

Allergic and Immunologic Reactions to Food Additives

Fatih Gultekin · Duygu Kumbul Doguc

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Abstract For centuries, food additives have been used for flavouring, colouring and extension of the useful shelf life of food, as well as the promotion of food safety. During the last 20 years, the studies implicating the additives contained in foods and medicine as a causative factor of allergic reactions have been proliferated considerably. In this review, we aimed to overview all of the food additives which were approved to consume in EU and find out how common and serious allergic reactions come into existence following the consuming of food additives.

Keywords Food additives · Allergic reactions · Hypersensitivity · Asthma · Urticaria

Introduction

Food additives are widely used for facilitating and complementing a wide variety of production methods in the modern food supply. Food additives' basic functions are that they make food safer by preserving it from bacteria and preventing oxidation and other chemical changes of foods, and also

they make food look or taste better or feel more pleasing in the mouth [1].

Allergic reactions to food additives are a part of food allergies. Food allergy (hypersensitivity) is due to an immunologic reaction resulting from the ingestion of a food. The ingestion of food itself ends up with the greatest foreign antigenic load confronting the human immune system. Tolerance develops to food antigens, which are constantly gaining access to the body proper in most of the individuals. However, if formation of tolerance fails, the immune system responds with some kind of a hypersensitivity reaction [2].

The spectrum of food-induced reactions ranges from benign manifestations of disease, such as flushing or rhinorrhea to life-threatening symptoms such as systemic anaphylaxis with shock or enterocolitis syndrome. Following immune-mediated mechanisms are the basic mechanisms of adverse food reactions: IgE-mediated, non-IgE-mediated, eosinophilic disorders and allergic responses due to combinations of immune mechanisms. The most usual type of food allergy occurs due to IgE-mediated mechanism, of which anaphylaxis should be the best example for this type of allergy. IgE-mediated food allergic reactions are rapid in onset (usually within minutes to 2 h) and are the most widely known reactions associated with food additives.

Food additives are potential hidden allergens, and every human being is inevitably exposed to them everyday. In this study, our purpose is to review all of the food additives and find out how common and serious allergic reactions come into existence following the consuming of food additives. Although it is mentioned that the calculation of food allergy prevalence is so hard, a prediction of food allergy is indicated between 3% and 35% in literature [3]. Among sensitive subjects, potential of allergic reaction to food additives is reported as 0.03–0.23% [4]. However, we have to note that these ratios should vary from one to another which

F. Gultekin · D. K. Doguc (✉)
Medical Biochemistry Department, Medical Faculty,
Suleyman Demirel University,
Cunur, Isparta, Turkey
e-mail: duygukd@yahoo.com

D. K. Doguc
e-mail: doguc@med.sdu.edu.tr

F. Gultekin
e-mail: drfatih2000@gmail.com

F. Gultekin
e-mail: drfatih2000@hotmail.com

depends on the investigation or regional properties. In this review, the food additives which may trigger allergic reactions are classified into eight groups: (1) antioxidants, (2) colours, (3) emulsifiers and stabilisers, (4) solvents, (5) glazing agents, (6) preservatives, (7) sweetening agents and (8) thickeners. Although these food additives are classified into eight separate groups, each may have more than one function or effect so that is why functions of food additives should not be separated with absolute borders. The one having more than one function is mentioned in the text. For example, benzyl alcohol is discussed in solvents but also it should function as flavouring agent. Some of the additives discussed here are also ingredients of cosmetics, medicines, furniture etc. Food additives which caused an allergic reaction by inhalation or by topical administration but not by ingestion up to date are also reviewed because any substance caused individual allergic reactions by topical administration may also exert allergic reactions in various systems of an individual when applied by different routes. The knowledge about food additives were elicited from PubMed and JECFA web sites. In this review, food additives only approved to consume in EU were discussed.

Antioxidants

Antioxidants are used to delay the onset or the progression of rancidity of fats, oils and fat or oil-containing foods. They are also used to prevent oxidative discolouration (browning) and to prevent change in character of foods caused by exposure of air. In this part, the following antioxidants will be considered: butylated hydroxyanisole (BHA; E320), butylated hydroxytoluene (BHT; E321), dodecyl gallate (E312), octyl gallate (E311) and propyl gallate (E310).

Butylated Hydroxyanisole (E320) and Butylated Hydroxytoluene (E321)

These two substance were generally evaluated together in literature. Reus et al. reviewed Medline to link a causal connection exists between food additives and various medical complaints and found that there was no demonstrable link with medical symptoms for BHA and BHT [5]. However, Goodman et al. reported two patients with chronic idiopathic urticaria having exacerbations of their urticaria when they were challenged with BHA and BHT [6]. After elimination of BHA and BHT from their diets, there was marked abatement of the frequency, severity and duration of their urticaria. In addition, two cases of allergic contact dermatitis from BHA in Timodine cream were reported. Patch tests of both patients were negative when tested to analytical grade BHA but positive when tested to pharmaceutical grade BHA, as supplied

by the manufacturer Reckitt & Coleman [7]. Yamaki et al. investigated the effect of BHT on IgE-dependent allergic responses in vivo and in vitro. In the in vivo study with the rat mast cell line RBL2H3, findings indicate that BHT may upregulate passive cutaneous anaphylaxis by enhancing mast cell degranulation associated with augmentation of intracellular Ca^{+2} concentration and PI3K activation, and these data were suggesting that BHT might affect allergic diseases such as allergic rhinitis and asthma [8]. A case of a 37-year-old woman who was suffering from contact dermatitis which was welded from tertiary butylhydroquinone (TBHQ) in a hair dye, with cross-sensitivity to BHA and BHT, was reported [9]. Patch tests were then performed with the 20 ingredients of the hair dye, and results showed a strongly positive reaction to TBHQ. Hydroquinone, BHA and BHT were finally tested; positive reactions at D2 and D4 to both BHA and BHT had been showed. Le Coz et al. emphasized that cross reactions seemed to be possible between TBHQ and BHA and even BHT. White et al. routinely tested patients who suffered from facial dermatitis with BHA and tertiary butylhydroquinone during a 2-year period. Seven patients are reported who have been shown to have an allergic contact dermatitis to an antioxidant in their cosmetics or toiletries [10].

Gallates [Dodecyl Gallate (E312), Octyl Gallate (E311) and Propyl Gallate (E310)]

Gallates have been used in the cosmetics, pharmaceutical and food industries as antioxidants. García-Melgares et al. evaluated 46 patients with suspected contact dermatitis having positive patch tests for one or more gallates [11]. They found that the main complaints were cheilitis (63% of the cases) and dermatitis of the hands (28.26% of the cases); 15.2% of sensitizing agents were bakery products. The main allergen was propyl gallate, and the most common gallate among bakers was octyl gallate which was considered to be clinically relevant in all cases studied. Lomaga et al. investigated the role of contact allergy in precipitating and/or perpetuating oral lichenoid lesions. Fifty-six percent of patients with positive patch test results (nine patients) showed reactions to fragrances, flavourings, gallates and/or diallyl disulphide, the majority improved after avoiding these allergens [12] (Table 1).

Table 1 Allergic reactions or symptoms caused by antioxidants

Butylated hydroxyanisole and butylated hydroxytoluene	Triggers chronic urticaria [6], contact dermatitis [7, 9, 10]
Gallates	Contact dermatitis [11], cheilitis [11], precipitating oral lichenoid lesions [12]

Colours

Colours are used to impart, preserve or enhance the colour of food and also shading of a food, including colour stabilisers, colour fixatives, colour-retention agents etc. Legally, they are usually designated artificial (synthetic) or natural, which indicates that they are, respectively, synthetically manufactured or obtained from natural sources. Natural colours are usually extracted from botanical sources and often contain several pigments [13] (p 37).

Despite of widespread usage of food colourings, allergic reactions related to food colourings including the reactions triggered by immune (immediate and delayed-type hypersensitivity) or non-immune (intolerance) mechanisms are supposed to be very rare in the population with the prevalence of 0.14% to around 2% [14–16]. The following colouring agents will be reviewed in this section: 4-hexylresorcinol (E586), annatto/bixin/norbixin E160(b), indigotine/Indigo carmine (E132), cochineal/carminic acid/carmines (E120), Ponceau 4R/Cochineal Red A (E124), tartrazine (E102), Allura Red AC (E129), ferrous lactate (E585), erythrosine (E127), Sunset Yellow FCF/Orange Yellow S (E110), riboflavin-5'-fosfat (E101(ii)), Fast Green FCF (E143) and FD&C Yellow 10 [Quinoline Yellow WS (E104)].

4-Hexylresorcinol (E586)

4-Hexylresorcinol is used to prevent the development of melanosis (black spot) in shrimps and related crustacean and acts as an antioxidant and a colour-retention agent. There are few studies which investigated the allergic property of this substance. Keil demonstrated that two of eight subjects reacted positively to 4-hexylresorcinol in patch tests of patients with resorcinol-induced dermatitis [17]. Burrows and Irvine also reported a patient with contact dermatitis following occupational exposure reacted strongly to 4-hexylresorcinol in a patch test [18].

Annatto/Bixin/Norbixin (E160(b))

Annatto is a natural carotenoid-based colour dye made from the seeds of the fruit of the *Bixa orellana* tropical bush [19]. Annatto dye has been shown to provoke a severe, adverse reaction in individuals with an uncommon hypersensitivity in rare cases and might have aggravated the symptoms of patients suffering from recurrent urticaria [20]. A case with severe anaphylaxis with urticaria, angiooedema and finally loss of consciousness within a few minutes after consumption of an annatto-containing cheese has been reported [21]. In another case, a patient who developed urticaria, angiooedema and severe hypotension within 20 min following ingestion of milk and Fiber One cereal, which contained annatto dye was also reported [22]. Mikkelsen et al. orally

provoked 56 patients suffering from chronic urticaria and/or angioneurotic oedema by annatto extract during elimination diet. Twenty-six percent of them showed positive reaction to this colour 4 h after intake [23]. In a clinical investigation, one third of 330 patient who were suffering from recurrent urticaria were applied provocation tests with various food additives such as azo dyes, benzoates, BHT, BHA, sorbic acid, quinoline yellow, carotene, canthaxanthine, annatto and nitrite and revealed one or more positive reactions [24].

Another case of annatto seemed to be interesting that a woman's experience in identifying annatto as a probable cause of her severe irritable bowel syndrome was described in a letter to the Editor. A gastrointestinal workup, including colonoscopy, failed to reveal a cause in this patient. She had been using the coffee creamer, Coffee-mate, daily until she made a 37-day vacation and her symptoms abated with the exception of one recurrence after a cup of coffee with a non-dairy creamer. Off Coffee-mate again, an attack occurred with the ingestion of vanilla ice cream. It was then noted that a common constituent in both the coffee creamer and vanilla ice cream was the food colouring additive, annatto [25].

