs

with adverse skin reactions, such as urticaria and angioedema, and aggravation of pre-existing atopic dermatitis (Wilson & Bahna, 2005), but evidence of a causal relationship is discrepant. Rajan et al. and colleagues studied 100 subjects with CIU, who were single-blind challenged with 11 food additives. The additives tested were Tartrazine (FD&C Yellow 5) (50 mg), potassium metabisulfite (100 mg), monosodium glutamate (MSG) (2500 mg), Aspartame (150 mg), sodium benzoate (100 mg), methyl paraben (100 mg), butylated hydroxy anisole (250 mg), butylated hydroxy toluene (250 mg), FD&C Yellow 6 (50 mg), sodium nitrate (50 mg) and sodium nitrite (50 mg). DBPCFCs were subsequently performed in patients with positive single-blind challenges. The authors concluded that sensitivity to food chemicals occurs in less than 1% (Rajan et al., 2014). FCs have also been found to be correlated with an increase in the incidence of allergies and asthma (Vojdani & Vojdani, 2015).

9.1. Natural colorants

Reports of allergic reactions to natural colorants are rare. It can be speculated that during the extraction process of the specific

Table 2
Clinical manifestations attributable to natural colorants.

Colorant name (EUcode)	Source	Clinical manifestation	References
Natural colorants			
Carmine E120	<i>Dactylopiuscoccus</i> (dried insect bodies)	No studies or case reports in children	
Annatto E160b	<i>Bixaorellana</i> (tropical tree)	Atopic dermatitis Urticaria Rhinitis, colic, vomiting	Fuglsang et al. (1994)
Saffron E164	<i>Crocus sativa</i> (flower)	Allergic rhinitis	Fiocchi et al. (2014)
Turmeric E100	<i>Curcuma longa</i> (rhizomes)	Contact dermatitis Atopic dermatitis Urticaria	Gomez-Gomez et al. (2010) Fuglsang et al. (1993)
B-carotene E160a	Plant and microbial sources	Rhinitis, colic, vomiting Atopic dermatitis Urticaria	Fuglsang et al. (1994) Fuglsang et al. (1993) Fuglsang et al. (1994)
Anthocyanins E163	<i>Vaccinium</i> species: blueberry, cranberry, raspberry, blackcurrant, grape, reed cabbage	"Natural colorants with anti-allergic proprieties"	
Paprika E160c	<i>Capsicum annum</i> (dried fruits)	No reports of grape color extract causing reactions Urticaria, facial swelling, severe cough Urticaria	Leitner et al. (1998) Gimenez and Zacharisen (2011)

Table 3
Clinical manifestations of synthetic colorants.

Colorant name Code (EU/US)	Color	Safety/Permission ^a	Clinical manifestation	References
AZO DYES				
Amaranth E123/FD&C Red No2	Red	Permitted in EU, Banned in US	Aggravation of pre-existing atopic dermatitis symptoms Urticaria	Park et al. (2008) Ehlers et al. (1998)
Ponceau 4R E124/- Tartrazine E102/FD&C Yellow No5	Red Yellow	Banned in US, Norway Banned in Norway and Austria	Urticaria Urticaria/angioedema Asthma	Ehlers et al. (1998) Nettis et al. (2003) Arden and Ram (2001)
Sunset Yellow E110/FD&C Yellow No6	Orange-yellow	Banned in Norway	Anaphylaxis Urticaria/angioedema Asthma, eczema, urticaria	Trautlein and Mann (1978) Park et al. (2008) Ehlers et al. (1998) Wilson and Scott (1989) Trautlein and Mann (1978)
Brilliant Blue E133/FD&C Blue No1	Blue	Approved	Anaphylaxis	
AlluraRed E129/FD&C Red No40	Red	Banned in EU, Permitted in US		
Non-azo dyes				
Erythrosine E127/FD&C Red No3	Red	Banned in Norway	Aggravation of pre-existing atopic dermatitis symptoms Urticaria/angioedema	Park et al. (2008) Martino et al. (1992)
Indigotin E132/FD&C Blue No 2	Blue	Banned in Norway		Ehlers et al. (1998)
Patent Blue E131/FD&C Blue No2	Blue	Banned in US, Australia	Urticaria	Chadwick, Hunter, Evans, and Hunter (1990) Ehlers et al. (1998)

EU: European Unit, US: United States.

