Anaphylaxis to food additives

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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 labeling 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.

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Diagnosics

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 antymycotic 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].

**Benzy alcohol:** The solvent benzy 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.

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

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