Indigotine/Indigo Carmine (E132)

Indigo carmine is generally believed to be safe, and in addition to its function as a food colouring, it has been widely used to identify and to examine the urinary tract by intravenous administration. However, adverse reactions to this dye should have been rarely seen. Gousse et al. presented a case of severe life-threatening anaphylactoid reaction followed by cardiac arrest which was associated with intravenous indigo carmine injection [26, 27]. A case of a 72-year-old woman who had a known sulfa allergy showed acute onset of chest pain and had difficulty in breathing after intravenous indigo carmine injection. Severe hypotension and bradycardia followed these complaints [28]. After eliminating the cardiac problems, authors indicated that in this case it was not clear if the reactions were anaphylactoid (related to the sulfa allergy) or idiosyncratic to indigo carmine.

Miller et al. documented a case of occupational asthma due to indigotine which was detected by bronchial challenge that was done according to the method of Pepys et al. [29]. A case which urticaria had occurred due to this dye in synthroid tablets was reported. After elimination of the dye from the tablets, urticaria was not recurred [30].

Cochineal/Carminic Acid/Carmines (E120)

Cochineal is a natural red colouring that is obtained from the dried bodies of the female insect *Dactylopius coccus* Costa. This dye does contain protein residues that were attributed to allergic reactions, sensitization and occupational asthma

[31–34]. A case of a worker with asthma and rhinoconjunctivitis for 5 months, related to carmine handling in his work, was reported and he also presented a similar episode after the ingestion of a red-coloured sweet containing carmine [31]. Tabar-Purroy et al. investigated the carmine induced occupational asthma at a natural dye processing factory and represented that incidence of sensitization and occupational asthma caused by carmine was 48.1% and 18.5%, respectively [34]. A 42-year-old non-atopic male presented with a 5-year history of rhinoconjunctivitis and asthma on occupational exposure to carmine dusts. Prick tests were positive to carmine and carmine-containing additives; also carmine-specific IgE and bronchial challenge tests were positive, and researchers suggested carmine as a potential sensitizer at the occupational asthma subjects [35]. Añibarro et al. reported two butchers with occupational asthma due to an IgE-mediated sensitization to carmine who used a mixture of additives with carmine as dye in sausages [36]. The responsibility of carmine in a case of anaphylaxis after ingestion of yoghurt was reported, and the results were confirmed with the skin prick test and leukocyte histamine release test. Although the acceptable daily intake is up to 5.0 mg per kg of body weight, 1 mg of carmine triggered an IgE-dependent mechanism in this case [37]. A case of a 33-year-old female who recurrently exhibited urticaria accompanied by vomiting, diarrhoea and dyspnea after taking red-coloured food was reported, and the prick and the scratch tests with cochineal dye and carminic acid were positive. These results indicated that type 1 allergy to cochineal dye caused urticaria in this patient [38]. A prospective open study over 8 months in a group of ten atopic children with repeated urticaria was conducted to find out the causative allergen, and carmine dye was presented to be the causative allergen in three of the subjects [39]. Yamakawa et al. encountered three and Wüthrich et al. reported five cases of anaphylactic reaction to carmine that appeared after consuming drinks containing cochineal extract [40, 41]. Greenhawt et al. reported a case of a woman with documented carmine hypersensitivity, who presented anaphylaxis 90 min after ingestion of a generic azithromycin. Investigations revealed that this was an allergy to the carmine dye in the tablet's coating rather than to the antibiotic [42]. A case of a 28-year-old woman developing allergic contact dermatitis within 6 to 24 h exclusively after using carmine-containing eye shadows and lipsticks was reported, and she had a positive patch test result. This case was suggested to be a delayed hypersensitivity reactions caused by carmine [43]. In conclusion, hypersensitivity reactions attributed to carmine ranging from anaphylaxis to occupational asthma were reported in several case reports [19, 44–46]. The possible allergen in carmine was investigated and results suggested that commercial carmine retained proteinaceous material from the source insects. These insect-derived proteins which would be possibly complexed with carminic acid were responsible for IgE-mediated carmine

allergy [32, 47]. Ohgiya et al. firstly identified a protein, which researchers named CC38K, with 335 amino acids, and a molecular mass calculated as 38 kDa was suggested to be the major allergen in cochineal extract [48].

Ponceau 4R/Cochineal Red A/New Cocchine (E124)

Ponceau 4R is an artificial azo dye. A case report was found in literature concerning allergic property of this additive, in which hypersensitivity reactions occurred following ingestion of a drug, Sintrom, an anticoagulant [49]. Allergic property has been confirmed by oral challenge test.

Twenty-five patients, aged between 18 and 153 months, were submitted to oral provocation test with different food additives included Ponceau 4R. The results showed a global level, 57.89% of positivities to dyes and the positive reaction to Ponceau 4R by oral provocation test was obtained in four patients [50]. Veien and Kroghdahl reported a case of a 24-year-old woman who was suffered from leukocytoclastic vasculitis (LCV). After placebo-controlled oral challenge with 50 mg Ponceau applied, a severe eruption of vasculitis occurred. The patient was asked to adhere to a diet free from food additives, and the vasculitis faded after a period of 2 months [51]. Sixty-one patients suffering from chronic urticaria and/or angioneurotic oedema were orally provoked by different food colourings, and 56 of them reacted to colouring additives, of which 15% of the patients reacted to Ponceau 4R [23].

Tartrazine (E102)

Tartrazine is an artificial azo dye commonly used in human food and pharmaceutical products. Tartrazine has been suggested to be responsible for triggering attacks of urticaria and asthma by several investigators, particularly in aspirin-intolerant patients [52]. A multicentric study, 156 patients who had aspirin-induced asthma underwent an open oral provocation test (OPT) at a dose of 25 mg of tartrazine which was confirmed on a double-blind trial. Only four patients reacted to the OPT, and the frequency of tartrazine intolerance was estimated to be 2.6% in aspirin-induced asthmatic patients [53]. In a more recent study, 102 patients (including two aspirin-intolerant patients) who experienced an acute episode of urticaria and acute angioedema following the ingestion of a meal or a product were investigated, and one of them was reacted to tartrazine (5 mg) resulted with facial oedema and urticaria associated with abdominal pain and slight hypotension [54]. Twenty-six atopic subjects with allergic rhinitis, asthma or urticaria were investigated if tartrazine was the potential cause or provocative factor of symptoms. Following the administration of 35 mg of the tartrazine dye no precipitation of any kind of significant cutaneous, respiratory or cardiovascular reactions were observed [55]. Ibero et al.

investigated 25 patients (18–153 month) with clinical symptoms suggestive of allergy to food antigens. Patients were performed oral provocation tests with various kind of food additives including tartrazine and the positive reaction to tartrazine by oral provocation test was obtained in five patients [50]. Two hundred and twenty-six non-atopic subjects with persistent rhinitis were investigated whether they might show the appearance of objective symptoms of rhinitis after the ingestion of a number of food additives including tartrazine and subjective symptoms of rhinitis (i.e. nasal blockage and nasal itching) and were induced in 45 challenges, two (4.4%) with tartrazine [56]. Sakakibara and Suetsugu reported that 15.1% of patients with aspirin-induced asthma were hypersensitive to tartrazine [57]. Eleven percent of 61 patients suffering from chronic urticaria and/or angioneurotic oedema reacted to tartrazine [23]. A systematic literature review by Arden and Ram found that only six of the 90 research papers had used suitable methodology to establish any positive association between tartrazine ingestion and asthma. These six studies presented that removal of tartrazine from the diet did not improve asthma outcomes and dietary avoidance of tartrazine improved only a few of the subjects who had proven hypersensitivity to this additive. Arden and Ram suggested that there was no evidence that tartrazine could make asthma worse or avoidance of tartrazine could make asthma patients better [58]. In a study, one of 12 children with atopic eczema showed intolerance to 50 mg of tartrazine [59]. Van Bever et al. showed six of 24 children with severe atopic dermatitis reacted to tartrazine [60]. An 11-year-old girl with a recurrent fixed drug eruption to tartrazine on the dorsum of the left hand which was confirmed by oral provocation test was presented by Orchard and Varigos [61]. Bhatia demonstrated that 83 of 2,210 patients (3.8%) exposed to tartrazine-containing psychotropic drugs developed allergic reactions [62]. Tartrazine has been reported to have a possible involvement of multiple chemical sensitivities in a 5-year-old girl suffering from recurrent reactions accompanied by urticaria, angioedema, headaches, dyspnea, loss of consciousness and abdominal pain [63]. Asero reported a patient with suspected tuna allergy that he actually had hidden tartrazine intolerance [64]. Although Reus et al. found no link between demonstrable medical symptoms and tartrazine in their review, tartrazine was suggested to cause urticaria, atopic dermatitis or hyperkinesia in occasional patients even if the prevalence of these reactions remained very low [5, 54, 59]. Two hundred and twenty-six non-atopic subjects with persistent rhinitis were investigated whether they might show the appearance of objective symptoms of rhinitis after the ingestion of a number of food additives including tartrazine. Forty-five challenges induced subjective symptoms of rhinitis (i.e. nasal blockage and nasal itching), two of them with tartrazine [56]. A case of a 58-year-old patient with hepatitis virus C infection had a secondary polyclonal IgG–IgM cryoglobulinemia and

suffered from progressive pigmented purpura (PPP). Food containing tartrazine triggered flares of the PPP, as demonstrated with controlled oral provocation testing [65]. Tartrazine was also implicated as a cause of LCV by Michaëlsson et al. and by Parodi et al. [66, 67].

Allura Red AC/FD&C Red 40 (E129)

Allura Red AC is a red azo dye. Fifty-six patients suffering from chronic urticaria and/or angioneurotic oedema were orally provoked and 16% of them reacted to this colouring dye [23]. A case of a 55-year-old woman who had LCV that had occurred after a change in her medication from tablet to capsule form was reported. Only the dyes used as the cover of medication was different. Two days later after usage of capsule had been discontinued, the patient was discharged while receiving prednisone. The preferred capsule form contained Allura Red 40, Fast Green FCF (E143), Sunset Yellow FCF and FD&C Yellow 10 (Quinoline Yellow WS (E104)). Specific challenge with the dyes had not been attempted to patient so the responsible dye/dyes had not been determined [68] (Table 2).

In another case, a 56-year-old woman with epilepsy who developed rhinorrhea, tearing and nasal stuffiness to Allura Red AC in the drug, Tegretol brand of carbamazepine, was reported [69]. One month later, allergic reaction to this form of drug was confirmed by a test dose.