^a Codex Alimentarius – www.fao.org; EFSA – www.efsa.europa.eu; FDA – www.fda.gov.

color the allergenicity of the offending proteins could be modified. Traditional extraction methods for Carmine resulted in varying amounts of toxic metal ions and allergenic proteins (insect-derived proteins, possibly complexes with carminic acid) in the final carminic acid preparation. New methods have been developed with the intent of reducing the allergenic protein content in the carminic acid originating from cochineal (Borges, Tejera, Díaz, Esparza, & Ibáñez, 2012). Pressurized liquid extraction, using high pressure and temperature to modify the properties of the extraction solvents, and supercritical fluid extraction, using environmentally benign carbon dioxide as solvent ensure rapid, safe, effective extraction of a wide variety of dye and food compounds (Herrero, Cifuentes, & Ibáñez, 2006).

9.1.1. Carmine

Atopy patch test (APT) with 15 food additives in 34 children with atopic eczema (AE) showed a positive result in 41.2% of the AE group compared with 15.2% of the control group, the difference being attributed to greater Carmine sensitivity in the AE group (Catli et al., 2015). In adults, the only report of a relationship between Carmine and AE was of four cases of allergic contact dermatitis (Shaw, 2009; Suzuki, Hirokawa, Yagami, & Matsunaga, 2011). The allergen in Carmine that causes delayed-type hypersensitivity has not been identified.

9.1.2. Annatto

Annatto dye has only rarely been shown to provoke a severe, adverse reaction in individuals with an uncommon hypersensitivity, aggravating the symptoms of recurrent urticaria (Lucas et al., 2001). Provocation tests with various food additives resulted in one or more positive reactions to Annatto in one-third of patients with recurrent urticaria (Juhlin, 1981). Annatto seed hypersensitivity was documented by immediate SPTs in two children who developed generalized urticaria with angioedema (Myles & Beakes, 2009; Ramsey, Tuano, Davis, Dillard, & Hanson, 2016).

9.1.3. Saffron

Spice allergy is rare in children (Chen & Bahna, 2011). Despite saffron allergy is uncommon in the general population, having been described mainly in adults and as an occupational allergen in those handling this plant (Hassan et al., 2015), due to Cro s 3 LTP (Gomez-Gomez et al., 2010). One 12 year-old boy developed a severe episode of allergic rhinitis after eating a small amount of saffron contained in risotto, attributed diagnostically to the Cro s 2 profilin allergen (Fiocchi et al., 2014).

9.1.4. Turmeric (Curcumin)

Colorants may be present in the picture stick-on tattoos that are popular with children. Curcumin is reported to have caused a few cases of contact allergy as a colorant in food or in disinfectants used prior to surgery (Rastogi & Johansen, 2005). In a multicenter Danish study, 335 children, aged 4–15 years were challenged with lemonades, containing lower and higher concentrations of turmeric (2.5 mg/100 ml). A significant association was observed between positive lemonade challenge and skin symptoms, in the form of either atopic dermatitis or urticaria (Fuglsang et al., 1994).

