

Food Colorings and Flavors

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KEY CONCEPTS

- Food flavorings and colorings are often derived from potential allergens.
- The overall prevalence of reactions attributable to food colorings and flavorings is thought to be low.
- Carmine/cochineal extract, annatto and spices are the most commonly implicated agents in this group.
- Current labeling regulations for these agents make identification of potential allergens a difficult task.
- The Food and Drug Administration has proposed a change in labeling requirements for carmine/cochineal extract.

Food colorings and flavors are essential parts of the experience of eating that have existed for centuries. Though their inclusion is often an afterthought in our consumption, ultimately, the colorings and flavorings are at the core of what we enjoy about eating our favorite foods. In many processed foods, coloring and flavoring are inseparable from the food's identity in the eyes of the consumer and the corporate production of the food itself.

The use of both synthetic and biogenic sources for color and flavor is a common practice. Most of these pose no risk of adverse events. However, there is a growing body of medical literature regarding adverse reactions involving food colorings and flavors derived from both synthetic and non-synthetic sources.

This chapter will discuss non-synthetic food colorings and flavorings that have been implicated in adverse food reactions. We will review known mechanisms of reaction, treatment strategy, and legislation involved in changing the way that colors and flavors are used in foods. Synthetic color additives are discussed elsewhere in this book.

Food colorings

Background history

According to the United States Food and Drug Administration (FDA), food colorants are any dye, pigment, or substance that imparts color when applied to food. Both synthetic and biogenic sources are used for this purpose [1]. Coloring influences one's acceptance of food, but also aids food

manufacturing in several ways. Coloring is essential to correcting loss of a product's true color from exposure to light, air, temperature, moisture, or the elements involved in storage. It can be useful in correcting natural variations in color between products, to make them appear more uniform in quality to the consumer, or to enhance and augment an appearance of a natural occurring color. Coloring is also a useful marketing tactic to give otherwise colorless substances identity, or to make them appear more festive. Coloring can also be essential to protect vitamins and flavors that can be damaged from direct sunlight [2–4].

There is a lengthy relationship between food coloring and adverse reactions attributed to such coloring. One of the first recorded case reports was from 1848, involving 21 individuals at a public dinner poisoned by copper arsenite, which was used to color a dessert green [4]. By 1900, it was estimated that there were 80 synthetic color additives available for use in foods, but there were no regulations pertaining to the quality and use for these dyes. The Food and Drug Act of 1906 created the first seven dyes "certified" for use in foods, and established a voluntary certification program for quality and purity. Initial control of this process was under the United States Department of Agriculture (USDA). However, in 1938, authority and responsibility for this process was transferred to the FDA [1–3,5]. Three separate categories were additionally created to delineate food manufacturing processes from other use of colors: FD&C (Food, Drug, and Cosmetic), D&C (Drug and Cosmetic), and External D&C (External Drug and Cosmetic) [1–3,5].

There was a paucity of further legislation until the Food Additive Amendment of 1958, which declared that food additives safely in use before 1958 were exempted from obtaining FDA approval. However, in 1960, the Color Additive

Amendments to the FDA act of 1906 created a “provisional” listing for all known colors in use for foodstuff [1–3,5,6]. This act required that all previously certified dyes and colors used in food undergo further testing to establish safety before they were re-certified. Manufacturers were given a provisional time allotment in which they could continue using the particular color on the market, while submitting the required data regarding safety to the FDA. Other types of additives were exempted from this act. This act also set limits to usable amounts of color in products, deemed good manufacturing practices [1–3,5].

Specifically, one section of the 1960 amendment, known as the Delaney Clause, placed a strict prohibition on the use of any amount of a substance shown to be carcinogenic in humans or laboratory animals [1–3,5,6]. This clause was applied to additives as well, though they were exempt from the rest of the amendment. The market effect of the 1960

Color Additive Amendments was the reduction of a list of 200 provisionally approved colors to a final list of 90 that were deemed safe for human consumption, after meeting newly applied regulations [1–3,5,6]. Colors that did not meet the new standards were removed from the market. Interestingly, the Delaney Clause had a vague definition of safety beyond establishing lack of carcinogenesis, and established no absolute standard for safety beyond “convincing evidence that establishes with reasonable certainty that no harm will result from the intended use of the color additive” [3,6].

The amendment also designated two distinct classes of colorants: certified and non-certified [1–3,5–7]. Colors exempt from certification were given this designation if certification was deemed unnecessary in the interest of public health to examine the color batch physical properties, including: purity, moisture, residual salts, unreacted intermediates, color

Table 34.1 Colors exempt from FDA certification (Adapted from www.cfsan.fda.gov, updated September 2006.)

Color additives approved for use in Human Food Part 73, Subpart A: Color additives exempt from batch certification:

21 CFR section	Straight color	EEC#	Year approved	Uses and restrictions
73.30	Annatto extract	E160b	1963	Foods generally
73.40	Dehydrated beets (beet powder)	E162	1967	Foods generally
73.75	Canthaxanthin	E161g	1969	Foods generally, NTE 30 mg/lb of solid or semi-solid food or per pint of liquid food; May also be used in broiler chicken feed
73.85	Caramel	E150a–d	1963	Foods generally
73.90	-Apo-8'-carotenal	E160e	1963	Foods generally, NTE: 15 mg/lb solid, 15 mg/pt liquid
73.95	-Carotene	E160a	1964	Foods generally
73.100	Cochineal extract	E120	1969	Foods generally
	Carmine		1967	
73.140	Toasted partially defatted cooked cottonseed flour	–	1964	Foods generally
73.160	Ferrous gluconate	–	1967	Ripe olives
73.165	Ferrous lactate	–	1996	Ripe olives
73.169	Grape color extract	E163?	1981	Non-beverage food
73.170	Grape skin extract (enocianina)	E163?	1966	Still and carbonated drinks and ades; beverage bases; alcoholic beverages (restrict. 27 CFR Parts 4 & 5)
73.200	Synthetic iron oxide	E172	1994	Sausage casings NTE 0.1% (by wt)
73.250	Fruit juice	–	1966	Foods generally
			1995	Dried color additive
73.260	Vegetable juice	–	1966	Foods generally
			1995	Dried color additive, water infusion
73.300	Carrot oil	–	1967	Foods generally
73.340	Paprika	E160c	1966	Foods generally
73.345	Paprika oleoresin	E160c	1966	Foods generally
73.450	Riboflavin	E101	1967	Foods generally
73.500	Saffron	E164	1966	Foods generally
73.575	Titanium dioxide	E171	1966	Foods generally; NTE 1% (by wt)
73.600	Turmeric	E100	1966	Foods generally
73.615	Turmeric oleoresin	E100	1966	Foods generally

NTE: Not to exceed.

impurities, other specified impurities, and presence of heavy metals [5]. Generally, this exemption was applied to a particular color that was from a biogenic source, with a history of use prior to the amendment, and without complaints of toxicity or allergic reactions to the FDA or its manufacturer [1–3, 5–7]. Colors exempt from FD&C certification are still subject to the standards of the Delaney Clause of the Color Additive Amendment [6]. In reality, there are virtually no restrictions applied to use of either non-certified colors in food manufacturing. One notable exception is for colors to be used in meat and poultry, which requires additional authorization from the USDA Food Safety Inspection Service (FSIS) above the FDA approval (Table 34.1 and Fig. 34.1) [5].

Color additives in the United States are regulated by the FDA Title 21 of the Code of Federal Regulations (CFR) part 73, subpart A (colors not subject to batch certification) and part 74, subpart A (colors subject to batch certification) [8]. As part of this legislation, all certified colors carry an FD&C or D&C color label and have undergone rigorous testing to establish their safety and batch purity, in contrast to their non-certified counterparts, as explained in the previous section. In 1990, the National Labeling and Education Act (NLEA) required that certified color additives must be declared on package labeling as individual ingredients as of July 1, 1991, regardless of their quantity in the item [9]. Biogenic colors were exempt from this requirement and

therefore may be referred to on labels as “artificial color,” “artificial color added,” or “color added” [8]. The use of the term “natural color” is not allowed as it could imply that the coloring might be derived from the food item itself, when in fact it is referring to an additive. As will be discussed in detail in the section on carmine, the unique labeling requirements for non-certified colors has become a controversial issue, as there are increasing numbers of case reports of biogenic color induced hypersensitivity [10]. Since certified colors (azo and non-azo dyes) are discussed in detail elsewhere in this book, henceforth, we will be referring to colors exempt from certification only.