Ferrous Lactate (E585)

Ferrous salt of lactic acid which functions to enrich and fortify the food is colouring adjunct and a nutrient. A patient who has been treated for iron-deficiency anaemia suffering from anaphylactic reactions caused by oral iron salts was reported. In this report, allergy to iron salts was confirmed by positive skin tests and positive controlled challenge [70].

Narama et al. studied with iron lactate-overloaded rats which their diet was containing 2.5% or 5.0% iron lactate for 3 months. Although some of type 1 hypersensitivity reaction signs like severe infiltration of eosinophils to gastroenterocolic system occurred, other features such as an increasing vascular permeability were not detected and IgE levels were not increased [71].

Erythrosine (E127)

It is a cherry-pink synthetic, primarily used for food colouring. Twelve percent of 56 patients with chronic urticaria and/or angioneurotic oedema represented positivity to oral provocation test [23]. Ibero et al. investigated 25 patients aged between 18 and 153 months with clinical symptoms suggestive of allergy to food antigens. Different synthetic dyes which included erythrosine was administered, and the results represented

Table 2 Allergic reactions or symptoms caused by colourings

4-Hexylresorcinol	Contact dermatitis [17, 18]
Annatto/bixin/norbixin	Triggers chronic urticaria [20, 23, 24], severe anaphylaxis [21, 22], irritable bowel syndrome [25]
Indigotine/indigo carmine	Severe anaphylaxis [26, 27], occupational asthma [29], urticaria [30]
Cochineal/carminic acid/carmines	Occupational asthma [32, 35–37] and rhinoconjunctivitis [31, 35], urticaria [38, 39], asthma [19], anaphylaxis [19, 40–42, 45–47], contact dermatitis [43]
Ponceau 4R/Cochineal Red A	Anaphylaxis [49], triggers allergic LCV [51], triggers chronic urticaria and angioedema [23]
Tartrazine	Triggers symptoms in asthmatic individuals [53, 57], urticaria and angioedema [23, 50, 54, 55], triggers atopic eczema [59], atopic dermatitis [55, 60], drug eruption [61, 62], anaphylaxis [63], triggers progressive pigmented purpura [65], triggers allergic LCV [66, 67]
Allura Red AC/FD&C Red 40	Urticaria and angioedema [23], triggers allergic LCV [68], rhinoconjunctivitis [69]
Ferrous lactate	Anaphylaxis [70]
Erythrosine	Triggers chronic urticaria and angioedema [23], triggers chronic vasomotor rhinitis [56]
Sunset Yellow FCF	Triggers chronic urticaria and angioedema [23, 50], triggers allergic LCV [68], aggravates orofacial granulomatosis [72]
Riboflavin-5'-fosfat	Urticaria and anaphylaxis [73]
Patent Blue V	Urticaria [74]
Carmoisine	Aggravates orofacial granulomatosis [72]
Fast Green FCF and FD&C Yellow 10	Triggers allergic LCV [68]

57.89% of positivities to dyes and out of 25 patient, five of them resulted with positivity to erythrosine [50]. Two hundred and twenty-six non-atopic subjects with persistent rhinitis were investigated whether they might show the appearance of objective symptoms of rhinitis after the ingestion of a number of food additives including erythrosine. Forty-five challenges induced subjective symptoms of rhinitis (i.e. nasal blockage and nasal itching) and seven of them occurred with erythrosine [56]. The researchers suggested that the frequent, probably daily, ingestion of small doses of a nontolerated substance was intriguing and it should be remembered that at least some patients with 'chronic vasomotor rhinitis' might be intolerant to a particular food additive. Fifty-six patients suffering from chronic urticaria and/or angioneurotic oedema were orally provoked by this dye, and 12% of the patients reacted to erythrosine 4 h after intake [23].

Sunset Yellow FCF/Orange Yellow S (E110)

Sunset Yellow FCF is a synthetic azo dye which has a reddish yellow hue and has good tinctorial strength. It has moderate compatibility with food components and is used in beverages, bakery goods, dessert confections and ice cream [13] (p 59).

Ibero et al. investigated 25 patients (18–153 months) with clinical symptoms suggestive of allergy to food antigens. Patients were performed oral provocation tests with various kind of food additives. In almost 50% of patients, positivities correspond to two of the additives: sodium benzoate and Sunset Yellow FCF. In eight patients, positive reaction to Sunset Yellow FCF was described [50]. Fifty-six patients

suffering from chronic urticaria and/or angioneurotic oedema were orally provoked by this dye, and 17% of the patients reacted to this colour 4 h after intake [23]. Sweatman et al. reported a case of a 8.5-year-old girl with orofacial granulomatosis associated with clinical atopy, in whom relapse of her granulomatous disorder was shown to be related to exposure to specific food additives: carmoisine, sunset yellow and monosodium glutamate (MSG) [72]. In this patient, double-blind challenge produced marked reactions to carmoisine, sunset yellow and monosodium glutamate, but overall regression of her symptoms was only achieved with a total elemental diet, and authors had suggested that these food constituents were the major provoking factors in orofacial granulomatosis in this case. A case of 55-year-old woman who had LCV that had occurred after a change in her medication from tablet to capsule form was reported. Only the dyes used as the cover of medication was different. Two days later after usage of capsule had been discontinued, the patient was discharged while receiving prednisone. The preferred capsule form contained a mixture of food colourings which contained Sunset Yellow FCF [68]. Specific challenge with the dyes had not been attempted to patient so the responsible dye/dyes had not been determined.

Riboflavin-5'-Fosfat (E101(ii))

Riboflavin-5'-fosfat is used for yellow colouring in food products. Unique case of allergy to riboflavin-5'-fosfat was reported by Masuda et al. which was a case of a 23-year-old Japanese woman with a personal history of rhinitis and allergy to buckwheat, developed urticaria and anaphylaxis

after drinking 100 mL of an energy drink. Skin test was conducted for each ingredient, and results of a prick test were negative but an intracutaneous test was positive to riboflavin sodium phosphate 0.1%; afterwards, a histamine release test was performed using the patient's basophils that showed a positive response with riboflavin sodium phosphate, whereas basophils from healthy controls showed a negative response. The patient had never experienced any allergic reaction to riboflavin-rich foods, such as milk, meat, eggs or cereal products, but the authors mentioned that clinicians had to keep in mind that riboflavin sodium phosphate in medicine or in energy drinks might be the causative of anaphylaxis [73].

Patent Blue V (E131)

Patent Blue V, also called Food Blue 5 or Sulphan Blue, is a dark bluish synthetic dye used as a food colouring. In medicine, Patent Blue V is used in lymphangiography and sentinel node biopsy as a dye to colour lymph vessels and also used in dental disclosing tablets as a stain to show dental plaque on teeth. There is a unique case report in which an allergic reaction occurred to Patent Blue V. A healthy 5-year-old girl with no atopic history experienced an erythematous urticarial rash which was noticed on her face after she had been given a disclosing tablet to demonstrate the presence of plaque on teeth [74].

Carmoisine/Azorubine/Food Red 3/Azorubin S/Brilliantcarmoisin O/Acid Red 14 (E122)

Carmoisine is a synthetic red food dye from the azo dye group. It is used for the purposes where the food is heat-treated after fermentation. Some of the foods it can be present in are blancmange, marzipan, Swiss roll, jams, preserves, yoghurts, jellies, breadcrumbs and cheesecake mixes.

Sweatman et al. reported a case of an 8.5-year-old girl with orofacial granulomatosis associated with clinical atopy, in whom relapse of her granulomatous disorder was shown to be related to exposure to specific food additives: carmoisine, sunset yellow and monosodium glutamate [72].

Fast Green FCF (E143) and FD&C Yellow 10 [Quinoline Yellow WS (E104)]

Fast Green FCF is a sea green triarylmethane food dye. It can be used for tinned green peas and other vegetables, jellies, sauces, fish, desserts and dry bakery mixes. FD&C Yellow 10 (Quinoline Yellow WS) is a synthetic dye produced from petroleum or coal tar sources.

There has been only one case of allergic reaction to these two food colourings in literature up to date. A case of a 55-year-old woman who had LCV that had occurred after a

change in her medication from tablet to capsule form was reported. Only the dyes used as the cover of medication was different. Two days later after usage of capsule had been discontinued, the patient was discharged while receiving prednisone. The preferred capsule form contained a mixture of food colourings including Fast Green FCF (E143) and FD&C Yellow 10 as well. Specific challenge with the dyes had not been attempted to patient; therefore, the responsible dye/dyes had not been determined [68].

Emulsifier and Stabilisers

The function of emulsifiers and stabilisers is to facilitate the mixing together of ingredients that normally would not mix, namely fat and water. This mixing of the immiscible aqueous and lipid phases is then maintained by stabilisers and become miscible. These additives are essential in many products such as ice cream, mayonnaise and chocolate. In this section, the following additives will be assessed: glycerol esters of wood rosins (E445), sodium stearoyl-2-lactylate (E481) and lecithin (E322).

Glycerol Esters of Wood Rosins (E445)

It is derived from purified natural rosin from pine trees combined with glycerin to form glycerol esters, which make it more soluble and minimizes tastes. In addition to its emulsifier and stabiliser function, it acts as a density adjustment agent for flavouring oils in beverages, and it is used as chewing gum base component. There are number of reports concerning allergic property of this additive, and the main content which is blamed of allergy is thought to be glyceryl-1-monoabietate [75] (<http://www.inchem.org/documents/jecfa/jecmono/v37je02.htm>, last accessed 12 Sep 2011). Two cases of contact allergy, one to lipstick and the other to hair removal strips, were reported. Following the patch tests and further tests with the individual components of the lipstick and hair removal strip, positive reactions to glyceryl hydrogenated rosin ate were shown [76]. Goossens et al. reported that out of 26 sensitized patient to cold/warm wax hair removal strips, five reacted positively to glyceryl rosin ate [77]. In addition, cases of contact allergy to ester gums from hypoallergenic tapes, hydrocolloid dressing and recently contact sensitization from medicated patch were reported [75].

Sodium Stearoyl-2-Lactylate (E481)

Sodium stearoyl lactylate (E481) has been reported in a case of cosmetic allergy which has been confirmed with a positive patch test result [78].

