



Anaphylaxis to food additives

Regina Treudler · Jan Christoph Simon

Received: 27 October 2021 / Accepted: 12 January 2022
 © The Author(s) 2022

Abstract A variety of additives found in foodstuffs have been associated with triggering of a number of clinical pictures. Hypersensitivity reactions of allergic and non-allergic etiology have been widely described, but are reported to be rare overall. This review presents a selection of food additives for which anaphylactic reactions have been described. These include colorants (e.g., tartrazine, carmine, patent blue), preservatives (e.g., sulfites, sodium benzoate), and thickeners/gelling agents (e.g., carboxymethylcellulose, guar, gum arabic). Possible diagnostic procedures (skin test, specific IgE, cellular antigen stimulation test, oral provocation) are presented. For those affected, avoidance of consumption is facilitated by the mandatory declaration (class name, E-number/designation) required in the European Union. Only sulfur dioxide and sulfites have to be highlighted as food allergens, depending on the concentration. Due to the limited diagnostic procedures available, it cannot be excluded that the frequency of hypersensitivity to food additives is underestimated.

Keywords Allergy · Dyes · Diagnostic techniques and procedures · Patent blue · E-number

Background

Food additives are intended to improve taste, appearance, shelf life and/or production. The Food Information Regulation (FID), adopted on October 25, 2011 as Regulation (EU) No. 1169/2011, regulates the label-

ing of foods in the European Union (EU) [1]. There are more than 300 approved additives that are labeled with an E-number (for EU) in the European Union [1]. The following major subgroups can be distinguished (www.zusatzstoffe-liste.de):

- Colorants (E 100–180),
- Preservatives (E 200–285),
- Antioxidants (E 300–321),
- Emulsifiers and acidifiers (E 322–375),
- Thickener/gelling agent (E 400–415), and
- Flavor enhancers (E 620–625).

Additives in foods have been associated with triggering a number of clinical pictures. These include respiratory and gastrointestinal symptoms, behavioral abnormalities, triggering of chronic urticaria, and anaphylactic reactions [2–4].

Hypersensitivity reactions of allergic or nonallergic etiology to food additives are reported to be rare overall, affecting 0.01–0.23% of the population but 2–7% of people with atopic background [3]. Mostly, these are mild reactions to the skin, gastrointestinal tract and respiratory tract. Severe anaphylaxis is rare. It must be said that the diagnosis of hypersensitivity to additives is complex and often difficult to establish, so that the true prevalence may be underestimated. Food additives are among the so-called hidden triggers of clinical signs and symptoms and can be easily overlooked [5].

Therapeutically, care must be taken to avoid the intake. In the European Union, there is an obligation to declare the class name (e.g., colorant) and the E-number or the special designation. Only sulfur dioxide and sulfites in concentrations of more than 10 mg/kg or 10 mg/l must be labeled as allergens. [1, 6]. A selection of additives for which anaphylactic reactions have been described is discussed below. Possible diagnostic procedures are presented.

Prof. Dr. R. Treudler (✉) · J. C. Simon
 Leipzig Interdisciplinary Center for Allergology—LICA-CAC,
 Department of Dermatology, Venereology and
 Allergology, University Leipzig Medical Faculty,
 Philipp-Rosenthal-Str. 23, 04103 Leipzig, Germany
regina.treudler@uniklinik-leipzig.de

Table 1 Commercially available in vitro diagnostics for the clarification of an immediate type reaction to food additives

Specific IgE	Cellular antigen stimulation test ^a	
Guar (E 412)	Amaranth (E 123)	Indigocarmine (E 132)
Gum arabic (E 414)	Azorubine (E 122)	Potassium metabisulfite (E 224)
Carob (E 410)	Brilliant black (E 151)	Sodium nitrite (E 250)
Crimson (E 120)	Carboxymethyl cellulose (E 466)	Sodium benzoate (E [8]211)
Tragacanth (E 413)	Quinoline yellow (E 104)	Sodium salicylate
α -amylase	Cochineal red A (E 124)	Patent blue (E 131)
Glucoamylase	Erythrosine (E 127)	Sorbic acid (E 200)
–	Yellow orange (E 110)	Tartrazine (E 102)
–	Glutamate (E 620)	–
IgE Immunoglobulin E, ImmunoCAP		
^a CAST, ELISA, Bühlmann Laboratories AG, Schönenbuch, Switzerland		

Diagnostics

Anamnestic suspicion of hypersensitivity to additives should result from symptoms associated with consumption of commercially processed and/or a variety of unrelated foods.