An important distinction of how colors are used in foods and drugs is between dyes and lakes. A color dye is a water-soluble form of color (liquid, powder, or granule), and a lake is a water-insoluble form. Lakes are more stable than dyes and are better for use with fat or oil. Most pharmaceuticals use lakes in their coatings. A major technical advantage of certified colors is that they often require less chemical to produce an intense color, allow for more uniform distribution of color, and do not influence the flavor [1,2].

Biogenic colors are believed to contain low molecular weight non-protein chemicals, most likely acting as haptens when they elicit reactions. Reactions to this class of colorants can be both immunologic and non-immunologic. There is growing concern that biologic source contamination

Name	Hue	Common uses
Annatto	Orange	Dairy products, popcorn oil, butter mixes, baked goods, icings, snacks, ice cream, salad dressing, yogurts
Beta-carotene	Orange	Margarine, non-dairy creamers
Beet powder	Purple	Ice cream, cake icings, mixes, yogurt, gelatin desserts, fruit chews, frozen products, chewable tablets
Caramel color	Brown to red	Dairy foods, drinks, colas, iced tea, cocoa, beer, coffee, icings, cereals, popcorn, gravies, sauces, candies
Carrot oil	Orange	
Carmine	Wine red	Cake icings, hard candy, bakery products, yogurt, ice cream, gelatin desserts, fruit syrups, pet foods, jams/preserves
Fruit juice	Many colors	Beverages, jellies, candy, gelatin desserts, dry mixes, dark chocolate
Paprika	Red-orange	Sausage, cheese sauces, gravies, condiments, salad dressings, baked goods, snacks, icings, cereals
Riboflavin	Yellow-orange	
Saffron	Yellow-orange	
Turmeric	Yellow	Baked products, dairy products, ice cream, yogurts, cakes, cookies, popcorn, candy, cake icings, cereals, sauces, gelatins
Vegetable juice	Many colors	

Figure 34.1 Pictorial of the non-certified color additives. (Adapted and modified from www.red40.com.)

in the colorant is the source of IgE-mediated reactions attributed to them [7,10]. Annatto and carmine/cochineal extract have both been linked to such reactions in the literature [7]. Because these colors are non-certified, it is difficult to ascertain the purity of a particular lot of these dyes. Thus, there could be varying levels of biogenic protein contamination due to technical discrepancies in different batches. There have been a few reports of SDS-PAGE analysis of carmine and cochineal insect protein fractions to determine their allergenicity, but there has been nothing conclusively nor consistently proven in this analysis [11–15]. At present time, despite several lobbying efforts by consumer groups, there has been no change made to the reporting of biogenic colors on food labels, though a specific petition to declare carmine on food labels is under consideration [16]. This petition and the subsequent FDA recommendation will be discussed in detail in the section covering carmine.

Biogenic colorants involved in hypersensitivity reactions

Only a few biogenic substances have been linked to allergic type reactions. These include carmine (cochineal extract), annatto, turmeric, saffron, beta-carotenoid, and grape anthocyanins. However, the majority of the literature pertains to carmine, with a small amount pertaining to annatto.

Carmine

Carmine is a red color derived from the female insect *Coccus cacti* or *Dactylopius coccus costa* [3,7,10,17–19]. This insect is commonly found in Peru, Central America, and the Canary Islands, where it grows as a parasite on the prickly pear cactus *Noplae coccinelliferna*. Its origins in Europe date back to the 1500s, when Hernando Cortez discovered its use by the Aztecs and brought the cochineal insects back to Spain [20]. The color is produced from the aqueous–alcohol extract of the dried, gravid, female insect, resulting in cochineal extract. Cochineal extract contains approximately 10% carminic acid, a hydroxyanthraquinone, and the rest is the residual insect body. Cochineal extract is acidic, and the color variation from deep red to orange is dependent on the pH. Carmine is produced from the aluminum or calcium aluminum lake on an aluminum hydroxide substrate of carminic acid. Since the lake is minimally soluble in water, strong acids or bases can be used to make the color more soluble. Commercial preparations of carmine are estimated to contain approximately 20–50% carminic acid, but it is usually diluted to 2–4% for sale. Commercial cochineal extract contains 1.8% carminic acid. Carmine is relatively expensive to produce. It is estimated that it requires 70,000 dried insects to make 1 lb of dye (Figs 34.2 and 34.3) [3,7,18].

Carmine was given approval by the FDA for use in food in 1967, and cochineal extract in 1968 [21,22]. As part of this approval, it was determined that carmine or cochineal extract had no carcinogenic or teratogenic properties in

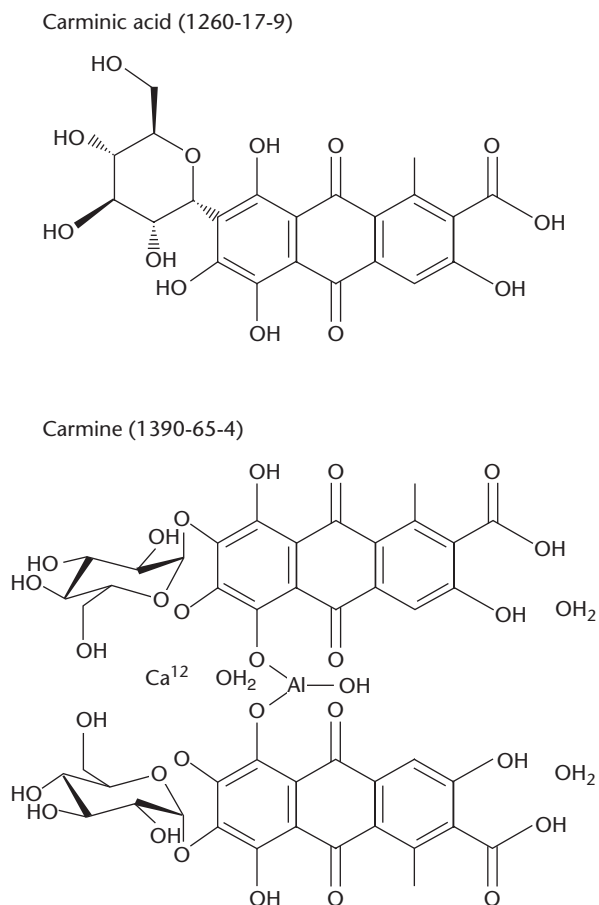


Figure 34.2 Chemical structures of carminic acid and carmine.

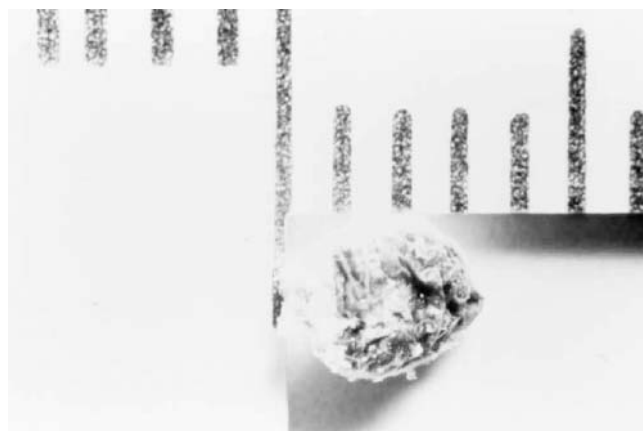


Figure 34.3 Photo of dried cochineal insect.

studies on rats. Carmine, as a biogenic color, is not certified, and therefore is exempt from specific declaration on food labels. It is generally labeled as “color added,” “artificial color” or “artificial color added,” “colored with carmine,” “cochineal extract,” or “carmine color.” In Europe it is designated as E120 by the European Union, and may be labeled as “Natural Red No. 4” or CI 75470 (color index).

Table 34.2 Commercial uses of carmine/cochineal extract

Water-insoluble carmine colors	Water-soluble carmine colors	Water-soluble cochineal
Cosmetics	Yogurt	Beverages
Pharmaceuticals	Ice cream	Yogurt
Dairy products	Fruit-based drinks	Ice cream
Baked goods	Beverages	Fruit fillings
Condiments	Fruit fillings	Puddings
	Puddings	Confections
	Bakery mixes	
	Confections	
	Cosmetics	
	Pharmaceuticals	

Carmine is also used in cosmetics, where it had been required to be declared as an ingredient since 1977, but in order of its relative weight per volume of cosmetic (Table 34.2) [3,7,8,10,23].