Lecithin (E322)

Lecithin is an emulsifier that is a mixture of phosphatides which are typically surface-active. Lecithin should also act as antioxidant in food. It is now commercially obtained from soybeans; previously, it was obtained from egg yolk [13] (p 83). Both egg and soy lecithins are widely used in the food industry as emulsifiers, especially in the composition of several extensively hydrolyzed infant formulas recommended for use in children with cow's milk allergy. Palm et al. reported a case of allergy to egg lecithin. A 15-month-old girl presented atopic dermatitis which was progressive from the age of 2.4 months, as she was fed with a milk formula. Allergy test result to egg lecithin was positive. The second case was a 4-year-old boy who presented asthma and atopic dermatitis and confirmed allergy to soy lecithin [79]. Renaud et al. reported a 3-year-old boy presented with weight retardation related to chronic diarrhoea and abdominal pain and postprandial emesis. Skin prick tests were positive for soy and when the diet was tightened by eliminating all food with soy lecithin, and the child became symptom-free [80]. Two cases of soybean–lecithin-induced asthma in bakers were reported, and skin tests to soybean–lecithin in these bakers were positive so soybean–lecithin was suggested to be one of the causative of occupational asthma by Lavaud et al. [81]. Soy lecithin is not only used in the food industry but it is widely used in topical skin care products, in various drugs administered either topically, orally or intravenously or by inhalation. A 3-year-old asthmatic boy who was allergic to peanuts and was treated at the emergency department for an exacerbation of asthma following an upper respiratory tract infection was reported. After medication, he developed respiratory distress and generalized urticaria, and the drug contained soy lecithin as an excipient in the metered dose inhaler and was strongly suspected of being responsible for this reaction. Drug products containing soy lecithin was suggested to be a causative factor for severe allergic reactions in patients who were allergic to peanuts or soy [82]. Some of the soybean proteins are included in the extract which is used for production of soy lecithin and soy oil, and small amounts of these proteins are present in both soy lecithin and soy oil and suggested to have little antigenicity with regard to soybean allergy [83]. Soy lecithin was shown to contain a number of IgE-binding proteins; thus, it might be a source of hidden allergens. These allergens might be a more significant concern for soy-allergic individuals who would consume lecithin products as a health supplement [84] (Table 3).

Solvents

Solvents have been used in production of food additives to make the additives more useful and effective without

Table 3 Allergic reactions or symptoms caused by emulsifiers and stabilisers

Glycerol esters of wood rosins	Contact dermatitis (http://www.inchem.org/documents/jecfa/jecmono/v37je02.htm , last accessed 12 Sep 2011) [76–78]
Sodium stearoyl-2-lactylate	Contact dermatitis [79]
Lecithin	Atopic dermatitis [79], asthma [79], gastrointestinal distress [80], occupational asthma [81], generated urticaria [82]

altering its function. The following additives will be evaluated in this part: propan-1,2-diol/propylene glycol (PG) (E1520) and benzyl alcohol (E1519)

Propan-1,2-Diol/Propylene Glycol (E1520)

Propane 1,2-diol also known as propylene glycol is an organic compound that is commercially produced by the hydration of propylene oxide but can also be derived from glycerol. It is used as a humectant, solvent stabiliser, for food colours and flavourings, and it has anti-microbial properties that inhibit the growth of fungi and bacteria and as a carrier substance used to dilute, disperse or dissolve a food additive or nutrient without altering its function, to enable better handling during application or use.

A case of allergy as systematic contact dermatitis was reported with several medicaments which includes PG [85]. Results of patch testing were positive. Also consumption of food which includes propylene glycol caused allergy at the same subject. In a retrospective cross-sectional analysis, 3.5% of subjects had allergic patch test reactions to 30% PG [86]. In another research, 45,138 patients' patch test data were analysed and 2.3% of patients were tested positively with the patch test who have been tested with 20% PG in water, and PG was suggested to exhibit very low sensitization potential [87].

Benzyl Alcohol (E1519)

Benzyl alcohol is an aromatic alcohol used in a wide variety of topical preparations as a fragrance component, solvent, preservative, anaesthetic and viscosity-decreasing agent and is found in a wide array of plants and plant products, foods, cosmetics and medications. Delayed contact dermatitis reactions as well as immediate, urticarial and systemic reactions have been reported to occur with its use in these various formulations [88]. A case of a 30-year-old woman who was suffering from allergic contact dermatitis of eyelids was reported, and the causative substance was benzyl alcohol which was confirmed with positive patch test results. First, balsam of Peru in which benzyl alcohol is a naturally occurring constituent caused allergic contact dermatitis, later on

administration of pimecrolimus cream as a medication which contained benzyl alcohol as a preservative worsening the symptoms [89].

A case of a 40-year-old woman experiencing allergic contact dermatitis after applying a semipermanent hair dye open test with conditioning colourant containing benzyl alcohol as well as patch test with this substance was reported [90]. Additionally, a case of allergic contact dermatitis caused by benzyl alcohol in a hearing aid impression material was described [91]. Benzyl alcohol has been reported as the cause of allergic contact dermatitis following administration of multiple medicaments such as antibacterial and antimycotic creams, topical corticosteroids, sunscreen, analgesic spray, sclerosing agent, epoxy adhesive and cutting oil [92–97]. A case of a 16-year-old female was reported who suffered from anaphylactic reactions following injection of a medicine: vitamin B12. Intradermal testing to all cyanocobalamin preparations and benzyl alcohol was positive, and results indicated that the patient was likely reacting to the benzyl alcohol preservative present in the cyanocobalamin injections. In this case, benzyl alcohol was documented as a cause of hypersensitivity reactions to parenteral medications [98]. In a letter to editor, allergic reaction from benzyl alcohol in the botulinum toxin was discussed. Botulinum toxin is purified neurotoxin complex which is reconstituted with saline containing the preservative, benzyl alcohol, which is not only efficacious but there is also a significant decrease in the pain on injection and increase in shelf life. This letter to editor described two cases (unpublished) of an author in which intractable eyelid dermatitis and recurrent localized delayed-type hypersensitivity reactions (allergic contact dermatitis) were observed after BOTOX injections. These patients were subsequently patch-tested, and positive reactions were noted in both patients to both balsam of Peru and benzyl alcohol. Authors decided that benzyl alcohol was associated with the BOTOX reaction, and along with the high incidence of balsam of Peru-based allergy, authors suggested that practitioners need to be aware of potential delayed-type hypersensitivity reactions to benzyl alcohol preserved injectable cosmetics [99] (Table 4).

Glazing Agents

Glazing agents, or polishing agents, are food additives providing shiny appearance or protective coating to foods.

Table 4 Allergic reactions or symptoms caused by solvents

Propan-1,2-diol/propylene glycol	Systemic contact dermatitis [85], contact dermatitis [86, 87]
Benzyl alcohol	Contact dermatitis [88–97, 99], urticaria [88], anaphylaxis [98]

Mostly they are based on waxes. The following additives will be discussed in this part: Shellac (E904), Carnauba wax (E903) and Beeswax [white and yellow (E901)]

Shellac (E904)

Shellac is a resinous secretion from the female of the insect *Laccifer lacca*, which acts as a protective cover on host trees, from which it is collected, washed and purified. It is used as a coating in cosmetics, including lipstick sealants, hair lacquers and mascara, as well as in dental impression material, coatings for slow-release tablets and a surface finishing agent in cementing book covers [100]. Shellac is suggested to have both irritant and sensitizing properties, but has a few reports as a cause of allergic contact dermatitis. Eight cases of contact dermatitis from shellac in mascaras have been reported to date [101–103]. Orton et al. reported five cases of allergic contact cheilitis who were all women ranging in age from 22 to 49 years from shellac in lip-care products [100]. Strauss et al. analysed their patch test database of 146 patients who were presenting allergic contact cheilitis over 19 years period. A positive allergic patch test reaction was determined in 22 patients (15%). Eighteen percent of this positivity was caused by shellac [104].

Carnauba Wax (E903)

Carnauba wax is a general purpose food additive which is obtained from the leaf buds and leaves of the Brazilian wax palm *Copernicia cerifera*. It is the hardest wax known and is used in candy glaze. In addition to its glazing function, it can act as a bulking agent, acidity regulator and a carrier. Prime yellow carnauba wax is a mixture of mainly esters, wax acids and alcohols. It is found in old phonograph records, furniture, shoe and floor waxes, candles, electrical insulation, cosmetics, lipsticks and cologne sticks. Reported skin sensitization or irritation is very infrequent. Chowdhury reported a case which was allergic to yellow carnauba wax in her mascara [105].

Jacob et al. reported a 6-year-old girl who had consumed chewable multivitamins which notably contained an ‘unspecified’ amount of carnauba wax and beeswax that caused dermatitis, and discontinuation of the vitamins resulted in clearance of both the cheilitis and dermatitis [106].

Beeswax [White and Yellow (E901)]

Beeswax is extracted from the honeycombs of the bees and then purified of other waxes. Beeswax is often contaminated with propolis, and carnauba wax which is a plant composition of approximately 10% cinnamic acid was collected from the leaves of the Brazilian carnauba palm (*Copernicia prunifera*).

In addition to its glazing function, it can act as a release agent and carrier for flavour. Also it is a chewing gum-based component. These two waxes are commonly added to food to produce edible coatings with a high gloss finish [107, 108]. As we mentioned at the above title, a case was reported that gummy vitamins caused dermatitis, and carnauba wax and beeswax were held responsible. In this case, researchers stated that gummy vitamins showed an exposure source, and there may be potential for cross-reactivity between propolis/beeswax and carnauba wax through their common ingredient, cinnamic acid, the oxidized form of cinnamaldehyde [106]. Beeswax is a common ingredient of numerous cosmetic formulations, including ointments, lipsticks and epilating waxes. A case of an 11-year-old girl with atopic dermatitis, an intensely itchy acute cheilitis which had developed 1 week after using an emollient lip formulation, was reported. Patch tests with the individual ingredients of the lip formulation showed positive reaction to beeswax. In this case, the source of sensitization was an emollient lipstick used for the treatment of atopic cheilitis [109]. Two additional cases—occupational beeswax sensitization from adhesive plasters and a case from artistic wax objects—have also been reported [110, 111] (Table 5).

Preservatives

Preservatives are used as anti-microbial agents to preserve food by preventing growth of microorganisms and subsequent spoilage, including fungicides, mould and rope inhibitors [13] (p 115). In this section, the parabens, sulphites and sulphur dioxide, benzoates and their salts will be discussed.

The Parabens [Methyl (E218)/Ethyl (E214)/Propyl *p*-Hydroxybenzoate (E216)] and Their Salts [Sodium Ethyl *p*-Hydroxybenzoate (E215)/Sodium Methyl *p*-Hydroxybenzoate (E219)/Sodium Propyl *p*-Hydroxybenzoate (E217)]

Parabens are alkyl esters of parahydroxy benzoic acid [112] and have been used extensively as anti-microbial preservatives as they are active against yeasts and moulds and are used in foods (baked goods and beverages), drugs and

cosmetics [113, 114]. Parabens, also named *p*-hydroxybenzoates, are known to be nonirritating and nonsensitizing in the population with normal skin, but in numerous studies, they are revealed as common skin sensitizer when applied in cosmetics like emollients to damaged or broken skin [115] and may lead to a delayed hypersensitivity reactions [116] and have been shown to elicit IgE-mediated hypersensitivity reactions when used as pharmaceutical preservatives. However, ingestion of parabens have occasionally been associated with adverse reactions [117]. Although allergic contact dermatitis to parabens has been reported, given the widespread use, it is relatively uncommon [118, 119]. Sakakibara and Suetsugu reported that 12% of patients with aspirin-induced asthma were hypersensitive to parabens [57].