9.1.5. Paprika

Allergy to spices is frequent, estimated at 2% of all food allergies, and 6.4% in adults, but spice allergy is rare in children (Chen & Bahna, 2011). The patients most at risk of spice allergy are young adults who are already sensitized to mugwort and birch allergens and share cross-sensitization with various food vegetal allergens (Moneret-Vautrin, Morisset, Lemerdy, Croizier, & Kanny, 2002). In 73% of 22 patients with the mugwort-birch-celery-spice syndrome the serum demonstrated IgE binding to pepper extract

and 95% to paprika proteins in immunoblot. As expected, the IgE binding to pepper and paprika allergens was markedly inhibited by pre incubating the sera with crude celery tuber, mugwort, and birch pollen extracts (Leitner et al., 1998). A prospective study of food hypersensitivity in 228 patients aged over 14 years suffering from atopic dermatitis recorded hypersensitivity reactions after the ingestion of capsicum in 13%. (Celakovska, Ettler, Ettlerova, & Vaneckova, 2014). A 17 month-old white boy who developed severe urticaria, conjunctivitis, facial swelling and severe cough minutes after eating venison prepared with cayenne pepper (*Capsicum annum*) is the only recorded case of capsicum anaphylaxis in a young child (Gimenez & Zacharisen, 2011).

9.2. Synthetic colorants

9.2.1. Erythrosine

Erythrosine has been shown to inhibit hematopoietic prostaglandin D2 synthase, which a glutathione transferase, catalyzing the isomerization of prostaglandin H2 to prostaglandin D2. This is a mediator of allergy and inflammation responses and could have implications for the treatment of allergy and asthma (Mazari, Hegazy, & Mannervik, 2015). This particular mechanism is unlikely to be responsible for any major health effect. As is well known, pediatric syrups are normally colored, with Erythrosine, among others. A recent investigational study demonstrated that colorants such as Erythrosine account for more than 50% of the ADI value, which is alarming and calls for modification by the regulatory authorities to safeguard the health of children (S. D. Rastogi, Dixit, Tripathi, & Das, 2015).

9.2.2. Indigo

Indigo has been described as an excipient to drugs and has been associated with allergic reactions, mainly in adults. Indigo was documented as the culprit agent for CIU after DBPCFC (Ehlers et al., 1998). A cohort of 11 patients with chronic, unexplained pruritic skin disorders responded to medication changes centered around avoidance of the coloring agents (Swerlick & Campbell, 2013).

9.2.3. Patent Blue

Reports on children are scarce, but allergic reactions to Patent Blue, even anaphylaxis, have been documented in adults (Low, McEwan, Karanam, North, & Kong, 2016). In a Finnish study of 530 patients (34% children) with severe allergic reactions, 68% were operation-related. Three cases were caused by the Patent Blue dye (E 131) used to locate sentinel lymph nodes (Makinen-Kiljunen & Haahela, 2008).

9.2.4. Amaranth

Urticaria (Ehlers et al., 1998) and possible aggravation of atopic dermatitis (Park et al., 2008) were attributed to Amaranth in studies on children. An investigation of 1,467 frequently administered formulations demonstrated Amaranth content in 1.7%, which significantly exposes patients to the risk of asthma and urticaria (Kolly, Pecoud, & Frei, 1989).

9.2.5. Ponceau

Only few cases of intolerance reactions to Ponceau, all in sensitive individuals, have been reported. Study was made of 25 children aged between 1.5 and 12.5 years with allergic reactions after food intake, who were challenged with individual dyes after a 48-h avoidance of colorants. Four subjects reacted to the challenge with Ponceau 4R at doses of 1 and 10 mg (5 mg for subjects <15 kg body weight), developing recurrent urticaria and/or angioedema, bronchoconstriction or objective worsening of pre-existing atopic dermatitis (Ibero, Eseverri, Barroso, & Botey, 1982).