Most foods colored with carmine contain very low levels that would limit exposure when consumed [7]. However, there are several case reports of hypersensitivity reactions attributed to carmine ranging from anaphylaxis to occupational asthma (see Table 34.3). Though these reports are uncommon, the actual incidence of these reactions is unknown under the current labeling regulations. This is because suspicion for a substance not listed by name on a label is generally non-existent. Hence, it is important for an allergist to be aware that this is a potential allergen.

Since levels of carmine in food are low, our group (Baldwin *et al.*) and others have hypothesized another likely route of sensitization (e.g. respiratory or dermatologic). Most of the reported cases involve workers with occupational exposure, or females with a prior history of use of carmine containing cosmetics [12]. Carmine was approved for use in cosmetics as a non-certified color in 1977, and is the only biogenic color allowed to be used around the eyes [23]. It is plausible that persons using makeup containing carmine can become sensitized through a cutaneous route. Upon re-exposure to carmine in food, an IgE-mediated reaction can occur. Similarly, occupational inhalation could cause sensitization in textile or dye workers exposed to high levels of carmine powder in the environment and cause an IgE-mediated reaction upon ingestion of carmine containing food or beverage. Carminic acid is a low-molecular weight molecule and may act as a hapten during sensitization. Protein remnants from the cochineal insects are likely candidate antigens as well. Most authors believe that there is chemical modification of the protein contaminants in the processing of the extracted carminic acid from the insect. Once sensitization occurs, low levels of exposure could result in hypersensitivity. However, no mechanism of sensitization has definitively been proven to date [7,10–12,19].

As of 2005, there were 35 reported patient-cases of hypersensitivity to carmine; 11 of these have been reported to the FDA under the MedWatch program, and the rest reported in the medical literature. There are no known reports of fatalities related to carmine [10,12]. The range of symptoms reported includes occupational asthma, extrinsic allergic aveolitis, chelitis, and food allergy manifesting as anaphylaxis, angioedema, bronchospasm and urticaria. There have been no consistent reports pertaining to time from exposure to symptoms, nor dose required to elicit symptoms [10,12]. The first case was reported in 1961, involving chelitis from a lip-salve that contained carmine [24]. In 1997, our group successfully showed there was a definitive IgE-mediated reaction in a 27-year-old-woman with anaphylaxis to a red-colored ice-pop containing carmine by the use of a Prausnitz–Küstner test [19]. Other groups have shown the reactions were IgE mediated through prick skin tests (PSTs) [11–15,19, 25–32], leukocyte histamine release test [29], radioallergosorbent testing (RAST) [12,27,28,30–32], and immunoblotting for specific IgE [11–15].

Reactions have been reported with two common predominating phenotypes, food hypersensitivity and occupational respiratory disease. In the occupational respiratory disease phenotype, these cases involve predominately males with no atopic background. In the food hypersensitivity phenotype, all case reports have involved females, half of whom were atopic. Two of these females also showed occupational disease features, and many have described prior episodes of itching and burning with application of makeup, suspicious for contact reactions [12]. There have been four distinct reports via the FDA MedWatch program of contact dermatitis, comprising a small third phenotype of reaction [10].

Immunoblot analysis of persons with occupational respiratory disease and food hypersensitivity phenotypes have shown mixed results. Typically, authors have used both carmine and pulverized cochineal insect extract, subjected to SDS-PAGE and column chromatography fractionation to determine protein bands. Subsequent immunoblotting with patient sera has determined IgE-recognized protein bands [10]. However, investigators who have performed these experiments have not found consistent recognition of any particular protein band in either carmine, pulverized cochineal insect, or carminic acid [11–15]. Our group found that commercial carmine could inhibit recognition of pulverized cochineal insect bands, strong evidence that there is insect protein contaminant in the commercial dye [25]. A recent immunoblot study confirmed this finding and inferred that these proteins undergo chemical modification in the commercial processing of carmine [12]. Groups have identified proteins 17, 28, 38, 50, 88, and 40–97kDa in size. However, there is no universally recognized specific protein band found in carmine or cochineal extract, and there is considerable overlap when examining the reported data [11–15]. Considering that carmine is non-certified and exempt from

Table 34.3 Known reported cases of carmine hypersensitivity

Author	Year	Refer- ence	Sex	Atopy	Exposure route	Reaction	Occupation	Prick test	Specific IgE	Challenge	Immunoblot Bronchial	Notes
Sarkany <i>et al.</i>	1961	[24]	three patients*	NA	Cutaneous-lip-stick	Contact dermatitis		Positive patch test	No	No	No	First known report in medical literature
Burge <i>et al.</i>	1979	[33]	M, M	Both	Inhalation	Bronchospasm	Factory workers	Not performed	Not performed	Not performed	Both positive	
Park <i>et al.</i>	1981	[37]	M	NA	Cutaneous-lip-stick	Anaphylaxis	Soldier	Not performed	Not performed	Not performed	Not performed	
Tenabene <i>et al.</i>	1987	[26]	F, M, M	None	Inhalation	Bronchospasm	Spice/food handlers	Female negative, males positive	Not performed	Not performed	All three positive	
Quirce <i>et al.</i>	1994	[27]	M, F, M	None	Inhalation	Bronchospasm	Dye factory workers: manufacturer (M), cleaning staff (F), ex-worker (M)	All positive	Manufacturer positive, other two negative	Not performed	Positive in manufacturer only	Ex-employee left company because of allergic aveolitis prior to discovery of this problem
Kägi <i>et al.</i>	1994	[28]	F	Yes	Ingestion – Campari-Orange	Anaphylaxis		Positive	Yes – initial RAST negative, class 2 at 1 year later	Not performed	Not performed	First case of reported anaphylaxis due to ingestion
Beaudouin <i>et al.</i>	1995	[29]	F	None	Ingestion – fruit-flavored yogurt	Anaphylaxis		Positive	Not performed	Not performed	Not performed	First positive basophil histamine release test reported
Stücker <i>et al.</i>	1996	[30]	F	None	Inhalation	Bronchospasm	Food factory worker	Positive	Positive	Not performed	Not performed	
Wütrich <i>et al.</i>	1997	[31]	F, F, F, F	Three of five	Ingestion – alcoholic beverage	Anaphylaxis		All five positive	All five positive	Not performed	Not performed	
Baldwin <i>et al.</i>	1997	[19]	F	Yes	Ingestion – red popsicle	Anaphylaxis		Positive	Positive (P-K test)	Not performed	Not performed	Only known P-K testing done to carmine. Additionally, this case was reported by patient to FDA MedWatch program
Acero <i>et al.</i>	1998	[13]	M	None	Inhalation and ingestion	Bronchospasm, rhinoconjunctivitis	Spice factory packer, non-manufacturing	Positive	Not performed	Positive (no molecular weight determined)	Positive	
DiCello <i>et al.</i>	1999	[25]	F, F	None	Ingestion – artificial crabmeat, fruit flavored yogurt	Anaphylaxis		Positive	Not performed	Not performed	Not performed	
Lizaso <i>et al.</i>	2000	[14]	M, F, F	None	Inhalation	Bronchospasm	Dye plant worker, dye plant worker, dye plant chemist	Positive	Not performed	28 and 50 kDa band to pooled serum	All positive	
Chung <i>et al.</i>	2000	[11]	F, F, F	All 3	Ingestion	Anaphylaxis		Positive	Not performed	Patient 1: 28, 50 kDa; patient 2: 23, 50 kDa; patient 3: 88 kDa	Not performed	No patient sera recognized the same protein bands. Sera also tested to pulvarized cochineal insect and had bands recognized, with cochineal insect inhibition of carmine band