The parabens, methyl- and propylparabens, are the most extensively used in foods and in cosmetics. Sánchez-Pérez et al. reported a patient with allergic contact dermatitis to methylparaben who developed a systemic contact dermatitis after the ingestion of an oral mucolytic [112]. A case of allergic contact dermatitis due to parabens in a compress was reported, and patch testing of the patient showed positive reactions to both methyl and propylparaben [120]. It is recognized that topical preparations which contained methylparaben and propylparaben were contraindicated for use on compromised skin. However, use of methylparaben or propylparaben as preservatives in cosmetic products intended for use on normal skin is considered safe [121]. Nagel et al. reported a case of bronchospasm and pruritus after intravenous administration of a hydrocortisone preparation containing methyl- and propylparabens to an asthmatic patient [122]. Skin tests resulted with immediate hypersensitivity to parabens, and the patient was able to tolerate a hydrocortisone preparation without the parabens. However, the sensitivity of this patient to ingested parabens was not described. A number of studies on the photocontact sensitization of products containing 0.2% methylparaben and/or 0.2% propylparaben were reported [115, 117].

Pacor et al. investigated whether non-atopic subjects affected by persistent rhinitis may show the appearance of objective symptoms of rhinitis after the ingestion of food additives such as tartrazine (E102), erythrosine (E127), monosodium benzoate (E211), *p*-hydroxybenzoate (E218), sodium metabisulphite (E223) and monosodium glutamate (E620). Two hundred and twenty-six consecutive patients (76 males and 150 females) aged 12–60 years (mean age 40.2±16.3 years) were included. Challenges were administered in a double-blind, placebo-controlled (DBPC) manner using the above-mentioned substances under investigation. In three challenges with *p*-hydroxybenzoate subjective symptoms of rhinitis (i.e. nasal blockage and nasal itching), without reduction of NPIFR $\geq 20\%$ of the basal value was induced [56].

Table 5 Allergic reactions or symptoms caused by glazing agents

Shellac	Contact dermatitis [100–104], contact cheilitis [100]
Carnauba Wax	Contact dermatitis [105], systemic contact dermatitis and cheilitis [106]
Beeswax	Systemic contact dermatitis and cheilitis [106], atopic dermatitis [109], occupational sensitization [110, 111]

Sodium ethyl *p*-hydroxybenzoate (E215), sodium methyl *p*-hydroxybenzoate (E219) and sodium propyl *p*-hydroxybenzoate (E217) are the salts of parabens. There is no allergic reaction data or case report of the salts of parabens in literature up to date. Nevertheless, it must be kept in mind that sodium ethyl *p*-hydroxybenzoate is a kind of paraben, so similar adverse effects which occurred to both methyl- and propylparaben may be valid for sodium ethyl *p*-hydroxybenzoate.

Sulphites and Sulphur Dioxide [Sodium Sulphite (E221)/Sodium Hydrogen Sulphite (E222)/Sodium Metabisulphite (E223)/Potassium Metabisulphite (E224)/Calcium Sulphite (E226)/Calcium Hydrogen Sulphite (E227)/Potassium Hydrogen Sulphite (E228)/Sulphur Dioxide (E220)]

Sulphites or sulphiting agents such as sodium and potassium sulphite, metabisulphite, bisulphites, calcium sulphite, calcium hydrogen sulphite, potassium hydrogen sulphite and sulphur dioxide (SO₂) are ubiquitous compounds with a variety of commercial uses. Sulphites are widely used as preservatives, anti-browning agents and antioxidant additives in food and pharmaceutical industry. Although sulphites seem to be safe for general use, they should cause serious allergic reactions in sensitive individuals, ranging from dermatitis, urticaria to life-threatening anaphylactic and asthmatic reactions [123]. Especially dermatologic, respiratory or gastrointestinal signs and symptoms with various severities were reported in literature [124]. First case of contact dermatitis who was exposed to potassium metabisulphite while working in the pharmaceutical industry was reported in 1968 [125]. Later on, adverse reactions following occupational exposure to sulphites in salad makers [126], bakers [127, 128], a wine producer and a hairdresser [123] were reported. Petersen and Menne, Vena et al. and Madan et al. performed patch test studies and presented positivity to sulphite exposure ranging between 1.4% and 4.1% in patients [129–131]. Occurrence of skin sensitivities like dermatitis and urticaria after medication which contains sulphites by topical administration were reported. There are a number of case reports which presented adverse skin reactions following exposure to sulphite additives in facial cosmetic creams, hair dyes, false tanning lotion and topical medications, such as antifungal cream, haemorrhoid creams and eye drops [131–135]. Besides topical exposure, occurrence of skin reactions to sulphite additives following ingestion and parenteral exposure were also reported in clinical studies and in case reports [123]. In addition to triggering episodic and acute symptoms, in some cases, sulphite additives were showed to play a clear role in the chronic symptoms of some individuals. Furthermore, a case of an allergic leukocytoclastic vasculitis and exacerbation of an atopic eczema have been observed following the sulphite exposure [136]. A case of a sulphite-induced anaphylactic reaction after injection of a local dental anaesthetic was

reported [137]. There are numerous reports of anaphylactic or asthmatic reactions associated with the use of sulphite-containing local anaesthetics, and some drugs like gentamicin, metoclopramide, doxycycline and vitamin B complex were presented in literature [138]. Adverse reactions to sulphites in nonasthmatics are extremely rare; sulphite sensitivity occurs most often in asthmatic adults [124]. Steroid-dependent asthmatics or the ones who have a higher degree of airway hyperreactivity were reported to have greater risk of experiencing a reaction to sulphite-containing foods. Reported respiratory sensitivities of sulphites were more serious; the first case of anaphylaxis following ingestion of sodium metabisulphite in a restaurant salad was reported in 1976 [139]. Wuthrich and Huwyler reported seven patients with pre-existing asthma and/or rhinitis, who experienced severe, life-threatening asthmatic and urticarial reactions after ingestion of wine, salads and other food which contained sulphites [140]. In another case, consumption of sulphite-containing wine was followed by fatal asthmatic reaction [141]. In the early 1980s, there were also a number of reports which represented asthma exacerbations and/or generalized skin reactions among asthmatic patients who were treated with sulphites containing bronchodilator medications [142–145]. Although many of allergic reactions to sulphites were asthmatic responses, urticaria and angioedema, abdominal pain and diarrhoea as well as anaphylaxis were reported [142, 146–148]. Occupational exposure to sulphites may also be resulted with asthmatic responses [123]. A case of a patient who experienced episodes of bronchospasm that required hospitalization after handling sodium bisulphite at work was reported [149], and metabisulphite-induced occupational asthma has also been reported in a photographic technician and a radiographer [150, 151]. Numerous occupational asthma cases such as a worker who sprinkled dry metabisulphite powder onto potatoes [152] and three cases which were related to metabisulphite exposure were reported in France [153]. Although there is some disagreement on this prevalence, it is generally agreed that between 5% and 10% of adults, chronic asthmatics may show varying degrees of sensitivity to sulphite additives, with a number of these individuals experiencing life-threatening reactions [154]. In susceptible individuals following ingestion, parenteral and topical exposure to sulphites, skin, intestinal and respiratory reactions may occur simultaneously and in various combinations and severities. In addition, Steinman et al. reported that sulphur dioxide triggered asthmatic attacks in 43.2% of asthmatic children [155]. Sulphite hypersensitivity is usually, but not exclusively, suggested to be found within the chronic asthmatic population. Steroid-dependent asthmatics or the ones who have a higher degree of airway hyperreactivity may be at greater risk of experiencing a reaction to sulphite-containing foods [124]. Bronchoconstriction is the most common sensitivity response in asthmatics. Arai et al. studied 20 adult asthmatic patients who were non-steroid-

dependent and without a suggestive history of sulphite sensitivity and who underwent challenge with oral solution of metabisulphite, of which 12 patients reacted to metabisulphite [156]. They demonstrated symptoms like airway obstruction (41.7%), urticaria (36.7%), skin manifestation (16.7%) and nasal congestion (8.3%).

Pacor et al. investigated whether non-atopic subjects affected by persistent rhinitis may show the appearance of objective symptoms of rhinitis after the ingestion of food additives such as tartrazine (E102), erythrosine (E127), monosodium benzoate (E211), *p*-hydroxybenzoate (E218), sodium metabisulphite (E223) and monosodium glutamate (E620). Two hundred and twenty-six consecutive patients (76 males and 150 females) aged 12–60 years (mean age 40.2 ± 16.3 years) were included. Six challenges induced subjective symptoms of rhinitis (i.e. nasal blockage and nasal itching), without reduction of NPIFR $\geq 20\%$ of the basal value with sodium metabisulphite [56].

Benzoic Acid and Its Salts (Benzoates) [Benzoic Acid (E210)/Sodium Benzoate (E211)/Potassium Benzoate (E212)/Calcium Benzoate (E213)]

Benzoic acid is an anti-microbial preservative that occurs naturally in some foods such as cranberries, prunes and cinnamon. It is most often used in the form of sodium benzoate because of the low aqueous solubility of the free acid. Sodium benzoate is effective against yeasts and slightly effective against bacteria and moulds. It is used in acidulated beverages, jams, jellies and relishes.

Food-associated allergies, especially to benzoates and cinnamon-related compounds, have been associated with orofacial granulomatosis, and both standard and urticarial patch testing have been used to detect such allergies. Standard patch tests were carried out in 41 of 103 individuals (40%) and 17 of them (41%) reacted positively; contact urticarial tests were carried out on 97 of 103 individuals (94%) and 63 of them (65%) reacted positively. Thirty-five patients (28%) underwent both forms of testing; 19 of the subjects (54%) reacted positively on at least one test to one or more of benzoic acid, cinnamaldehyde and cinnamyl alcohol [72]. A case of sodium benzoate-induced chronic generalized pruritus was reported [157]. Hong et al. reported that oral provocation tests with aspirin and a mixture of food additives which contains sodium benzoate should cause a clinically significant bronchoconstriction in asthmatic patients [158]. Coupling of aspirin and sodium benzoate was suggested to create a synergistic effect on asthmatic people about allergic reactions. Sakakibara and Suetsugu reported that 14.3% of patients with aspirin-induced asthma were hypersensitive to sodium benzoate [57]. Two hundred and twenty-six non-atopic subjects with persistent rhinitis were investigated whether they might show the appearance

of objective symptoms of rhinitis after the ingestion of a number of food additives including monosodium benzoate [56]. In 20 subjects, monosodium benzoate induced both objective (i.e. sneezing and rhinorrhoea) and subjective symptoms (nasal blockage and nasal itching) of rhinitis. It also induced only subjective symptoms of rhinitis (i.e. nasal blockage and nasal itching) in 19 subjects. The researchers suggested that the frequent, probably daily, ingestion of small doses of a nontolerated substance was intriguing, and it should be remembered that at least some patients with ‘chronic vasomotor rhinitis’ might be intolerant to a particular food additive. Ibero et al. investigated 25 patients (18–153 month) with clinical symptoms suggestive of allergy to food antigens. Patients performed oral provocation tests with various kinds of food additives including sodium benzoate. In almost 50% of patients, positivities correspond to two of the additives: sodium benzoate and Sunset Yellow FCF [50].

