

# Adverse Reactions to Benzoates and Parabens

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## KEY CONCEPTS

- Benzoates and parabens are used extensively as chemical preservatives in foods and beverages throughout much of the developed world and have essentially no toxicity at approved concentrations.
- Although investigated frequently in association with chronic urticaria, well-designed studies place the incidence of benzoate- or paraben-induced urticaria/angioedema at no more than 2–3% of all cases.
- Well-designed trials have not provided a conclusive link between persistent asthma and benzoates or parabens.
- Some studies have implicated food additives including benzoates in provoking atopic dermatitis in a minority of patients. A potential mechanism may be via increased production of leukotrienes.
- Anaphylactic-type reactions have been rarely reported with ingested benzoates. Paraben ingestion has not been reported as a potential cause of anaphylaxis.
- A variety of other adverse reactions to benzoates and parabens have been reported ranging from cutaneous vasculitis to rhinitis to hyperactivity in children. Additional studies are needed to confirm these associations.

Benzoic acid and sodium benzoate (benzoates) are widely used as antimycotic agents and antibacterial preservatives in foods and beverages. The methyl, *n*-propyl, *n*-butyl and *n*-heptyl esters of *p*-hydroxybenzoic acid (collectively referred to as parabens) are utilized as preservatives in a limited number of foods and beverages. Parabens, however, are used extensively as preservatives in pharmaceuticals and cosmetics. Benzoic acid, sodium benzoate, methylparaben, propylparaben, and heptylparaben are approved as direct food additives by the US Food and Drug Administration (FDA) and have generally recognized as safe (GRAS) status [1].

## Benzoates and parabens as food and beverage additives

Benzoates have been used since the early 1900s as preservatives in foods and beverages. Annual consumption worldwide has been estimated at greater than 10 million pounds, making benzoates one of the most commonly used additives. The benzoates have a broad range of antimicrobial

activity, exhibit little or no toxicity in the concentrations used for food applications, and are relatively inexpensive to produce.

The chemical structures of benzoic acid and sodium benzoate are shown in Fig. 33.1. Benzoic acid is a white crystalline solid with an acidic pH and limited water solubility [2]. Sodium benzoate is a white crystalline powder with alkaline pH that readily dissolves in water [3]. When sodium benzoate is dissolved in acidic solutions, it is partially converted to the free acid. Benzoates appear to be most effective as antimicrobial agents at acidic pH.

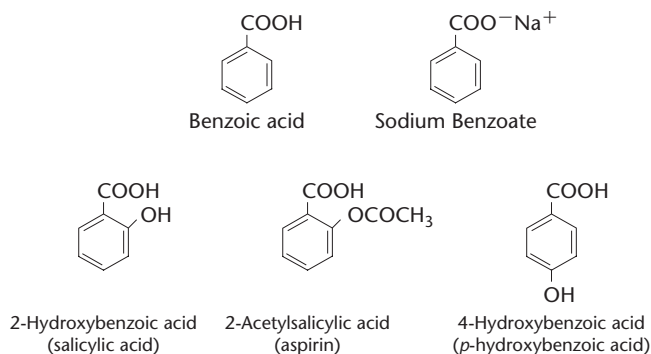


**Figure 33.1** Benzoates and closely related conveners.

Benzoates are widely distributed in nature in the form of the free acid or as simple salts, esters, and amides. They occur naturally in prunes, cinnamon, cloves, tea, anise, and many berries. Raspberries and cranberries contain up to 0.05% by weight [2,4]. Benzoates are found as preservatives in alcoholic beverages, fruit juices, soft drinks, baked goods, cheeses, gum, condiments, frozen dairy products, relishes, and sugar substitutes, to name a few. Orally administered benzoates are rapidly absorbed through the intestine and transported to the liver. Benzoate is converted to a thioester with coenzyme A to form benzoyl-CoA. Benzoyl-CoA then reacts with glycine to form hippuric acid, which is excreted in the urine.