Tabar <i>et al.</i>	2003	[32]	F, F	Yes in 1	Inhalation	Bronchospasm	Dye factory clerical worker, dye factory laboratory worker	Positive	Positive	Not performed	Positive	
Anibarro <i>et al.</i>	2003	[15]	M, M	Both yes	Inhalation	Inhalation	Bronchospasm	Both butchers	Positive	Not performed	Both 10kDa	Positive
Ferrer <i>et al.</i>	2005	[12]	M	None	Inhalation	Bronchospasm	Spice blender	Positive	Positive	28 kDa	Positive	
Greenhawt <i>et al.</i>	2006	[36]	F	Yes	Ingestion and topical – generic azithromycin, fruit-flavored, yogurt colored pasta, eye makeup	anaphylaxis, local rash and angioedema	Office worker	Positive	Not performed	Not performed	Not performed	This is the first case report of exposure from a pharmaceutical source, in a patient with past history of carmine-induced anaphylaxis. She had tolerated the trade- named medication before and after the incident, and tested positive to both carmine and the generic tablet coating, which contained a carmine lake.
<i>The following 10 case reports were submitted to the FDA under the MedWatch program. All products reported in the table were verified to contain either carmine or cochineal extract</i>												
FDA MedWatch	1997	[10]	F	NA	Ingestion – Tropicana ruby red grapefruit juice; topical – purple eye shadow	Anaphylaxis; skin rash		Positive				PST positive to the grape- fruit juice, good and plenty candy, eye shadow also
FDA MedWatch	1997	[10]	F	NA	Ingestion – custard style strawberry banana yogurt	Anaphylaxis		Positive	Syrum tryptase of 18			PST positive to yogurt also
FDA MedWatch	1998	[10]	F	NA	Ingestion – SoBe fruit juice	Anaphylaxis		NA				Cochineal extract was declared on the bottle label; patient was admitted to the hospital for observation
FDA MedWatch	2000	[10]	F	NA	Ingestion – Crab soup, yogurt, candy, ruby red grapefruit juice, pasta salad with artificial crab meat	Anaphylaxis		Positive				
FDA MedWatch	NA	[10]	F	Yes	Ingestion – gelatin- based desert	Eyelid angioedema		Not performed				Patient called case in to the FDA, no work up done
FDA MedWatch	NA	[10]	F	NA	Ingestion – custard style yogurt, multiple cosmetics	Anaphylaxis (to the ingestion)		NA				Patient reports she was treated by an allergist but not specified

(Continued)

Table 34.3 (Continued)

Author	Year	Refer- ence	Sex	Atopy	Exposure route	Reaction	Occupation	Prick test	Specific IgE	Immunoblot	Bronchial challenge	Notes
FDA MedWatch	NA	[10]	NA	NA	NA	NA		NA				FDA conducted by a law firm to indicate that they were considering implicating carmine in the case of an allergic reaction in a client attributed to carmine
FDA MedWatch	1999	[10]	NA	NA	Ingestion – yogurt	Anaphylaxis		Positive				
FDA MedWatch	2000	[10]	F	NA	Ingestion, topical – neither specified	NA		NA				
FDA MedWatch	2000	[10]	F	NA	Topical – eyeliner	NA						Patient informed the FDA that she carries an EpiPen® for treatment when needed

Adapted from Refs. [10,12] and modified by author.
NA: Not applicable; F:Female; M: Male.
* Gender not listed.

batch certification, batch to batch variability secondary to this regulation might be playing a role in this finding.

Diagnostic investigations to determine IgE-mediated sensitivity to carmine are problematic due to lack of available standardized allergenic extract. Furthermore, the same problem of batch to batch variability of the commercially available stock could create reliability problems with development of a standardized PST using carmine extract. For these reasons, in a patient with high suspicion for carmine allergy, we generally recommend a simple PST using the suspicious foodstuff. If this is positive, then one should attempt to obtain a small aliquot of the dye from that particular food manufacturer for a confirmatory PST. If possible, obtaining a small commercial lot of carmine dye would be helpful for future testing, but our experience with this has been difficult, though we were ultimately able to do so. Most importantly, it has been this author's experience that the wheal and flare reaction to carmine-containing foods and manufacturer supplied carmine develops slightly later than with other extracts, generally between 20 and 30 minutes [11,19,25]. We do not perform intradermal challenge to carmine, nor do we routinely test to pulverized cochineal insect extract. Dried cochineal insects are more readily available than carmine dye, but of course the proteins present in the raw extract lack any of the potential chemical modifications contained in commercially processed carmine. A commercial IgE RAST does exist, but its validity has not been determined due to the small frequency of reported events.

Our group published the one study that used passive transfer to prove there was an IgE-mediated reaction, in which we were able to consent a married couple for a Prausnitz-Küstner (P-K) test [19]. This reaction, while exceptionally helpful in determining the presence of an IgE-mediated reaction, is no longer advocated for infection control reasons. Eight authors have described bronchial provocation challenges to carmine, cochineal extract, and carminic acid to measure a 20% decrease in FEV1 and to determine the dose that caused a 20% drop in FEV1, or PC₂₀ [12–15,26,27,32,33]. Other diagnostic techniques that have been used in practice include blinded oral challenge [11,25] and ocular challenge [11,13,27,33].

Persons with hypersensitivity to carmine face two large obstacles. The first is having a provider who can recognize this entity and has the resources to test for it. The second is being able to recognize and avoid products containing carmine. The exemption in labeling declaration for non-certified dyes creates a potentially dangerous environment for the uninformed consumer. Commercially sold cosmetics for general retail must declare all ingredients in "descending order of predominance," but colors can be declared without respect to predominance [34]. Presently, foods, prescription drugs, and cosmetics intended for "professional use only" (or are given as samples/free gifts and not meant for general

purchase) do not have to specifically declare the presence of any single color additive, by individual name, and instead can use the declaration "artificial color" or "artificial color added." Professional use cosmetics include salon products, studio products, and camouflaging makeup for disfigurement dispensed by a physician [21–23]. Foods such as butter, cheese, and ice cream are sometimes exempt from having to declare color additives [34]. Over-the-counter medications have recently been required to declare all inactive ingredients, including any type of color additives, as do non-oral prescription drugs [35].

Other than a small list of products anecdotally compiled by diagnosing providers, several MedWatch reports to the FDA, and the cases from the medical literature mentioned in this discussion, there is little information for sensitive individuals. Most recently we have reported a case that is believed to be the first case of carmine hypersensitivity from pharmaceutical exposure [36]. This is a further source of regulatory frustration, as it is presently voluntary as to what inactive ingredients are declared on the package insert for prescription drugs, though the FDA is presently recommending that this loophole be closed to require declaration of all inactive ingredients [10].

Carmine is the focus of a grass-roots style consumer-driven petition to change the labeling requirements for non-certified dyes. Presently, carmine/cochineal extract can be referred to for labeling purposes as "artificial color," "color added," but not "natural color" [21,22]. It is distinct from and should not be confused with Indigo Carmine (FD&C Blue #2), Cochineal Red (E124), Food Red 7, or Ponceau 4R. In 1998, The Center for Science in the Public Interest (CSPI), filed a petition with the FDA to review the labeling policies for carmine and cochineal extract, additionally requesting designation of the insect source for these dyes, formal study to determine the exact antigen in cochineal/carmine to see if it was a key component of the coloring, and to ban the dyes if necessary [10,16]. This petition was supported by the several known case reports in the medical literature at the time.

In January of 2006, the FDA published a proposed rule to amend the labeling regulations after an in-depth examination of the allergic properties of carmine and cochineal extract [10]. This was prompted after reviewing 11 MedWatch reports of allergic reactions attributed to carmine/cochineal extract, and 35 patient case reports in the medical literature, of which most had established the reactions were IgE mediated (see Table 34.3). The FDA investigation concluded the following [10]:

- Carmine/cochineal extract dye can cause hypersensitivity, but it is a rare event and they were unable to estimate neither an incidence nor report a conclusive mechanism.
- There is presently no conclusive evidence that there is biologic contamination of the cochineal insect proteins in the dye that cause hypersensitivity, though several groups

had discovered distinct protein bands in cochineal extract that were inhibited by carmine. This was based on no conclusive evidence in the medical literature that any one particular protein fraction was recognized universally in affected individuals studied.

The FDA's ultimate recommendation was that although carmine/cochineal extract is a definitive allergen, it poses no harm to the general public and therefore did not need to be prohibited from use. Furthermore, they felt there was no need for any further FDA-directed testing necessary to determine if the allergenic fraction is essential to the color. However, they did recognize that requiring specific name declaration of carmine and cochineal extract in products would aid recognition of the allergen in food sources for affected individuals. They are currently considering a proposal to amend the Federal Food, Drug, and Cosmetic Act, Title 21, part 73, § 73.100, 73.2087; and part 101, § 101.22 to allow the following changes, beginning January 30, 2008 if approved [10]:

- Require all foods, including butter, cheese, and ice cream, containing carmine or cochineal extract to label it as such by its "respective or common name," and immediately disallow it to be generically referred to as artificial color or color added.
- Require all cosmetics to declare the presence of carmine.
- Require all prescription drugs to declare the presence of carmine.