Lysozyme (E1105)

Lysozyme, an egg protein, is a still unlabeled additive currently used in cheese production. It was reported that it may cause hypersensitivity reactions [159]. Frémont et al. showed that 35% of 52 egg-allergic patients had antilysozyme IgE [160]. However, Iaconelli et al. reported that the use of lysozyme as an additive in Grana Padano cheese does not appear to be harmful in egg-allergic subjects [161] (Table 6).

Sweetening Agents

Sweetening agents, as the name implies, perform an obvious function making food sweet. Sweeteners can be classified as natural (nutritive) or artificial (non-nutritive). In this part, aspartame (E951), salt of aspartame–acesulfame (E962), xylitol (E967) and erythritol (E968) will be evaluated. In addition to their sweetening function, the following sweeteners can act as flavour enhancer except xylitol.

Aspartame (E951)

Aspartame is a synthetic dipeptide formed by the reaction of L-aspartic acid with L-phenylalanine methyl ester [162]. Bradstock et al. evaluated 231 cases which included consumers’ complaints about symptoms associated with aspartame. Seventeen percent of all cases with allergic symptoms, such as a red rash on the face, was reported [163]. A case of a 9-year-old boy who had a history of mild atopic dermatitis experiencing severe systematized dermatitis after taking chewable montelukast tablet containing aspartame was reported. Formaldehyde, which is created by metabolization of aspartame in body, was responsible for this systemic

Table 6 Allergic reactions or symptoms caused by preservatives

Parabens	Contact dermatitis [115, 118–120] systemic contact dermatitis [112, 116], triggers asthmatic reactions in asthmatic individuals [57, 122]
Sulphites and sulphur dioxide	Contact dermatitis [123, 125, 129–131], urticaria [123, 140, 142–145], rhinitis [56, 156], anaphylaxis [123, 137, 138, 142–148], angioedema and gastrointestinal distress [142, 146–148], allergic LCV [136], occupational asthma [123, 149–154], triggers asthmatic reactions in asthmatic individuals (especially bronchoconstriction) [123, 124, 139–145, 155, 156]
Benzoates	Contact dermatitis [72], urticaria [72], triggers asthmatic reactions in asthmatic individuals (especially bronchoconstriction) [158], triggers chronic generalized pruritus [157], triggers chronic vasomotor rhinitis [56]
Lysozyme	–

contact dermatitis [164]. In another case, 60-year-old woman presented with a 6-month history of eyelid dermatitis who had positive reactions to formaldehyde in patch test and within 1 week of discontinuing the aspartame, her eyelid dermatitis resolved completely and has not recurred over 18 months without specific treatment. Again formaldehyde was reported to be the causative derivative of aspartame to be responsible for allergic reaction in this case report [165].

Salt of Aspartame–Acesulfame (E962)

Salt of aspartame–acesulfame is an artificial sweetener and consisted of a mixture of aspartame and acesulfame potassium at a ratio of 2:1. Although there are no data of allergic reactions to this salt reported up to date, one who has allergic reaction to aspartame may also have the same complaints because one of the main ingredient of this additive is aspartame.

Xylitol (E967)

Xylitol is a polyhydric alcohol that is a natural sugar substitute commercially made from xylan-containing plants (birch) hydrolyzed to xylose. In addition to its sweetening function, it is a humectant in food. It is used in chewing gum, throat lozenges and chocolate. Hanakawa et al. presented a case of a patient who manifested oral erosions as a result of contact allergy to xylitol-containing chewing gum. In this case, patch testing to various chewing gums showed that only xylitol-containing gums elicited severe allergic reactions [166].

Erythritol (E968)

Erythritol is an artificial sweetener (polyol) manufactured by fermentation of glucose, the glucose-rich substrate being obtained by the enzymatic hydrolysis of starch. It can act as sweetening agent, flavour enhancer, humectant and carrier. It is 60–70% as sweet as sugar and is the only polyol produced by fermentation. It can be used as a sugar replacement in confectioneries, beverages and desserts. A case of

24-year-old female presented severe urticaria which occurred after she had drunk a glass of canned milk tea. When she examined, erythritol was found to be the cause of her skin reactions [167] (Table 7).

Thickeners

Thickeners are the substances used to produce viscous solutions or dispersions, to impart body, improve consistency or stabilise emulsions, including suspending and bodying agents, setting agents, jellying agents, bulking agents etc. Gums are the main class of thickeners. By thickening or gelling the water, gums perform numerous roles such as stabilisers, film formers, binders, suspending agents, whipping agents, coating agents and crystallization inhibitors. The additives discussed in this section are as follows: soybean hemicellulose (E426), propan-1,2-diol alginate/propylene glycol alginate (E405), karaya gum (E416), acacia gum/gum arabic (E414), guar gum (E412), locust bean gum (E410) and tragacanth gum (E413). These additives have additional functions as stabiliser and emulsifier.

Soybean Hemicellulose (E426)

In addition to its thickener, stabiliser and emulsifier function, soybean hemicellulose is an anti-caking agent. Allergic reactions to soybean has been reported [168]. Although there is no case of soybean hemicellulose allergy in literature, the absence of allergy risk is not guaranteed in persons who have been known allergic to soybeans in the presence of residual proteins in soybean hemicellulose [169, 170].

Table 7 Allergic reactions or symptoms caused by sweetening agents

Aspartame	Systemic contact dermatitis [164], contact dermatitis [165]
Salt of aspartame	–
Xylitol	Contact allergy [166]
Erythritol	Urticaria [167]

Propan-1,2-Diol Alginate/Propylene Glycol Alginate (E405)

Propylene glycol alginate is one of the gum derivative. Especially in sensitive individuals, various dilutions of propylene glycol alginate showed slight to moderate skin reactions. In 30% of these sensitive subjects, ingestion of propylene glycol alginate showed mild allergic reactions which were duplicated in repeated tests [171].

Gums

Gums are in certain brands of foods to add bulk, thickness and binding quality for providing enrichment to foods and making them heavy [172]. Vegetable gums are classified into two broad groups: gums obtained as plant exudates and gums obtained from seeds. Important gums from exudates are acacia, tragacanth and karaya gums, and gums from seeds are carob and guar gums. Although vegetable gums are used widely used in food processing, pharmaceutical, textile and printing industry, case reports of occupational asthma have appeared infrequently. In spite of their widespread use in food products, development of sensitization through the oral route is uncommon, but sensitization by inhalation is seem to be much more frequent [173]. Figley carried out an ingestion experiment in which gum mixture (karaya, tragacanth and arabic gum powder) had been ingested by five subjects between 300 and 2,100 mg in food. All five subjects suffered from allergic reactions like vasomotor rhinitis, bronchial asthma and epigastric distress. Out of five subjects, two of them reacted to arabic gum, one of them reacted to tragacanth gum and two of them reacted to tragacanth and karaya gum together in direct skin and serologic tests [172].

Karaya Gum (E416)

Karaya gum is the dried exudate from the *Sterculia urens* tree which is native to India [13] (p 80). First case report to karaya gum was presented by Bullen et al. in 1934. Their patient developed vasomotor rhinitis following the contact with the gum in hair-waving lotion [174]. This report was followed by a case of a bronchial asthma in a hairdresser from the same cause [175]. Bowen reported five cases of urticaria due to karaya [176]. Figley observed 16 cases with allergic symptoms all of whom gave positive reactions to scratch tests with karaya gum [173], and various cases of allergic reactions including asthma, dermatitis and gastrointestinal distress to karaya gum were reported [177]. Ten cases of allergic reactions to foods (cream cheese, marshmallows, commercially prepared pie crust mixtures, commercially prepared cake icing, gelatine etc.) which contained vegetable gums were reviewed by Figley, and out of ten subjects, eight of them

reacted to karaya gum [172]. In addition, as a food additive function, one of the current uses of karaya gum is in the routine care of ileostomies and colostomies. The karaya gum serves as a skin barrier and is available in a variety of forms, including seal rings, paste and a dry powder in a plastic squeeze bottle. A case of allergic respiratory symptoms (nasal congestion, coughing and wheezing) following exposure to karaya gum powder has been reported in a 27-year-old female nurse who employed for 3 years as an enterostomal therapist [178]. Diagnosis was confirmed by allergy skin testing which demonstrated a pruritic wheal and flare response to the karaya gum. A case of a 48-year-old man who presented an elective proctocolectomy and ileostomy following a 10-year history of ulcerative colitis suffered from ulcerations on the stoma [179]. This lesion corresponded to the area which karaya seal ring came into contact with the stoma, and after discontinuing the use of karaya seal pouch, the denuded stomal area was almost completely healed. Similar to this case, Camarasa and Alomar reported a 40-year-old woman suffering from a severe itchy dermatitis around colostomy opening in which a drainable polyethylene bag with an integral karaya gum seal ring was used and positive reaction to karaya ring was obtained with the patch test [180]. Two cases—a 15-year-old woman and a 14-year-old woman who was treated with electrotherapy using karaya pads as a conductive medium—had contact dermatitis on the application areas that urging discontinuation of the treatment [181]. A study of electrical stimulation for the treatment of progressive idiopathic scoliosis in which karaya gum pads as the conductive medium were used presented only two out of 90 patients (2.2%) with a skin rash requiring discontinuation of treatment [182].