An orienting examination can be carried out by means of a *skin prick test*, whereby it is best to use the original products consumed, but also pure substances if necessary. An IgE-mediated reaction has only been described for a few substances and can also only be serologically investigated for a limited number of substances by means of commercially available *enzyme-linked immunosorbent assay* (ELISA; Table 1). As a cellular in vitro test, a *cellular antigen stimulation test* (CAST) is commercially available for selected additives only (Table 1; [7]). For *oral exposure testing*, amounts of 5 mg can usually be used for colorants, 0.25–1 g for preservatives, and 0.1–0.5 g for flavor enhancers [8]. However, obtaining the pure substances is not always easy.

Anaphylaxis to dyes

Azo, non-azo and natural dyes are distinguished. Azo dyes are associated with non-immunologically mediated immediate type reactions. Triggering of chronic urticaria has been described for cochineal red A (E 124), tartrazine (E 102) and yellow orange (E 110) [3]. Tartrazine was largely banned in Germany, Austria and Switzerland in 1989 (exception: certain alcoholic beverages), among other reasons because a connection with hyperactivity syndrome was discussed. In 1993, this ban was partially lifted again due to European rules on standardization. Since July 2010, warning labels must be found in Germany on foods containing certain azo dyes (e.g., yellow orange [E 110], quinoline yellow [E 104], azorubine [E 122], allura red [E 129], tartrazine [E 102], cochineal red A [E 124]) [9].

The azo dye *tartrazine* (E 102) can be found, for example, in drinks, confectionery, puddings, mustard and pâtés. In earlier studies, a link was established with chronic urticaria and asthma; the latter could not be confirmed in further analyses [6].

Cochineal red A (E 124) is an azo dye used, for example, in salmon substitutes, mouthwash, throat lozenges, Jell-O and Aperol [6].

Anaphylactic reactions have been described for these two as well as for other azo dyes (e.g., indigo carmine [E 132], riboflavin [E 101]), only very rarely [3, 10, 11]. Diagnostically, a commercial CAST is available for the clarification of immediate type reactions for several azo dyes (see above).

On the one hand, the non-azo dye *patent blue* (E 131) can be found in cheese, sausage, cakes, beverages, sweets and desserts. On the other hand, it is also used in textiles, solvents, cold juices, and cosmetics. Due to the many possibilities of sensitization, anaphylaxis can also occur for the first time, for example, in the case of deliberate first contact in the context of the use of patent blue in a sentinel lymph node operation. A skin prick test may be positive; a CAST is commercially available [12–16].

The natural dye *carmine* (E 120) is extracted from scale insects and used for example in sweets, sauces and medicines, but also in Campari. An IgE-mediated reaction has been described, can be tested by commercially available ELISA, and might be related to possible insect components. Occupational asthma is reported to occur more frequently than anaphylaxis [17–20]. In the Network for Online Registration of Anaphylaxis, only two cases of anaphylaxis to carmine have been documented so far (personal communication Prof. M. Worm 9/2021). There is a commercially available ELISA for IgE diagnostics.

The yellow–brown natural dye *annatto* (E 160b) is obtained from the fruit peels of the annatto shrub; it is used, for example, to color liqueurs, snacks, hard cheeses, and smoked fish. Casuistically, anaphylactic reactions, but also the triggering of chronic urticaria have been described [21, 22].

Anaphylaxis to preservatives

Severe immediate type reactions to preservatives are rather rare. The following are examples of possible reactions to sulfites (which are among the allergens subject to mandatory labeling in the EU) and sodium benzoate.

Sulfites Sulfites (E 220–228) inhibit discoloration caused by enzymes (e.g., fruit) and have an antimicrobial effect. A high content can be found, for example, in dried fruits, pickled vegetables, wine, a medium content in wine vinegar and a low content in shrimps, sauerkraut, corn flour, and jams. There is an obligation to declare if the amount exceeds 10 mg/kg or 10 mg/l. Casuistically, anaphylactic reactions to

sulfites have been described, while gastrointestinal complaints, headaches, asthma and skin changes, for example, itching, urticaria, seem to be more frequent [23–25]. The pathophysiology is not conclusively clarified, IgE-mediated reactions (as haptens), defects of sulfite oxidase and cholinergic reflexes are discussed. CAST and oral provocation with metabisulfite (0.5–200 mg/20 ml) are recommended for diagnosis [6].

Sodium benzoate Sodium benzoate (E 211) has antibacterial and antimycotic activity and occurs naturally in, for example, cranberries, plums, anise and cinnamon. The incidence of hypersensitivity reactions appears to be low. For diagnostic purposes, a CAST is possible. Doses of 50–500 mg are recommended for provocations [6].