Annatto

Annatto is a natural carotenoid-based color dye made from the seeds of the fruit of the *Bixa orellana* tropical bush. The fruit has a pod full of approximately 50 seeds the size of grape seeds, covered in a red-pulp covering that serves as the base material from which the color is made [7,38]. The major pigment is cis-bixin, which gives a red coloration, but upon heating becomes trans-bixin, and with further heating breaks down to two compounds. One of these compounds is water-soluble for extraction (norbixin) and the other oil-soluble (bixin) [7,38]. In addition to yielding color extracts, it also yields edible vegetable oils and fats. Approximately 10,000 tons are produced each year, mainly in Latin America, Africa, and Asia. Annatto, as the bixin extract, is used as a colorant in fatty dairy products such as butter and margarine, and also leather [7,38,39]. As the norbixin extract it is used as a colorant in cheese. Norbixin is a very strong colorant in small quantities [7,38,39]. Annatto is also used as both a color and flavor in confections, meats, soda, and processed snacks [40]. It has particular use as an additive to butter and cheese flavorings to produce the desired color. It has been used for centuries, dating back to the ancient Aztec and Mayan civilizations, and imported for use later by the Spanish when they conquered Mexico [7,38,39].

Annatto is purported to have medicinal properties such as a cure for diabetes (no evidence), as an antimicrobial

(partial evidence), and as an anti-toxin for snake bites (partial evidence) [39]. As a natural color, it is classified as a non-certified dye under Title 21 CFR § 73.30 [41]. Outside of the United States, it is also labeled as CI Natural Orange No. 4, E160b, bija, rocou, orlean, or achiote.

Allergic reactions including urticaria, anaphylaxis, angioedema, asthma, and contact dermatitis have been attributed to annatto [42–48]. However, given the long-standing use of this colorant and the paucity of reported reactions, this is likely a rare hypersensitivity [7]. We do not know the actual prevalence of this hypersensitivity. In a 1987 study of the prevalence of food additive intolerances, Young *et al.* estimated the general population prevalence of hypersensitivity to annatto to be between 0.01 and 0.07 with a 95% confidence interval. This was extrapolated from data on 81 children in a study examining several additives [42].

The first report in the medical literature regarding annatto provoked hypersensitivity was from a 1978 study in patients with chronic urticaria, in which they were administered a dose of annatto. Though this study was severely flawed because it lacked double-blind placebo controls and took place in patients who had their controlling medications withdrawn, it did suggest that annatto could provoke reactions [43]. A similar study in 1981 in the same population type had identical flaws and similar conclusions [44]. Other attempts at using annatto to provoke symptoms in two open challenges and one double-blind placebo challenge were also either inconclusive or were flawed similarly to the earlier studies [45–47]. However, a 1991 case of a man with anaphylactic shock (urticaria, angioedema, and hypotension) developing within 20 minutes of consuming Fiber One® cereal colored with annatto, was the first reported case of anaphylaxis attributed to annatto. The authors were able to demonstrate positive PSTs at 1:1000 dilution and full strength annatto, in the setting of negative PSTs to corn, wheat, and milk. Subsequent SDS-PAGE fractionation of annatto yielded two bands between 50 and 60kD, of which the 50kD band was recognized by the patient's serum when an immunoblot was performed [48]. There is one report of annatto-induced bronchospasm attributed to a pharmaceutical product containing annatto, but the author did not attempt skin testing or other challenge to prove the suspected association [49].

There is limited data supporting an IgE mechanism for annatto hypersensitivity. This is based on the fact that there has been only a single case report of positive PSTs and specific protein fractionation and positive immunoblot analysis [48], and that the oral challenge data have not proven conclusive in the multiple trials, as discussed above [43–47]. Much like carmine, the significance of the recognized protein band on immunoblot is suggestive of a protein contamination from the biogenic source as the likely allergenic culprit, and not the actual pigment, but this is based on the interpretation of a single study [39]. Neither carmine nor

annatto has been studied further to determine if the pigment fraction is distinct from the protein recognized by IgE of patients with clinical sensitivity. In our clinics, we do test to annatto with PSTs in patients with a history suspicious for possible annatto-induced hypersensitivity. In such cases, we would recommend a stepwise workup analogous to that described for suspected carmine hypersensitivity. A commercial IgE RAST does exist (IBT Reference Laboratory, Lenexa, KS; Mayo Medical Laboratories, Rochester, MN) but its validity has not been determined due to the small frequency of reported events.

Other natural colors causing allergy

Table 34.4 summarizes the major case reports for several other colors to which clinical hypersensitivity reactions have been attributed. However, only a handful of these agents have had any conclusive test results.

Saffron is made from the dried stigmas and styles of the flower of the *Crocus sativa* L. plant [7,50,51]. This dark-yellow to dark-orange spice is among the most expensive of all spices. Its color is comprised of several components, including carthamine, saffron yellow A and B (saffron yellow), saffloamine A, ethereal oils (safranin, pinen, cineol), glycosides (picrocrocin), and pectins [50]. It is identified as E164 in Europe, by CI 75100, or as CI Natural Yellow 6. It is most commonly used as both a spice and color in soups, sauces, rice dishes, cakes, cheese, and chartreuse liqueur [7]. An anaphylactic reaction developing 5 minutes after eating a meal with saffron rice and mushroom was reported in a 21-year-old farmer with known oral allergy syndrome (OAS), who required emergent resuscitation after developing laryngeal edema, urticaria, oral itching, and gastrointestinal (GI) cramping [51]. His PST was positive to saffron and negative to the other components of the meal; furthermore, an IgE RAST to both retail saffron and pure saffron revealed specific IgE, and SDS-PAGE fractionation and immunoblotting to this patient's serum produced 40 and 90 kDa bands. However, he also tested positive by skin test and RAST to celery and cooked celeriac, though the reaction was ultimately attributed to saffron [51]. Additionally, another investigator demonstrated occupational disease in three saffron workers in a group of 50, one with asthma and two with rhinoconjunctivitis by history (confirmed with saffron provocation testing), who had positive PST and RAST to specific saffron pollen [52]. Ten controls from a general allergic population in this area (all were non-saffron workers without history of symptoms attributed to exposure to saffron) also displayed positive prick and RAST to saffron pollen. SDS-PAGE immunoblotting to saffron pollen and stamens revealed a 15.5 kDa protein with similarity to profilin in the combined 13 patients that had positive PSTs and RAST scores. In cross-pollen studies, immunoblot inhibition occurred with *Lolium*, *Salsola* (Russian Thistle), and *Olea* in the 8 of the 13 patients that had a class 3 or greater RAST

score. Thus it was thought that this cross-reactivity could potentiate an OAS, though it has not been reported [52].

Turmeric, an orange-yellow dye made from the ground powder of rhizomes of *Curcuma longa* Linnaeus plant, is a non-certified color additive and spice. Curcumin is responsible for the imparted natural color [7,53,54]. It is also labeled as E 100 in Europe, CI #75300, CAS (Chemical Abstract Society) #458-37-7, INS 100(i), and CI Natural Yellow 3. Turmeric has been used for centuries to enhance taste, and has much promise as a potential therapeutic agent for many diseases, mediated through curcuminoid induced decrease in NF- κ B expression [55]. It was studied, along with annatto and several other additives, in a series of oral challenges that were either inconclusive, or flawed in their design [45–47]. Thus, no evidence exists that turmeric causes a clinical allergy. However, there have been reports attributing allergic contact dermatitis to Turmeric [56]. A recent review of the immunomodulatory properties of curcumin goes beyond the scope of this chapter [313].

Carotenoids are another yellow-orange natural color used in butter, cheese, cereal, and other items. These compounds are derived from either biologic or synthetic sources carotenoids and are Vitamin A precursors. The natural coloring is from carotene, but the synthetic version is made from acetone, and is all-trans in chemical structure. Beta-carotene is an isomer of carotene. A related compound, canthaxanthin, isolated from the edible mushroom *Cantharellus cinnabarinus*, is another carotenoid compound used in food and also available as a synthetic color [7,50]. Carotenoids are also labeled as CI 40800 and CAS# 514-78-3. These coloring agents have rarely been implicated in causing allergic reactions. Oral challenges to beta-carotene were part of the studies discussed in the annatto and turmeric sections that were both flawed in design and inconclusive in determining if any of the additives studied, including carotenoids, caused hypersensitivity [44–46]. However, there is a 1978 case report describing atopic dermatitis, vomiting, colic, and restlessness in an infant being fed a diet with vitamin A drops and foods rich in beta-carotene. This author could not prove skin test reactivity to beta-carotene, but did show clinical sensitivity to vitamin A drops via a double-blind challenge. Thus, no mechanism for the reactivity of beta-carotene was shown in this case [57].