Acacia Gum/Gum Arabic (E414)

Acacia gum/gum arabic is obtained from *Acacia* spp. and used in food, pharmaceutical and printing industries. The first case of allergy to acacia was a patient under treatment for elephantiasis of the leg who had an operation and received an intravenous solution which included 6% acacia. The symptoms had not occurred at the time, but 7 months later when the second therapeutic injection was repeated, the patient developed nasal obstruction and respiratory symptoms [183]. Studdeford reported much more severe reaction to acacia in 1937. Three patients who were suffering from postpartum haemorrhage had been infused with acacia glucose solution, and subjects produced constitutional reactions (cyanosis, tachycardia, dyspnoea and pulmonary oedema). Two of the patients died and the authors suggested that acacia preparation caused the reaction [184]. The first case of an occupational sensitization and allergy to gum arabic was in a candy factory [185] and that was followed by a number of reports in which gum arabic had caused bronchial asthma in printers [186–188]. Ten cases of allergic reactions

to foods (cream cheese, marshmallows, commercially prepared pie crust mixtures, commercially prepared cake icing, gelatine etc.) which contained vegetable gums were reviewed by Figley, and all of ten subjects reacted to tragacanth gum [173]. Symptoms of the subjects were ranging from urticaria, vasomotor rhinitis, gastrointestinal allergy to bronchial asthma and angioedema. Skin tests and positive serologic findings confirmed the causative agent. Fotish et al. firstly identified a carbohydrate-specific IgE in a chocolate confectioner with cough and dyspnea. More recently, sensitization to gum arabic carbohydrate structures was reported to occur casually in atopic patients with pollen sensitization without obvious exposure to gum arabic and that allergy to gum arabic was suggested to be mediated preferentially by IgE antibodies directed to polypeptide chains of gum arabic [189–191].

Guar Gum (E412)

Guar gum is a kind of plant seed gum which is derived from the outer part of *Cyamopsis tetragonoloba*, a vegetable that grows in India. It is incorporated into numerous foods and pharmaceutical products and is used as a fixing agent for colours. Guar gum has been shown to cause occupational rhinitis and/or asthma [192]. Three cases of allergic rhinitis from guar gum have been presented by Kanerva et al. [193]. Two subjects were exposed to fine guar gum powder by an insulator in rubber cables, when opening cables in a power cable laboratory and rhinitis developed after 1–2 years following the exposure in the patients. Scratch-chamber tests, nasal provocation tests, nasal eosinophilia and a radioallergen sorbent test (RAST) test proved their allergy to guar gum. The third subject developed allergic rhinitis from another guar gum product after 2 years exposure in a paper factory, and again a positive skin test and nasal provocation test confirmed the diagnosis. A case of a man who experienced oral syndrome after eating food containing guar gum (ice cream and salad dressings) and an anaphylactic shock to guar gum contained in a meal substitute which was amplified by the almost concomitant ingestion of acetylsalicylic acid was reported by Papanikolaou et al. [194]. Guar gum allergy was confirmed by skin prick tests with evidence of an IgE-mediated mechanism. Roesch et al. reported a case of a life-threatening, immediate type reaction after mucosal contact to a guar derivative which was used as a local anaesthetic [195]. Guar gum was charged with occupational asthma in the paper of Lemi re et al. in which four of 16 workers have specific bronchial reactivity caused by guar gum, and when the exposure to guar gum was prevented, no longer evidence of persisting asthma was shown [196]. Malo et al. investigated the prevalence of occupational asthma and immunologic sensitization to guar gum among employees at a carpet-manufacturing plant, and out of 162

employees, eight subjects (5%) demonstrated immediate skin reactivity to guar gum and 11 subjects (8.3%) had serum IgE antibodies to guar gum [197]. In addition, three individual cases of occupational asthma had been reported by Lagier et al. [192]. The first subject worked for a pharmaceutical company, and he also had experienced oedema of the lips and laryngeal tickling after eating foods containing guar gum (ice cream and salad dressings); the second and third subjects worked at a carpet-manufacturing plant where guar gum was used to fix colours. All three subjects developed symptoms of rhinitis and asthma after the onset of exposure to guar gum, the subjects were atopic and skin prick tests demonstrated an immediate skin reaction to guar gum and also the subjects had high levels of serum IgE antibodies in sera to guar gum [192].

Locust Bean/Carob Bean Gum (E410)

Locust bean/carob bean gum is a galactomannan obtained from the plant seed from the locust bean tree known as *Ceratonia siliqua*. This gum is used as a thickening, stabiliser and gelling agent in jams, marmalades, yoghurt, meats, infant food and also as an egg substitute in food product manufacturing. A case of a 5-month-old female infant, suffering from gastroesophageal reflux, developed recurrent vomiting, urticaria and facial rash after administration of that milk formula was reported, which had been thickened with carob bean gum [198]. Alarc n et al. reported another case of urticaria and angioedema after ingestion of cr me caramel containing carob bean gum. Positive skin prick test results and high titres of serum-specific IgE of subject to carob bean and carob gum demonstrated that an IgE-mediated mechanism had occurred [199]. A case of 52-year-old male presented with burning sensations, discomfort in his throat and chest tightness when chewing on carob pods and allergy to carob pods was confirmed with prick testing which resulted with an immediate positive reaction [200]. Carob bean flour was reported to be responsible for the occurrence of occupational asthma in 30-year-old man who had been working as an ice cream maker for 2 years, routinely employing carob bean flour as a thickening in his products. Diagnosis was confirmed by a prick test for carob bean flour and a RAST [201]. Another occupational asthma case was reported: a 48-year-old man who had been employed for 16 years in a jam factory. Complaints of the patient was work-related rhinitis, irritated eyes and 3 years later asthma appeared. Positive allergic results to carob bean flour and guar gum was confirmed with RAST [202].

Tragacanth Gum (E413)

Tragacanth gum is produced from *Astragalus gummifer*. It swells in water to give a highly viscous sol or paste, and also

it is used in printing industry [203]. Although there are only a few reports on sensitization to tragacanth gum, it is suggested to be a powerful allergen capable of causing extremely severe reactions which may occur following inhalation or oral ingestion of tragacanth gum [170, 204]. Ten cases of allergic reactions to foods (cream cheese, marshmallows, commercially prepared pie crust mixtures, commercially prepared cake icing, gelatine etc.) which contained vegetable gums were reviewed by Figley and out of ten subjects, eight of them reacted to tragacanth gum. Symptoms of the subjects were ranging from urticaria, vasomotor rhinitis to bronchial asthma and angioedema. Skin tests and positive serologic findings confirmed the causative agent [172]. A 26-year-old female who was working in a factory which imports various commercial gums suffered from severe asthma attacks after spending 1 year in work [183]. Direct skin tests to tragacanth gum and also to gum arabic produced strong reactions. The first case report of allergic reaction to tragacanth gum by ingestion had occurred from drug tablets (pyribenzamine tablets) [183]. Strobel et al. investigated the immunogenicity and non-specific irritant properties of exudate gums in an animal model [205]. The materials studied included gum tragacanth, and delayed hypersensitivity responses were measured by a footpad swelling test. Some of the gum preparations, particularly tragacanth and karaya gum, caused considerable footpad swelling when injected intradermally. Purification of the gum led to a marked reduction of the immune response.

Pectin (E440)

Pectin is a kind of plant extracted gum which is the methylated ester of polygalacturonic acid. It is obtained from citrus peels and apple pomace [13] (p 106). Pectin was suggested to be added to the list of the substances known to induce occupational asthma. A case of pectin-induced occupational asthma was reported in a 35-year-old man whose job involved mixing powdered pectin into a fruit puree during the manufacture of jam. A prick skin test was used for confirmation of allergy and result with the pectin powder was positive [206, 207]. Ferdman et al. suggested that not only inhalation but ingestion of pectin might cause hypersensitivity reactions. A case of a 3.5-year-old boy developed anaphylaxis once after eating cashews and later after eating a pectin-containing fruit 'smoothie'. A positive skin prick test reaction to pectin and a high RAST reaction to cashew has been shown. In this case, cashew allergy was suggested to be associated with pectin allergy [208].

Konjac (E425)

Konjac is a plant of the genus *Amorphophallus*. Konjac flour is a powder derived from the processing of tubers of

the *Amorphophallus* plant and is commonly used as a gelling agent, thickener, emulsifier and stabiliser in the food manufacturing industry throughout the world. In Japan, in the konjac manufacturing plant workers, following the inhalation of konjac powder cases of occupational asthma has been reported [209, 210].

A case of 49-year-old man who worked as a laboratory technician in a food manufacturing facility for 20 years presented with three separate episodes of progressive worsening of diffuse urticaria, shortness of breath, chest tightness and wheezing. A screening peak expiratory flow rate (PEFR) was normal for his age, and the remainder of his physical examination was unremarkable. The subject elicited a significant positive prick skin test response to konjac glucomannan (KGM). The control subject's skin test response was negative. Increased serum-specific IgG but not IgE responses were identified for the patient to KGM. Following the specific provocation test to KGM, symptoms developed which coincided with a 35% decrease in PEFR. The control subject did not exhibit a response to any of the agents used for specific provocation. In this case, occupational respiratory sensitization to KGM was supported by a specific prick skin test and a specific provocation test to KGM. This case demonstrates the potentially sensitizing nature of konjac and its potential for causing severe allergic reactions [211].

A 56-year-old man who had worked as a Konnyaku manufacturer suffered from hypersensitivity pneumonitis caused by inhalation of powder during the manufacture of Konnyaku as reported by Tajima et al. [212]. Konnyaku is a paste made from Konjak flour, powdered *Hijikia fusiforme*, quicklime and powdered scallop shell. The diagnosis of hypersensitivity pneumonitis was confirmed immunologically by the detection of serum precipitins to powdered *Hijikia fusiforme* and by the positive result of in vitro lymphocytic proliferative response (Table 8).

Flavouring Agent

Flavouring agent provides the sensory impression of a food or other substance and is determined mainly by the chemical senses of taste and smell.