The use of parabens as antimicrobial agents in pharmaceuticals, cosmetics, and food began in Europe in the 1920s and spread to the United States in the 1930s. While primarily used as preservatives in pharmaceuticals and cosmetics, parabens are also approved for use in foods by the FDA, the European Community, the Joint FAO/WHO Expert Committee on food additives, and by the regulatory agencies of several other countries. Methylparaben and propylparaben are the forms most commonly used as food additives. Parabens are contained in coffee extracts, fruit juices, pickles, sauces, soft drinks, processed vegetables, baked goods, fats and oils, seasonings, sugar substitutes, and frozen dairy products. Concentrations vary between 450 and 2000 ppm. The use limit for parabens as chemical preservatives in foods is 0.1%. Parabens are not described as occurring naturally. Oral administration normally results in rapid absorption and subsequent hydrolyzation to *p*-hydroxybenzoic acid. Glycine, glucuronic acid, and sulfuric acid conjugates are then formed and all are eliminated in the urine [5]. Toxicity studies have demonstrated little or no adverse effects either acutely or chronically at doses far exceeding the current ADI of 55 mg/kg/day [6].

The chemical structures of the parabens are shown in Fig. 33.2. They are white crystalline or powder solids that have essentially no odor or taste. Bactericidal activity is

present over a wide pH range in contrast to the benzoates [7]. Methylparaben has antimicrobial properties against cold-tolerant bacteria and has been used frequently as a preservative in prepared chilled foods [8].

## Benzoates, parabens, and associations with chronic urticaria–angioedema

The prevalence of reactions to food additives in the setting of chronic urticaria has been studied frequently. Unfortunately, due to design issues with oral challenge studies in this patient population, variable study design, and lack of adequate controls in many studies, the prevalence of such reactions has not been definitively elucidated. Design considerations in food-additive challenge studies are of critical importance. Selection of patients may include, for example, all patients with a history of chronic idiopathic urticaria, only those with histories suggestive of food-additive reactions, or only those patients who appeared to improve on an additive-free diet. Depending on the selection criteria, different percentages of positive reactors have been reported. These variables have not been explicitly stated in many reports and add confusion to the already difficult task of comparing studies.

The relative activity or inactivity of the urticaria at the time of challenge appears to be a key factor. In a study by Lumry *et al.* [9], only 1 of 15 patients whose urticaria was in remission experienced a reaction to aspirin (ASA). However, 7 of 10 patients whose urticaria was active at the time of challenge reacted to ASA. These challenges were performed using a semi-quantitative reaction criteria. Reactions were judged in comparison to a baseline observation period in each individual patient.

In most reported studies, a period of baseline observation for comparison with reaction data was never made. Further, most challenge studies report loosely defined criteria for identifying urticarial responses. Other potential confounding factors include discontinuation of medications (particularly antihistamines), timing and number of placebo challenges, and additive doses. Finally, the importance of the double-blind challenge cannot be overemphasized. A more detailed description of design considerations for oral challenge protocols in chronic urticaria–angioedema can be found in Chapter 23.

One of the earliest open additive challenge studies in chronic urticaria patients was reported by Doeglas [10]. He observed that 4 or 5 of 23 patients reacted to sodium benzoate. Placebo-controlled challenges were not performed. Patients with physical urticarias were included. Thune and Granholt [11] reported that 2 of 32 patients reacted to parabens while 4 of 41 patients reacted to benzoates after oral challenge. Overall, 62 of 100 patients reacted to at least 1 of 22 different additives used in the challenges. Again, placebo controls were not utilized making any firm conclusions difficult to support.

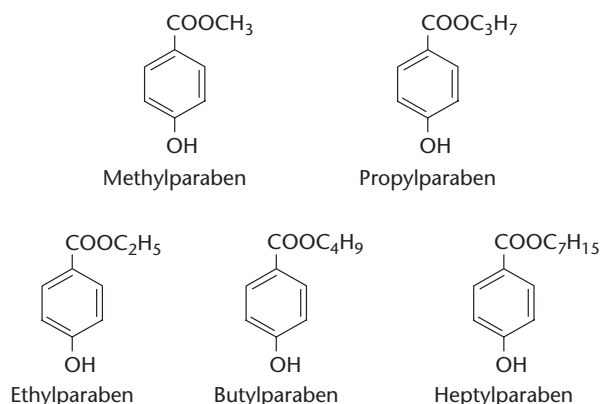


**Figure 33.2** The paraben family of food additives.

A study performed by Juhlin [12], involved single-blind challenges using multiple additives. The prevalence of benzoate hypersensitivity was reported to be 11% among 172 participants. Overall, one or more positive reactions were observed in 31% of patients. This study utilized only a single administration of placebo, which was always given first, followed by multiple additive challenges. Reaction criteria were subjective and were determined to be “uncertain” in 33% of patients. Previous studies by the same group reported a prevalence range of 44–60% for benzoate hypersensitivity in chronic urticaria patients [13,14]. Due to study design limitations, firm conclusions are again difficult to support.