Anthocyanins are plant-derived glycosides that, in combination, are responsible for a red, blue, or purple color in fruits and vegetables [7,53]. Anthocyanoids are closely related to flavanols, and are produced from the same flavanoid biosynthetic pathway [58]. Grape color extract and grape skin extract are anthocyanin-containing colors that are used as non-certified color additives, as both an aqueous solution and water-soluble powder [53]. They are also labeled as INS 163 (ii). Grape color extract is made from Concord grapes, and is very similar to grape juice. However, its ratio of anthocyanins, tartrates, malates, sugars, and minerals differs. The water-soluble color is derived from 3-mono- and 3, 5 di-glucosides

Table 34.4 Known case reports of hypersensitivity to other non-certified colors besides carmine/cochineal extract

Coloring	Author	Year	Reference	Reaction	Specific IgE	Study comments
Saffron	Feo <i>et al.</i>	1997	[52]	Bronchospasm, rhinoconjunctivitis	PST, RAST, BCT, 15.5 kDa protein band	Case report
	Wuthrich <i>et al.</i>	1997	[51]	anaphylaxis	PST, RAST, 40 and 90 kDa protein bands	Case report
	Vein <i>et al.</i>	1987	[47]	Studied in children with eczema as part of double-blind placebo-controlled food challenge (DBPCFC) to multiple colorants	Not tested	Study inconclusive as it failed to achieve statistical significance of reactions versus placebo, and results were not reproducible in a second challenge
Turmeric, curcumin	Fugeisang <i>et al.</i>	1993, 1994	[45,46]	Studied as part of open challenge to multiple additives including natural colorants in these two related studies involving children with atopic symptoms	Not tested	Both studies inconclusive. Data in both was confounded as to true cause of observed reactions, as a color mixture was used for testing
	Greenbaum	1979	[57]	Atopic dermatitis, colic, irritability	PST negative, double-blind challenge to vitamin A drops positive	Case report of 9-month-old baby, no causative role of carotenoids confirmed however
Carotenoids	Juhlin	1981	[44]	Studied in open challenge in patients with chronic angioedema/urticaria see above	Open study	Poor study design with inconclusive results
Anthocyanins (grape) (see also references [58–74] for other cases related to grape)	Fugeisang <i>et al.</i>	1993, 1994	[45,46]	10 patients study examining the importance of lipid transfer proteins in fruits	Not tested, but demonstrated that grapevine lipid transfer protein has 60% sequence homology to that of apple	No actual reports of grape color extract or grape skin extract causing reactions, but because of presence of endochitinases and lipid transfer proteins, there is theoretical possibility of reaction if these remain
	Sanchez-Morge <i>et al.</i>	1999	[59]			

Pastorello <i>et al.</i>	2003	[60]	Study of 14 patients with history of reaction to grape (11) and wine (3)	Demonstrated that endochitinases 4A and B, as the key proteins responsible for allergy to grape but that 4A is responsible for reactions to wine. Also showed the lipid transfer protein had homology to peach lipid transfer protein and 24-kd protein homologous to the cherry thaumatin-like allergen was a minor allergen	This is one of the first characterizations of grape allergens
Kalogeromitros <i>et al.</i>	2005, 2006	[61,62]	Most recent case series involving anaphylaxis in 11 patients attributed to grape products including wine, grape leaves, raisins, grape juice, vinegar	PST; RAST; 9/11 patients HLA-DR11 positive	This is the first study with grape to look at HLA genes to see if there is allergen recognition effect. Additionally, demonstrated that grape and grape product allergy is more prevalent than thought in a Mediterranean population.
Paprika (see also references [79–81] for other cases)	Jensen-Jarolim <i>et al.</i>	1998	[63]	Study of sera of 11 patients with bell pepper allergy	Shows that bell peppers contain Bet v 1 and profilin homologues, and P23. Unlike the Bet v 1 homologue and profilin homologue, the P23-related protein was not destroyed in processing of paprika.
No actual cases of allergic reactions attributed to the use of paprika as a color have been reported, but these cases demonstrate that this is theoretically possible	van Toorenenbergen <i>et al.</i>	2000	[64]	Study of sera from three symptomatic greenhouse workers (multiple-allergic symptoms) and three food-allergic patients to see if paprika pollen sensitization existed in both groups	Recognition of paprika pollen is seen in non-horticultural workers and can be seen in the food-allergic population
Willeroider <i>et al.</i>	2003	[65]	34 serum positive patients allergic to bell pepper had serum drawn for cDNA cloning of bell pepper antigen	Used cDNA to clone the profilin protein Cap a 2 in <i>Capsicum annuum</i> and showed recognition of patient specific IgE by immunoblot analysis of a 14-kDa protein	Defines a clinical marker for profilin sensitivity and cross-reactivity in the bell pepper-allergic population

of malvidin, delphinidin, cyanin, and their acylated derivatives. Grape skin extract is made by steeping (aqueous extraction) fresh, de-seeded marc that is residual after pressing grapes into wine or juice. Again, its composition is similar to that of grape juice, but in different proportions [7,53,54]. Both grape skin extract and grape color extract are very expensive to produce because the color is found in trace quantities in most flowers, fruits, and vegetables (780–5000 ppm) and is difficult to extract. Anthocyanins are also found in purple corn, black carrot, passion fruit, and other exotic fruits as well. Most of the commercial color comes from either grapes or red cabbage [54]. Internationally, the color is known as E163 (Europe), cyaniding, delphinidin, malvidin, pelargonidin, peonidin, and petunidin.

Grape color extract is used in non-beverage foods. Grape skin extract is used in carbonated drinks, ades, beverage bases, and alcohol; additionally, both forms can be found in cherries used in ice cream and yogurt, fruit fillings, and candy/confections [54]. To date, there have been no case reports of allergy to grape skin extract or to grape color extract. Though rare, there are, however, several reported cases and a case series of grape and grape product (wine) induced allergic reactions, ranging from anaphylaxis to OAS to exercised-induced anaphylaxis [61,62,66–81]. One group found a trend of human leukocyte antigen (HLA) matching to HLA-DR11 in 9 of 11 patients, and additionally reported extensive cross-reactivity with other fruits (apples, cherries, peaches) [61,62]. It has been suggested by data in one study that grape products might have a common allergen in endochitinases 4A and B, which are lipid transfer proteins [60]. It is unknown if this protein is present in grape color extract or grape juice extract, but it could be a potential allergen in susceptible individuals if it is found in the extracts [60,62].

Paprika is a dark red, sweet powder made from dried, ground pods of the bell pepper *Capsicum annuum*. Paprika oleoresin is colored principally from capsanthin and capsaorubin, amongst other compounds. They are labeled as CAS # 68917-78-2 and INS 160c. Both paprika and paprika oleoresin are used as a color and a spice in canned goods, vegetable oils, processed meats, salad dressings, snack food coatings, popcorn oil, cheese, and confections [3]. Neither is allowed in cosmetics nor in drugs [82,83]. *Capsicum annuum* contains a profilin, Cap a 2, and the pollen of this plant has also been shown to sensitize horticultural workers and provoke IgE-mediated reactions [63,64,65,84–86]. Specifically, SDS-PAGE fractionation of paprika and sera immunoblot analysis revealed binding to protein bands at 30 and 60 kD [64]. There are also certain bell pepper species that express Bet v 1 and profiling homologues, and a pathogenesis-related protein P23 that can be key for IgE binding [63,87]. Despite the presence of profilin and Bet v 1 homologues, and evidence that there is a potential role for *Capsicum annuum* in latex-fruit syndrome [84], there have been no reported

reactions specifically attributed to paprika's use as a color. This is probably because the IgE binding capacity of the homologue to Bet v 1 and profilin is destroyed in the processing of the color/spice, though P23 has been shown to survive this processing [87]. Its allergenicity as a spice will be discussed later in the chapter.

Beet powder (CAS# 7659-95-2, INS 162, beetroot red, betanine), carrot oil, and toasted partially defatted cooked cottonseed flour have not been implicated in causing clinical allergy when used as a coloring agent. Cottonseed has shown homology to Jug r 1 and Jug r 2 in walnut (63) [88,89]. Cottonseed has caused anaphylaxis but its derived color has not [90–92]. Beet powder (beet juice base color) is used in fruit preparations, condiments, dairy, sauces, fillings, and candies. Carrot oil has been used in sauces, salad dressings, meat seasoning, pasta, margarine, and other foods. Additionally, titanium dioxide (CAS# 13463-67-7, CI 77891, INS 171, CI Pigment White 6) is also a non-certified dye for use in foods, such as confections, icings, cheese, medications, and cosmetics. It is restricted to 1% total of the product weight. There are no reports of allergy to its use as a colorant [3].