Monosodium Glutamate (E621)

Monosodium glutamate, also known as sodium glutamate, is a sodium salt of glutamic acid, a naturally occurring non-essential amino acid. It is used as a food additive and is commonly marketed as a flavour enhancer for gravies, meats, poultry, sauces and in other combinations (<http://chemicaland21.com/lifescience/foco/MONOSODIUM%20GLUTAMATE.htm>). Sweatman et al. reported a case of a

Table 8 Allergic reactions or symptoms caused by thickeners

Soybean hemicellulose	—
Propan-1,2-diol alginate/ propylene glycol alginate	Moderate skin reactions [171]
Gum/karaya gum	Contact dermatitis [177, 179–182], vasomotor rhinitis [174, 178], bronchial asthma [175, 177], urticaria [176], gastrointestinal distress [172, 177], allergic respiratory symptoms (nasal congestion, coughing and wheezing) [178]
Gum/acacia gum/gum arabic	Urticaria and angioedema [173], vasomotor rhinitis [172, 173], allergic respiratory symptoms (nasal congestion, coughing and wheezing) [173, 183], gastrointestinal distress [172, 173], asthma [173], occupational asthma [185–188], anaphylaxis [184]
Gum/guar gum	Occupational asthma [192, 196, 197], occupational rhinitis [192, 193], anaphylaxis [194, 195]
Gum/locust bean/carob bean gum	Urticaria [198, 199], angioedema [199], gastrointestinal distress [198], occupational asthma [201, 202]
Gum/tragacanth gum	Urticaria [172], vasomotor rhinitis [172, 183], asthma [172], gastrointestinal distress [172], angioedema [172]
Pectin	Occupational asthma [206, 207], anaphylaxis [208]
Konjac	Occupational asthma [209, 210], urticaria and allergic respiratory symptoms (nasal congestion, coughing and wheezing) [211], hypersensitivity pneumonitis [212]

8.5-year-old girl with orofacial granulomatosis associated with clinical atopy, in whom relapse of her granulomatous disorder was shown to be related to exposure to specific food additives: carmoisine, sunset yellow and monosodium glutamate [72]. MSG was reported in 1968 as the ‘Chinese Restaurant Syndrome’, which was characterized by the triad of palpitations, generalized weakness and sensory numbness originating at the nape of the neck with radiation to the arms and back. The beginning of MSG and asthma connection started with the report of Allen and Baker in which two asthmatic patients had described asthma attacks 12 h after ingesting a meal in a Chinese restaurant [213]. The authors reported that both patients’ asthmatic attacks were associated with declines in PEFR by oral challenges with capsules containing 2.5 g of MSG after 10 and 12 h. One patient developed such severe asthma that she had to be intubated. The authors concluded that MSG was responsible for their bronchospasm. Since then, hypotheses have been put forward that MSG may be associated with food allergies in human being. Subsequently, Allen et al. carried out an expanded study about this issue [214]. Out of 32 asthmatic patients, 14 gave a history of wheezing attacks after ingesting an oriental meal, and 18 were recruited because they had ‘unstable asthma, usually with sudden, severe, unexplained attacks’ and ‘sensitivity to other chemicals (aspirin, benzoic acid, tartrazine and sulphites)’. All 32 asthmatic subjects were admitted to hospital, underwent single-blind oral challenges with MSG, followed by PEFR measurements for 12 h. In summary, Allen et al. reported that 14 of 32 patients experienced asthma attacks after ingesting 1.5 g MSG (one patient) or 2.5 g MSG (13 patients), with elapse times from ingestion of MSG to onset of a 20% decline in PEFR ranging from 1 to 12 h [214]. Stevenson had stated a point that none of the patients was said to react to MSG in 1 h after ingestion, the time when circulating glutamate concentrations would most likely have been elevated [215]. Also

experimental circumstances of this study was criticised and mentioned that to make meaningful comparisons between placebo and active treatment days was impossible [215]. Moneret-Vautrin carried out a study with high dose MSG (2.5 g) that was tested in 30 asthmatics (7 allergic asthma, 15 intrinsic asthma with intolerance to aspirin, 8 intrinsic asthma with aspirin intolerance, intolerance to alcohol or to food additives) and six healthy controls. A positive broncho-spastic response, defined as a 15% decline from baseline in PEFR, occurred in two subjects who presented a mild bronchospasm, occurring 6 to 10 h after the ingestion. The author studied patients in a single-blind, placebo-controlled protocol and used declines in PEFR determinations as evidence for asthma attacks [216]. Schwartzstein et al. showed no MSG-sensitive asthmatics in their study of 12 mild asthmatics who were given DBPC challenges with 1.5 g capsules of MSG [217]. Germano et al. carried out a study which investigated 30 asthmatic patient and MSG relation [218]. During single-blind screening oral challenges with MSG (up to 6 g; 7.5 g cumulative dose over 2 h), one of 30 participants experienced a significant reduction in FEV1 values. However, the response to MSG challenge was negative when this one preliminary ‘reactor’ was rechallenged with the same dose (6 g of MSG), under DBPC conditions [218]. Woods et al. conducted DBPC challenges with 1 and 5 g of MSG in 12 clinically documented asthmatics (seven women, mean age 35.3 years) who perceived that MSG might be responsible for worsening of their asthma symptoms. None of the subjects experienced significant decreases in forced expiratory volumes (FEV1) or PEFR, no immediate or definite late asthmatic reactions occurred in the subjects [219]. An oral challenge study in self-identified MSG-sensitive subjects was conducted to determine whether they had a statistically significant difference in the incidence of their specific symptoms after ingestion of MSG compared with placebo. Sixty-one subjects entered the study and on

initial challenge, 22 (36.1%) responded to MSG ($p=0.324$) but symptom characteristics do not support an IgE-mediated mechanism. The investigators suggested that according to Food and Drug Administration recommendations, the symptoms, originally called the Chinese restaurant syndrome, are better referred to as the MSG symptom complex [220]. Another study aimed to determine whether MSG ingestion induced asthma attacks in 100 asthmatic subjects who were challenged with 2.5 g of MSG with single-blind, placebo-controlled screening challenges. As a result of this study, MSG challenges in subjects with and without a perceived sensitivity to MSG failed to induce signs or symptoms of asthma [221].

Williams et al. mentioned that the bulk of the studies to date which examined the potential role for MSG as a trigger of attacks of bronchospasm in asthmatic subjects has failed to demonstrate an association [222]. In a different study done by Geha et al., the reaction of 130 subjects who had reported as sensitive to MSG was tested. DBPC trials were performed and only subjects with at least two symptoms proceeded. Only two people out of the whole study responded in all four challenges. This prevalence was mentioned to be low, and the researchers concluded that the responses were not observed when MSG was given with food and the response to MSG was not reproducible and the responses reported were inconsistent [223]. As a result of several studies, investigators concluded that MSG was unlikely to be a significant contributing factor to adverse respiratory events in asthmatics [222]. Although some limitations of following studies were mentioned in the review of William and Woessner, urticaria from MSG ingestion was reported; the first was carried out by Supramaniam and Warner in which possible role of MSG and seven other food additives in 36 children with urticaria with or without angioedema was examined. Participants were required to have recurrent or persistent urticaria for at least 2 months with a remarkable improvement in symptoms after 4–6 weeks on a diet free of artificial food additives. Double-blind challenges with capsules containing placebo, MSG 100 mg, or one of seven other food additives were conducted at 4-h intervals. Three of the 36 children had a positive reaction to MSG, which was defined as the appearance of urticaria or angioedema within the 4-h interval between challenges [224]. The second study was reported by Botey et al. in which four cases of urticaria or pruritic cutaneous erythema following an uncontrolled oral challenge with 50 mg of MSG was documented [225]. The possible relationship between MSG and urticaria was tried to be clarified by Simon who conducted food additive challenges in 65 patients with active chronic urticaria, including four subjects who gave a history of MSG induced urticaria. All of the participants had urticaria for 6 weeks without discernible aetiology. Two subjects had positive single-blind, placebo-controlled challenges, but none of them had a positive DBPC challenge. Sensitivity to MSG

likely accounts for 0–3% of the chronic urticaria population, and with these findings, MSG was concluded as an unusual exacerbation of chronic idiopathic urticaria [226]. The highlighting case report of Asero supported the MSG sensitivity as a possible but rare cause of urticaria. A patient with a 12-year history of chronic urticaria was administered multiple series of skin prick tests (SPT) for airborne and food allergen sensitization and reacted negative. Afterwards, the patient was placed on an additive-free diet, which was associated with a significant decrease in urticaria severity and a need for anti-histamines. An open challenge consisting of a 3-week unrestricted diet was associated with increased urticaria severity, followed by improvement once again on resumption of the additive-free diet. Two separate DBPC challenges resulted with the appearance of ‘severe urticaria’ within 45 min with a relatively low dose of 100 mg of MSG on both occasions (but not placebo) [227]. Squire reported a case of a 50-year-old man who suffered from recurrent attacks of angioedema of the face and extremities which was related to ingestion of a soup base containing MSG. An open challenge with the soup base, a blinded challenge with the soup base and a single-blind placebo-controlled challenge with MSG 250 mg all resulted in angioedema within 16–24 h. In addition, dietary avoidance of MSG was resulted with an extended remission of attacks [228]. Asero documented two separate reports of three patients with chronic rhinitis symptoms associated to dietary MSG ingestion, two patients with perennial rhinorrhoea, nasal itching and episodes of sneezing paroxysms and one patient with chronic rhinosinusitis with nasal polyposis, associated anosmia and obstructive nasal symptom. Evaluation for specific IgE sensitization to common airborne allergens (as measured by SPT) was negative in all three patients. Following the initiation of an ‘additive-free’ diet marked and sustained improvement in nasal symptoms were experienced by the patients and with the resumption of an unrestricted diet, within few days relapse in nasal symptoms initiated and a second remission of symptoms with re-institution of the elimination diet. DBPC challenges with 100 mg capsules of MSG had been shown to induce ‘severe’ rhinitis symptoms within 4–24 h of MSG ingestion and lasted 1–2 days in all three patients [229, 230].

Pacor et al. investigated whether non-atopic subjects affected by persistent rhinitis may show the appearance of objective symptoms of rhinitis after the ingestion of food additives such as tartrazine (E102), erythrosine (E127), monosodium benzoate (E211), *p*-hydroxybenzoate (E218), sodium metabisulphite (E223) and monosodium

Table 9 Allergic reactions or symptoms caused by flavouring agents

Monosodium glutamate	Triggers orofacial granulomatosis [72], triggers asthmatic reactions [213, 214], urticaria [224–227], angioedema [224, 228], rhinitis [229, 230]
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glutamate (E620). Two hundred and twenty-six consecutive patients (76 males and 150 females) aged 12–60 years were included. MSG was reported to induce subjective symptoms of rhinitis (i.e. nasal blockage and nasal itching), without reduction of NPIFR >20% of the basal value [56] (Table 9).

Conclusion

In this paper, our objective was to overview the allergic features of food additives. As their side effects are very speculative, we tried to represent a comprehensive data about this issue. Allergic reactions following exposure to additives are not very frequent but when they do occur, they are likely to produce severe and explosive symptoms. The reactions mostly occur individually in sensitive subjects, and although there have been clinical researches, most of the data were case reports. Most of the clinical researches about this issue have been discussed afterwards in several reviews about limitations of the work. The diagnosis of allergic reactions to food additives should lead to proper investigation to confirm the diagnosis objectively. For example, the diagnosis of occupational asthma, skin prick tests and/or specific IgE tests should be useful tools to support the diagnosis but does not confirm it. Objective evidence of asthma by monitoring of peak expiratory flows at and off work or specific inhalation challenges which should be accepted by most of the clinicians/researchers would offer a better diagnostic value. So criteria for positive challenge results have to be specified, double-blind placebo-controlled studies should be carried out, and oral challenge doses used in studies should have practical meaning in daily life.

As a result, allergic reactions to food additives can be considered triggers or aggravating factors in sensitive individuals, rather than aetiological factors. Clinicians and consumers especially the sensitive individuals have to keep in mind allergic features of food additives.

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