9.2.6. Tartrazine

Tartrazine has been rarely reported to cause urticaria. It was found consistently to produce a flare-up in eczema in one of 12 children studied using DBPCFC, although all 12 children had a history of eczema exacerbation on exposure to this colorant (Devlin & David, 1992). Tartrazine has been reported to trigger symptoms in some children with CU (Supramaniam & Warner, 1986), (Pollock & Warner, 1987), but in a sample of 18 children with CU, apparently triggered by Tartrazine, who subsequently eliminated this additive from their diet, reintroduction of the colorant 1–5 years later caused no symptoms (Pollock & Warner, 1987). A double-blind study documented an association between Tartrazine and asthma exacerbation in young children (Hariparsad, Wilson, Dixon, & Silverman, 1984). Cochrane meta-analysis to investigate a link between Tartrazine and asthma, concluded that none of the 6 studies included clearly demonstrated that Tartrazine challenge makes asthma worse or that Tartrazine avoidance makes it better. The authors concluded that there may be a need for further randomized controlled trials to confirm the absence of any effect of Tartrazine on asthma (Arden & Ram, 2001).

9.2.7. Sunset Yellow

A 15 year-old pregnant girl went into anaphylactic shock after being administered an enema containing Yellow 5 and Yellow 6 (Trautlein & Mann, 1978). In a DBPCFC clinical study, a group of 43 children with angioedema and/or CU responded to an additive free diet, presenting noticeable improvement in their skin symptoms. The patients were then challenged with individual food colorants 'hidden' in opaque capsules. Ten of the 36 children reacted to Sunset Yellow FCF, developing urticaria or angioedema, rhinitis and wheezing (Supramaniam & Warner, 1986).

9.2.8. Brilliant Blue

To date, no reports have been published regarding intolerance or allergic reactions to Brilliant Blue.

9.2.9. Allura Red

Although Allura Red is one of the most frequently used colorants in food products for children, to our knowledge, no case has been described of intolerance or allergic reaction to it in children. Only two adult cases of allergic reactions to capsules containing Allura Red have been documented. In a series of 56 adults suffering from CIU and/or angioneurotic edema, 16% reacted to Allura Red on oral provocation (Mikkelsen, Larsen, & Tarding, 1978).

10. Diagnosis

The diagnosis of food chemical intolerance is difficult because of the lack of reliable, scientifically validated blood or skin tests or histopathological examination. The skin and *in vitro* tests are of limited value with the exception of some natural colorants. Oral challenge constitutes a definitive diagnostic tool, although there are no standardized protocols. A proposed diagnostic approach is as follows:

Detailed dietary history taking is of utmost importance when additives are suspected to be the cause of a reaction. Food additives should be suspected when patients report a history of reactions to a number of unrelated foods or to a certain food when commercially prepared but not when prepared at home (Randhawa & Bahna, 2009). Reaction to the main food components should be ruled out first. If the patient is known to have an allergy to certain foods, the inadvertent consumption of such a food as a contaminant or under an unfamiliar name should be excluded. Physical examination may reveal other causes of the patient's symptoms.

Ruling out a hidden food allergy will require careful checking of food labels. Food laws strictly regulate labeling for allergens, but in some cases contacting the food provider (i.e., restaurant or manufacturer) can be helpful. In special situations, sending the food for analysis in a specialized laboratory can the agent responsible (Wilson & Bahna, 2005). There is a need to scale the regulation of the detailed information regarding the relative allergenicity of food products and ingredients according to the hazards they pose (i.e. mandatory labeling) (Houben et al., 2016). The labeling alerts typically pertain to food proteins, but they also encompass food additives.

Skin testing, and *in vitro* testing, when available, can be helpful in screening for some natural additives, such as Carmine (Anibarro, Seoane, Vila, Mugica, & Lombardero, 2003; Beaudouin et al., 1995), Annatto (Tabar-Purroy et al., 2003), saffron (Moneret-Vautrin et al., 2002), mannitol (Hegde & Venkatesh, 2004) and vegetable gums (Tarlo, Dolovich, & Listgarten, 1995). Park and colleagues reported reactive SPT to food additives in 3.7% of patients with allergy (Park et al., 2008). A recent study revealed that about one-third of allergic patients with a reaction to food additives showed a positive response on oral challenge (Moghtaderi, Hejrati, Dehghani, Dehghani, & Kolahi, 2016).