Food flavorings

Food flavorings are a heterogeneous group of supplements added in small quantities to foods to enhance flavor and quality. Flavorings are not primary ingredients because they are present in minute quantity compared to the main ingredients. Flavorings may be synthetic (artificial), natural, or derived from natural sources. The manufacturing process is thought to reduce the protein content of naturally derived flavors as protein is separated from the flavorful molecules, and therefore would generally be expected to reduce allergenicity. However, many parent compounds from which these natural flavors are derived may be allergenic [93]. Artificial flavors, products synthesized from aromatic alcohols or terpenes, are used either as solo agents or in combination to mimic natural occurring flavors [94]. The overall incidence of allergy attributed to food flavors is low, and these are rare events, but Type I and IV hypersensitivities have been described [93].

Taste and flavor have a unique biochemistry and neuro-proprioception. Flavor perception is a multi-factorial sensory input that is integrated into an overall unique experience [95,96]. It allows us to fully appreciate food while at the same time serving as a warning system against toxins, spoilage, smoke, or other unpalatable experiences [97]. This sensation has been conserved through our evolution [98]. Taste serves as an upstream trigger for digestive secretions [97]. Taste buds are located in specific areas of the tongue, palate, pharynx, larynx, epiglottis, uvula, and proximal esophagus. These require constant salivary secretions to maintain optimal taste perception [97]. Cranial nerves VII, IX, and X participate in receiving

and transmitting signals from taste receptors located within the taste buds when stimulated by a food molecule [97]. This process is transmitted from these receptors through selective ion channels, structure-specific receptors, and G protein coupled pathways. These signals are ultimately processed in the brainstem nuclei of cranial nerves VII, IX, and X, and the relative rates of signaling along these nerves is interpreted in the brain as a particular flavor [98,99].

Flavor components are generally considered to be low-molecular weight proteins, and thus too small to be considered allergens. Often these are considered volatile components [93]. Many natural flavors we encounter are the end product of chemical reactions that modify the original parent structure to arrive at the molecule that delivers flavor. This may involve heating, fermentation, distillation, concentration, or microencapsulation. The final product becomes a distinct form, such as an essence, powder, crystal, or emulsion. Artificial flavors are often similar in structure but unrelated to the natural component, yet they impart the same taste when we consume these flavors [93]. If a parent compound is allergenic, there is a distinct possibility that the derivative will be allergenic also. Though processing quite often separates the volatile flavoring from the protein, there can still be some contamination of protein allergens. Despite small molecule sizes, these particles may become allergenic as haptens. This is typical in Type IV reactions, seen when food has contact with mucosa for a prolonged period of time. It can also be a route of sensitization for Type I reactions as well. Many reactions attributed to flavors are seen in patients with a continual, high concentration occupational exposure [93].

Regulations and definitions

Flavorings are food additives and are regulated by the FDA in the United States, under the Food, Drug, and Cosmetic Act, CFR, Title 21, Part 101, § 101.22 [34]. All ingredients in commercially sold food must be labeled on the package, in descending order of quantity contained in the product. Unlike colors, flavors can be group labeled under the term “artificial and natural flavors” and do not have to be individually declared [34]. This contrast to the regulations for color was initially intended as a protection for corporations in the marketplace to maintain trade secrets (e.g. the formula to Coca-Cola®) [93]. There are several exceptions to this requirement for ingredients widely thought or known to cause reactions, such as sulfites [100]. However, many allergens still are undeclared [93]. This is problematic to the unsuspecting patient.

Flavorings derived from known allergens have produced reactions as “hidden” allergens. “Hidden” allergens are not so much hidden on the label as they are disguised by their true chemical names. One such example is milk, which is often labeled as casein, a milk protein, or when broken down further called hydrolyzed sodium caseinate, a natural flavor

derived from milk but conserving its antigenicity [101]. Protein derivatives, prior to 2006, were allowed to be labeled cryptically as their chemical breakdown product, or if they were natural flavors, did not have to be specifically labeled at all. The Food Allergen Labeling and Consumer Protection Act of 2004 (FALCPA) now mandates that as of January 1, 2006, all products containing the “big 8” protein allergens (milk, egg, fish, crustacean shellfish, tree nuts, peanuts, wheat, soy) must explicitly declare these items in the ingredient list in plain English (e.g. contains milk or soy) [102]. This measure is intended to allow patients to clearly identify potential allergens on the labels. These allergens were chosen because they cause approximately 90% of food allergies. However, in cases of factory-level contamination, such as ambient dust or use of the same conveyor belt line for different products, there is no requirement to label products with a “may contain ...” statement. Many products do have such a designation, but it is purely voluntary at this point [103].

The current definition of a spice, under the US CFR is “any aromatic substance in the whole, broken, or ground form, except for those substances which have been traditionally regarded as foods ... whose significant function in food is seasoning rather than nutritional, that is true to name, and from which no portion of any volatile oil or other flavoring principle has been removed” [34]. Spices are a special category of flavor, as they are derived exclusively from plants. Thus, they potentially harbor antigenicity. They are often used as both ingredients and additives. Spices that are also natural colors can be labeled as “spice and coloring” (e.g. paprika, turmeric, saffron). Spices can otherwise be labeled as spice, or as the actual spice if so desired. “Substances obtained by cutting, grinding, drying, pulping, or similar processing of tissue derived from fruit, vegetable, meat, fish, or poultry ... are commonly understood ... to be food rather than flavor and should be declared by their common name, meaning garlic powder must be labeled as such” [34].

Of the estimated 2% prevalence of food allergy internationally, spices represent 2% of this total [87]. Spices have been reported to cause anaphylaxis, asthma, and contact dermatitis [56,87]. Moreover, further confounding prevalence data on spice allergy is the fact that use of certain spices is dictated by cultural and regional dietary preference [87,104]. Prevalence of allergy to spice might also be influenced by occupational exposure, leading to increased sensitization, as has been noted with saffron and bell pepper workers [52,105,106]. As spices are flavors, they are present in minute quantities compared to the other ingredients, but have been known to cause allergy even at the low doses at which they are typically used. There is some question as to whether there is a threshold effect below which allergy cannot occur because the relative concentrations of spices in food are low [87]. However, the European Food Safety Authority (EFSA) issued a statement in 2004 that stated it failed to find sufficient evidence to establish such an intake

Table 34.5 Reported allergic reactions to spices

Spice	Family	Allergy	Specific IgE	Bet v 1 homolog	Profilin homolog	Other protein	Reference
Allspice	Myrtaceae	Contact dermatitis	None	None	None		[37, 107]
Anise	Apiaceae	Rhinoconjunctivitis, anaphylaxis	12, 20, 33, 34, 35, 37, 39, 40, 42, 48, 50–70kDa	Pim a 1	Pim a 2		[59, 108–115]
Basil	Lamiaceae	Contact dermatitis	PST, CAP-RAST	None	None		[115–119]
Bay leaf	Lauraceae	Contact dermatitis, perioral dermatitis, asthma	PST, RAST	None	None		[120–123]
Caraway seed	Apiaceae	Rhinoconjunctivitis, GI	20, 33, 34, 37, 39, 42, 48kDa	None	None		[59]
Cardamom	Zingiberaceae	Dermatitis	PST	None	None		[124, 125]
Cayenne	Solanaceae	Atopic dermatitis, bronchospasm	PST, RAST	None	None		[123, 126–130]
Celery	Apiaceae	Anaphylaxis, OAS	30–70kDa, including 55/58kDa (Api g 5)	Api g 1	Api g 4		[131–135]
Chervil	Apiaceae		None	None	None		None
Chili	Solanaceae	Atopic dermatitis, bronchospasm	None	None	None		[123, 126–130]
Chives	Alliaceae	Contact dermatitis		None	None		[136]
Cinnamon	Canellaceae	Bronchospasm, rhinoconjunctivitis, contact dermatitis, stomatitis, Type IV hypersensitivity	None	None	None		[37, 59, 85, 107, 117, 121, 124, 125, 128, 137–155]
Cloves	Myrtaceae	Contact dermatitis	None	None	None		[37, 85, 137, 151, 153, 154]
Coriander	Apiaceae	Bronchospasm, anaphylaxis, contact dermatitis	12, 20, 21, 33, 34, 35, 37, 39, 40, 42, 34, 35, 37, 39, 40, 42, 48, ~70kDa	Cor s 1	Cor s 2		[59, 85, 108, 117, 126–128, 155–160]
Cumin	Apiaceae	Anaphylaxis, contact dermatitis	20, 33, 34, 37, 39, 42, 48, ~70kDa	Cum c 1	Cum c 2		[59, 108, 109, 155, 161]
Dill	Apiaceae	Anaphylaxis, contact urticaria	12, 21, 35, 40kDa	None	None		[59, 111, 162–165]
Fennel	Apiaceae	Rhinoconjunctivitis, bronchospasm, atopic dermatitis	20, 33, 34, 37, 39, 42, 48, 50–70, 65, 75kDa	Foe v 1	Foe v 2		[59, 108, 110, 130, 155, 166–173]
Garlic	Alliaceae	Contact dermatitis, bronchospasm, rhinitis, anaphylaxis	10, 12, 20, 31–60, 40, 42, 54, 56kDa (alliin lyase)	None	None		[166, 174–200]
Ginger	Zingiberaceae	Contact dermatitis, bronchospasm, contact dermatitis	14, 23, 34kDa	None	None		[111, 117, 128, 155, 158, 201, 202]
Jalapeno	Solanaceae	Same as chili	None	None	None		[123, 126–130]
Lovage	Apiaceae		None	None	None		None
Mace	Myrsicaceae	Bronchospasm, contact dermatitis	See nutmeg	None	None		[85, 117, 120, 123, 125, 128, 155, 157, 158, 201, 203–205]
Marjoram	Lamiaceae	Atopic dermatitis, perioral dermatitis	PST, RAST				[119, 121, 206, 207]