Anaphylaxis to thickening agents

Carboxymethylcellulose Carboxymethylcellulose (E 466) has been described casuistically as a possible allergen leading to anaphylaxis in foods, for example, in ice cream [26, 27]. Sensitization may occur, among other things, through its use in drugs for injection (e.g., in preparations containing triamcinolone crystal suspension) [28–30]. For diagnostics, a CAST is possible; positive skin prick tests have been described [6].

Guar gum Guar gum (E 412) can be found in yogurt, cheese, soft ice cream, prepared sauces, puddings, dressings, and soups. IgE-mediated anaphylaxis has been described; testing by commercially available ELISA is possible [31].

Gum arabic Anaphylactic reactions with an IgE-mediated mechanism have also been described for gum arabic (E 414), which can be found, for example, in pastries, dairy products, ice cream, canned meats, and also in pharmaceutical products. Diagnosis is possible using a commercially available IgE test [6].

Anaphylaxis to other food additives

Glutamates Glutamates (E 620–625) are particularly abundant as flavor enhancers in East Asian foods, which may contain up to 6 g of monosodium glutamate. Cereals, legumes, tomatoes, mushrooms and various cheeses, for example, may also contain glutamate. In 1968, the *Chinese restaurant syndrome* was described, which can manifest itself approximately 15–30 min after consumption with headaches, anxiety, nausea and sweating [6]. Anaphylactic reactions to glutamate have rarely been reported [32, 33]. A CAST is commercially available. Increasing doses of 0.5–5 g are recommended for provocation testing [6].

Benzyl alcohol: The solvent benzyl alcohol (E 1519) is used in parenteral drugs (e.g., anesthetics) but also in cosmetics and in foodstuffs (as a carrier in the production of flavors). Anaphylactic reactions have only been suspected casuistically, based on, among other things, a positive intradermal test. In contrast, late type reactions seem to occur more frequently [3, 34].

Conclusion

A variety of additives may be present in foods, especially if they have been commercially processed. Anaphylactic reactions to these additives are rare overall, but have been ascribed to colorants, and less frequently to preservatives, thickeners and others. Since hidden triggers/allergens are involved and diagnostic capabilities are limited, it cannot be excluded that the true prevalence of hypersensitivity reactions to food additives is underestimated.

Funding Open Access funding enabled and organized by Projekt DEAL.

Conflict of interest R. Treudler and J.C. Simon declare that they have no competing interests.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

References

1. Europäisches Parlament. Verordnung (EU) Nr. 1169/2011 – Information der Verbraucher über Lebensmittel. 2011. <https://eur-lex.europa.eu/legal-content/DE/TXT/HTML/?uri=CELEX:02011R1169-20180101&from=DE>. Accessed: 28.02.2022
2. Randhawa S, Bahna SL. Hypersensitivity reactions to food additives. *Curr Opin Allergy Clin Immunol*. 2009;9:278–83.
3. Gultekin F, Doguc DK. Allergic and immunologic reactions to food additives. *Clin Rev Allergy Immunol*. 2013;45:6–29.
4. Laura A, Arianna G, Francesca C, et al. Hypersensitivity reactions to food and drug additives: problem or myth? *Acta Biomed*. 2019;90:80–90.
5. Skypala JJ. Food-induced anaphylaxis: role of hidden allergens and cofactors. *Front Immunol*. 2019;10:673. <https://doi.org/10.3389/fimmu.2019.00673>.
6. Jäger L, Wüthrich B, Ballmer-Weber B, et al., editors. *Nahrungsmittelallergien und -intoleranzen: Immunologie – Diagnostik – Therapie – Prophylaxe*. 3rd ed. München: Urban & Fischer Verlag/Elsevier GmbH; 2012.
7. Bühlmann Laboratories AG. *BÜHLMANN allergen list*. 2013. <http://www.buehlmannlabs.ch/files/documents/>