The Atopy Patch Test (APT) is a useful tool for determining delayed-type hypersensitivity reactions to foods and aeroallergens in AE (Edwards & Martinez, 2014). In a recent study the frequency of APT positivity to a number of food additives in children with AE was examined and the authors postulated that they might have a causative or aggravating role in some cases of AE (Catli et al., 2015).

Numerous reports confirm the usefulness of the Basophil Activation Test (BAT) in various allergic diseases, but for food additives BAT has not yet been sufficiently studied. Ebo and colleagues reported the case of a patient with a history of recurrent anaphylaxis after eating cheese, due to hypersensitivity to the natural dye Annatto, confirmed by a positive BAT (Ebo et al., 2009). Kang and colleagues studied BAT in patients with CIU, whose symptoms were suspected to be related to hypersensitivity to food additives. A total of 13.3% of participants showed a positive BAT to at least one of 15 common food additives tested (Kang et al., 2014). False negative results on BAT, with positive oral challenges, could be a possibility, according to the same authors (Lee et al., 2013). The offending agent may not be clearly identified through history, food diaries, SPT for common food allergens or other additional laboratory tests. In spite of the issues surrounding the use of the BAT for food additives, it could be a good alternative for evaluating hypersensitivity to additives in patients with CIU, as BAT results are not affected by anti-histamine or steroid use (Sturm et al., 2009). BAT can be used to avoid the exacerbation of urticaria stemming from the discontinuance of such drugs required to conduct consecutive oral provocation tests for the numerous potential candidate additives (Kang et al., 2014).

The DBPCFC is recognized as the gold standard for the diagnosis of hypersensitivity to foods or food additives (Sicherer & Sampson, 2010). To reduce the number of challenges, mixtures of additives can be used initially (e.g., dyes of similar color) (Wilson & Bahna, 2005). The components of the positive challenge mixture must then be tested individually to identify the specific offending additive. The challenge doses used in the few published studies varied widely (Pacor, Di Lorenzo, & Corrocher, 2001; Simon, 2000), partly explained by methodological variations. The outcome of a DBPCFC should be interpreted with caution, because there is no international agreement on a standardized protocol. Park and colleagues used mixtures of 7 food additives and chose 1/10 of the ADI as the maximal dose for each additive (Park et al., 2008). In everyday life, individuals are exposed simultaneously to several food additives, which raises the possibility of the combinatorial and synergistic effects (Park et al., 2008). In earlier studies the doses were

Table 4
Diagnostic doses for food colorant challenges.

Additive	Dose given	References
Food dyes or colorants(not mentioned)	1, 5, 10, 15 mg each every 20–30 min	Wilson and Bahna (2005)
Food colorant mixture (Amaranth, Tartrazine, Sunset Yellow, Erythrosine)	(1/6, 2/6, 3/6 of ADI) every 30 min	Park et al. (2008)
Tartrazin	35 mg	Pestana, Moreira, and Olej (2010)
	5, 10, 20 mg every 2 h	Nettis et al. (2003)
	10, 10, 20 mg	Di Lorenzo et al. (2002)
Erythrosine	50, 50, 100	Di Lorenzo et al. (2002)
Ponceau 4R	50 mg	Veien and Kroghdahl (1991)
	20 mg	Virchow et al. (1988)
Carmines	1,5,10 mg	Chung et al. (2001)
Amaranth	25 mg	Pollock and Warner (1990)
	5 mg	Ehlers et al. (1998)
Sunset Yellow FCF	25 mg	Pollock and Warner (1990)
	5 mg	Ehlers et al. (1998)
Indigotine	5 mg	Ehlers et al. (1998)

ADI – Acceptable Daily Intake.

selected without consideration of the levels obtained from average food items and daily food intake (Nettis, Colanardi, Ferrannini, & Tursi, 2003); (Fuglsang et al., 1994). In Table 4 recommended challenge doses for FCs are presented. These doses are related to a mixed age population, based on the commonly consumed quantities of each agent, and are determined according to DBPCFC.