Mustard	<i>Myrtaceae</i>	Anaphylaxis, Type IV hypersensitivity, contact urticaria	None	None	None	14 kDa (Bra j 1, Sin a 1) seed storage proteins	[89,127,158,208–212, 311]
Allspice							
Nutmeg	<i>Myristicaceae</i>	Bronchospasm, contact dermatitis	PST, RAST, histamine release assay	None	None		[85,117,120,123,125, 128,155,157,158,201, 203–205]
Onion	<i>Alliaceae</i>	Anaphylaxis, bronchospasm, contact dermatitis, rhinoconjunctivitis	12, 43 kDa	None	None	15 kDa lipid transferase	[182,193,213–222]
Oregano	<i>Lamiaceae</i>	Systemic reactions	PST, RAST	None	None		[117,119,123,207]
Paprika	<i>Solanaceae</i>	Contact urticaria, rhinoconjunctivitis	10, 17, 23 (Cap a 1w = osmotin-like), 24, 28, 29, 30, 32, 36, 40, 46, 69 kDa	None	Cap a 2		[63,64,85,105,106, 120,127,128,158,202, 223–231]
Parsley	<i>Apiaceae</i>	Angioedema, urticaria	None	Pet c 1	Pet c 2		[167,193,232–235]
Pepper	<i>Piperaceae</i>	Bronchospasm, contact dermatitis	11.8, 13.6, 14, 25, 28 (glucagon-like peptide), 30, 35, 40, 60 kDa	None	None		[63,85,120,124,126, 128,155,157,224,227, 229–231,236–239]
Pink peppercorns	<i>Anacardiaceae</i>	Atopic dermatitis (canine)	None	None	None		[240]
Peppermint	<i>Lamiaceae</i>	Contact allergy, anaphylactoid reactions, stomatitis	PST	None	None		[119,151,241–247]
Poppy seed	<i>Papaveraceae</i>	Anaphylaxis, exercise-induced anaphylaxis	5, 20, 25, 30, 34, 40, 45 kDa	None	None		[248–256]
Rosemary	<i>Lamiaceae</i>	Bronchospasm, contact dermatitis	PST, RAST	None	None		[123,257,258]
Saffron	<i>Iridaceae</i>	Anaphylaxis, bronchospasm, rhinoconjunctivitis	21 kDa (Cro s 1)	None	None		[51,52,93,201]
Sage	<i>Lamiaceae</i>	Bronchospasm, contact dermatitis	PST	None	None		[117,119,259–261]
Savory	<i>Lamiaceae</i>	Bronchospasm	PST	None	None		[123]
Sesame seed	<i>Pedaliaceae</i>	Anaphylaxis, bronchospasm, rhinitis, urticaria	10, 12, 14, 15–20, 15 (Ses i 5, oleosin), 17 (Ses i 4, oleosin), 25, 29, 32, 34, 45, (Ses i 3, vicilin-type globulin), 45, 52, 30–67, 78 kDa, Ses i 4, Ses i 5	None	None	7 (Ses i 2 2S), 9 kDa (Ses i 1 2S) seed storage proteins	[250,262–286]
Star anise	<i>Illiaceae</i>	Contact dermatitis	None	None	None		[287,288]
Tarragon	<i>Asteraceae</i>	Subglottic edema	28–46, 60 kDa in related mugwort (<i>Artemisia vulgaris</i>)	None	None		[285,289]
Thyme	<i>Lamiaceae</i>	Bronchospasm, atopic dermatitis, systemic reactions	PST, RAST	None	None		[119,123,206,290]
Turmeric	<i>Zingiberaceae</i>	Bronchospasm, contact dermatitis	None	None	None		[93,117,291–294]
Vanilla	<i>Orchidaceae</i>	Atopic dermatitis, contact dermatitis	None	None	None		[152–154,295–298,312]

Adapted and modified from Ref. [85].

threshold for spices that are on the food allergen list [299]. Because spices are also used to flavor other commercial products besides edible foods, there have been cases of reactions attributed to spices contained in cosmetics, toothpaste, fragrances, and massage oils [107,137,241,295,296,300–305].

Hot spices have some unique properties that make them more susceptible to potentially causing allergy. Piperine, in black pepper, can produce local swelling as a means to inhibit paracellular transport. Capsicum may increase its own paracellular transport across epithelium. Saponin, commonly found in plants, might have a detergent-like effect on gastric epithelium. In general, hotter spices can be sensitizing adjuvants by promoting transport of 70kDa or smaller molecules, a size previously determined to be relevant for IgE binding and sensitization in spice allergy [87].

Because spices have plant origins, they often contain their parent plant allergens that might survive processing, most commonly the birch pollen allergen Bet v 1 and profilin [116]. In hot spices, the grinding process destroys Bet v 1 (and homologues) and some profilins, but in roasted poppy seed they remain intact [108,157,248,307]. *Apiaceae* and *Solanaceae* family proteins tend to remain stable through various processing procedures, including roasting, grinding, and even cooking, increasing their allergenic potential in foods that are flavored with these spices [87]. Freezing was shown in certain lyophilized foods to increase the strength of PSTs [86]. Extensive cross-reactivity exists in oral pollen syndrome (OAS), most notoriously as described with celery–mugwort–birch–carrot, the so-called condiment syndrome [87,116,306]. The OAS is discussed in full detail elsewhere in this text. Spice allergy in this context would be secondary to a primary pollen allergy sensitization [87]. The cross-reactivity is stronger and more prevalent the more related the spice is to the primary pollen. Molecules such as Bet v 1 (and homologues) and profilins are generally responsible for the cross-reactivity, and therefore it can be inferred that the expression of these proteins in spices is testament to their functional importance in the plant from which the spice is derived. With sesame specifically, there is a seed storage 2S protein, identified in edible seeds and nuts including peanut that has been identified as binding IgE in both mustard and sesame [87].

In testing for spice allergy, clinical history is of utmost importance, as spices are minor food ingredients, and thus they might represent an unidentified cause of an allergic reaction (Table 34.5). Based on older data, skin testing, including prick-to-prick method in the absence of commercial extract, has shown more accuracy than RAST for specific IgE, though a combination approach is most commonly recommended [126,127,308]. Naturally, some ingredients in spice, when applied to the skin could be irritants. With both onion and garlic, bronchial provocation tests have been performed in the setting of spice workers [309]. One author described a leukocyte histamine release assay used with several different spices [310].

Summary

Food flavorings and colorings are a heterogeneous group of compounds that are often derived from potential allergens. Despite processing, allergenic epitopes or haptens that are recognized by specific IgE or cause Type IV reactions have been reported in the medical literature. Though the overall prevalence of reactions attributable to food colorings and flavorings is unknown, it is thought to be low. Current labeling regulations continue to make identification of potential allergens a frustrating process in susceptible individuals. Recent legislation has clarified the language used to label common allergens, and the FDA has created a proposal that is currently under consideration to require declaration of carmine/cochineal extract on product labels.

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PART 5

Contemporary Topics in Adverse Reactions to Foods