- [core/CellularAllergy/Corporate/allergenliste-ml15e.pdf](#). Accessed 25 July 2005.
8. Reese I, Zuberbier T, Bunselmeyer B, et al. Diagnostic approach for suspected pseudoallergic reaction to food ingredients. *J Dtsch Dermatol Ges*. 2009;7:70–7.
 9. Amchova P, Kotolova H, Ruda-Kucerova J. Health safety issues of synthetic food colorants. *Regul Toxicol Pharmacol*. 2015;73:914–22.
 10. Schneiweiss F. Tartrazine anaphylaxis. *Ann Allergy*. 1981;46:294.
 11. Desmond RE, Trautlein JJ. Tartrazine (FD & C yellow #5) anaphylaxis: a case report. *Ann Allergy*. 1981;46:81–2.
 12. Aurich S, Seitz A-T, Tömm J, et al. A case of anaphylaxis to patent blue in a patient with sentinel lymph node excision. *Iran J Allergy Asthma Immunol*. 2016;15:547–50.
 13. Azevedo JP, Alves M, Ribeiro C, et al. Anaphylactic shock perioperative to patent blue dye. *BMJ Case Rep*. 2018;2018:bcr2018224330.
 14. Korbi A, Khaskhoussy A, Cherif O, et al. Anaphylactic shock due to patent blue: case report and review of literature. *Pan Afr Med J*. 2018;31:7.
 15. Perenyi M, Barber ZE, Gibson J, et al. Anaphylactic reaction rates to blue dyes used for sentinel lymph node mapping: systematic review and meta-analysis. *Ann Surg*. 2021;273:1087–93.
 16. Leung M, McCusker C, Ben-Shoshan M. Anaphylaxis to patent blue dye in a 17-year-old boy. *BMJ Case Rep*. 2019;12(1):e226191.
 17. Miyakawa M, Inomata N, Sagawa N, et al. Anaphylaxis due to carmine-containing foods induced by epicutaneous sensitization to red eye-liner. *J Dermatol*. 2017;44:96–7.
 18. Takeo N, Nakamura M, Nakayama S, et al. Cochineal dye-induced immediate allergy: review of Japanese cases and proposed new diagnostic chart. *Allergol Int*. 2018;67:496–505.
 19. Kazbek BK, Yilmaz H, Kazancı B, et al. Severe hypertension and tachycardia during transforaminal endoscopic discectomy—is indigocarmine to blame? *Neurocirugía*. 2019;30:50–2.
 20. De Pasquale T, Buonomo A, Illuminati I, et al. Recurrent anaphylaxis: a case of IgE-mediated allergy to carmine red (E120). *J Invest Allergol Clin Immunol*. 2015;25:440–1.
 21. Nish WA, Whisman BA, Goetz DW, et al. Anaphylaxis to annatto dye: a case report. *Ann Allergy*. 1991;66:129–31.
 22. Ebo DG, Ingelbrecht S, Bridts CH, et al. Allergy for cheese: evidence for an IgE-mediated reaction from the natural dye annatto. *Allergy*. 2009;64:1558–60.
 23. Dean RK, Subedi R, Christiano P, et al. More than a drink: a rare anaphylactic reaction to sparkling water. *Am J Emerg Med*. 2018;36:170.e1–170.e2.
 24. Cifuentes L, Ring J, Brockow K. Clonal mast cell activation syndrome with anaphylaxis to sulfites. *Int Arch Allergy Immunol*. 2013;162:94–6.
 25. Roth JV, Shields A. A dilemma: how does one treat anaphylaxis in the sulfite allergic patient since epinephrine contains sodium metabisulfite? *Anesth Analg*. 2004;98:1499. author reply 1500.
 26. Ohnishi A, Hashimoto K, Ozono E, et al. Anaphylaxis to carboxymethylcellulose: add food additives to the list of elicitors. *Pediatrics*. 2019;143(3):e20181180. <https://doi.org/10.1542/peds.2018-1180>.
 27. Brockow K, Bauerdorf F, Kugler C, et al. “Idiopathic” anaphylaxis caused by carboxymethylcellulose in ice cream. *J Allergy Clin Immunol Pract*. 2021;9:555–557.e1.
 28. García-Ortega P, Corominas M, Badia M. Carboxymethylcellulose allergy as a cause of suspected corticosteroid anaphylaxis. *Ann Allergy Asthma Immunol*. 2003;91:421.
 29. Oppliger R, Hauser C. Anaphylaxie nach Injektion von Kortikosteroidpräparaten – Carboxymethylzellulose, ein verstecktes Allergen. *J Dtsch Dermatol Ges*. 2004;2:928–30.
 30. Al Hadithy A, van Maaren M, Vermes A. Anaphylactic reactions following Kenacort—A® injection: carboxymethylcellulose is involved once again. *Contact Derm*. 2011;64:179–80.
 31. Papanikolaou I, Stenger R, Bessot JC, et al. Anaphylactic shock to guar gum (food additive E412) contained in a meal substitute. *Allergy*. 2007;62:822.
 32. Trent JS, Tassin S. A case of possible monosodium glutamate-dependent, exercise-induced anaphylaxis. *Cureus*. 2019;11:e5345.
 33. Inomata N, Chin K, Nagashima M, et al. Late-onset anaphylaxis due to poly (γ -glutamic acid) in the soup of commercial cold Chinese noodles in a patient with allergy to fermented soybeans (natto). *Allergol Int*. 2011;60:393–6.
 34. Turvey SE, Cronin B, Arnold AD, et al. Adverse reactions to vitamin B12 injections due to benzyl alcohol sensitivity: successful treatment with intranasal cyanocobalamin. *Allergy*. 2004;59:1023–4.