A pseudoallergen-free diet can be an alternative option to for determining the possibility of hypersensitivity to food additives as a cause of CIU. A pseudoallergen-free diet has been reported to reduce the severity of CIU (Di Lorenzo et al., 2005; Magerl, Pisarevskaja, Scheufele, Zuberbier, & Maurer, 2010). Magerl and colleagues tested a pseudoallergen free diet on 140 patients with CIU and showed that in one in three this resulted in improvement of the urticarial symptoms and/or quality of life (Magerl et al., 2010). A pseudoallergen-free diet, however, restricts consumption of all preserved and processed food, and even all spices and herbs, eggs, cakes, biscuits, tomatoes, fresh and dried fruits, apart from salt and chives, and is therefore, it is hard to carry out in real life and might cause nutritional imbalance (Bunselmeyer et al., 2009).

11. Treatment

Patients with confirmed sensitivities to FCs should avoid foods with these additives under the guidance of an allergist and a clinical dietician. FCs are characterized as food additives; hence a food color additive-free diet is effectively an additive free diet. A trial of the effectiveness of a food color additive-free diet for 3–5 weeks in ameliorating symptoms, can be of substantial help in supporting or ruling out suspicion of FCs (Bunselmeyer et al., 2009; Magerl et al., 2010). Patients on such a diet need to consume only homemade meals prepared with known ingredients and to avoid all commercial and pre-prepared food during the diet period. If the patient improves on the additive-free diet, the next step is to perform a series of challenges with the available additives (Wilson & Bahna, 2005). Once the offending color additive is identified, the patient (or parent) should be provided with all the names of that specific additive and the products that might include it. It is important also for the patient (or parent) to read labels and ask questions about commercially prepared foods, in order to avoid consumption of FCs shown to cause reactions (Rangan & Barceloux, 2009). Antihistamines are usually adequate to treat mild hypersensitivity symptoms such as itching, urticaria, and rhinitis. Certain patients with mild, predictable reactions may benefit from daily prophylaxis or pretreatment with antihistamines to enable them to tolerate the offending food ingredients (Ramesh, 2008). Patients with asthma who have food sensitivity should carry rescue inhalers at all times; patients with a history of severe reactions may also need to carry

rapid self-injectable epinephrine devices (Shah & Pongracic, 2008). Since there is always a chance of inadvertent exposure, an appropriate treatment plan should be developed for individual patients, particularly those with anaphylactic or severe reactions. Such patients should wear a medical identification tag (e.g., MedicAlert) and have self-injectable epinephrine available at all times (Lieberman, 2014).

To the best of our knowledge, no studies have demonstrated any role for desensitization to food additives.

12. Concluding remarks

The role of FCs is becoming ever more important with the increase in consumption of highly processed foods due to the changing lifestyles of modern world citizens. Adverse reactions of FCs can be IgE and/or non IgE mediated and are usually mild, rarely leading to anaphylaxis. Currently, the food industry is attempting to limit the use of FCs by decreasing to a minimum the amount in each product and/or by replacing FCs with foods with coloring properties, where this is possible. Nevertheless, the daily intake of FCs by children can be high in cases of excessive consumption of various foodstuffs containing FCs. Despite this, the prevalence of adverse reactions attributed to their use is very low in the general population, although it is slightly higher in atopic individuals. A discrepancy between self-reported or parent-reported adverse reactions to FCs and those proven by DBPCFC has been described clinical practice. With the exception of relatively few natural additives, skin testing and *in vitro* testing are unreliable as screening methods. The institution of a trial of an additive free diet may be helpful for diagnostic purposes. There is a current tendency for the food industry to use more natural colors as an immediate alternative to FCs. Careful studies regarding natural additives must be carried out, to demonstrate their safety and to ensure that they do not become a source of further controversy.

Conflict of interest

This study did not receive any specific grant from funding agencies in the public, commercial, or non-profit sector.

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