Supramaniam and Warner [15] reported that 4 of 27 children with urticaria reacted to sodium benzoate. Overall, 24 out of 43 children reacted to one or more additives. The study did utilize a double-blind challenge design. However, only one placebo was interspersed with nine different additives and a baseline observation period to determine the relative activity of the chronic urticaria was not utilized. Whether antihistamines were withheld or continued was not mentioned. Genton *et al.* [16] also reported a significant reaction rate to benzoates in single-blind additive challenges in 17 patients with chronic urticaria and/or angioedema. Among these patients, 5 of 17 reacted to successive doses of sodium benzoate (10, 50, 250, and 500mg). Urticaria developed in 15 of the 17 patients after at least one of the six additives was used. If urticaria or angioedema were “noticed by a physician during the 18-hour period after the test,” the challenge was considered positive. All patients considered for the study were observed to have had “sufficient improvement” in their disease while on a 2-week elimination diet (free of additives). Explicit baseline disease activity was not reported.

Ortolani *et al.* [17] studied 396 patients with chronic urticaria and angioedema. Based on history, 179 patients were considered for treatment with an elimination diet and 135 were elected to proceed. Eighty-seven of the 135 patients had an 80% or greater reduction in urticaria symptom scores during the 2-week elimination diet compared to the 2-week baseline observation period. Only eight of the 87 patients who had improved on the elimination diet had a positive double-blind challenge to foods. Of the 79 patients who did not react to foods, 72 underwent double-blind, placebo-controlled, oral food-additive challenges. Three of the 72 had urticarial reactions with sodium benzoate (60, 410, and 410mg). Twelve of the 72 reacted to one or more additives including tartrazine and sodium metabisulfite. Parabens were not tested.

Hannuksela and Lahti [18] reported 1 of 44 patients reacted to benzoic acid in a double-blind, placebo-controlled challenge study. One of the 44 patients also reacted to placebo. Several other food additives were tested in this study but no other reactions were observed. In a study with similar design, Kellett *et al.* [19] reported that 10% of 44 chronic

idiopathic urticaria patients reacted to benzoates and/or tartrazine. Ten percent also reacted to placebo.

Simon [20] studied 65 patients with active chronic idiopathic urticaria who continued antihistamines at the minimum effective dosage. Twenty of the participants reported a history of adverse reactions to additives. A baseline urticaria skin score was obtained in each patient using a semi-quantitative method utilizing the “Rule of Nines.” Initially, participants were challenged with capsules containing multiple additives (including benzoates and parabens) or placebo in a single-blind fashion. Two of the participants had positive additive reactions. These two individuals were then re-challenged utilizing a double-blind, placebo-controlled design at least 2 weeks later. Neither of them had a positive reaction. The author concluded with 95% confidence limits that the prevalence of additive sensitivity in patients with active chronic idiopathic urticaria is somewhere between 0% and 3%. A different study by Nettis *et al.* [21] also found the prevalence of sodium benzoate-induced urticaria/angioedema to be 2%. The Nettis study included 47 patients who had reported episodes of acute urticaria with or without angioedema after ingesting products containing sodium benzoate. The patients underwent skin prick tests for common inhalant and food allergens in addition to measures of serum-specific IgE to common food allergens. Allergy testing revealed 5 subjects (11%) with at least one positive reaction to an IgE test for food. The patients then underwent double-blind, placebo-controlled challenges with sodium benzoate. A placebo was given on day one followed by either placebo or sodium benzoate 48 hours later on day 3. A washout day was allowed followed by either placebo or sodium benzoate on day 5. The sodium benzoate was given at increasing dosage from 25mg to 50mg and finally 100mg with 2 hours of time after each dose. The patients were monitored closely but only the appearance of urticaria and/or angioedema were considered positive responses. Only one subject (2%) had a reaction after ingestion of sodium benzoate. The patient had an atopic history but negative IgE tests for food extracts and did not react to placebo. Her reaction consisted of urticarial lesions 40 minutes after ingestion of 50mg of sodium benzoate. Based on history of prior reactions, the patient underwent double-blind, placebo-controlled food challenges with suspected foods and all were negative. The patient then agreed to undergo a second confirmatory double-blind, placebo-controlled challenge 2 weeks later and again had a positive response to sodium benzoate with urticaria. This study evaluated patients with a history of acute, not chronic, urticarial reactions to food additives and found the prevalence of urticaria/angioedema reactions to sodium benzoate to be very low at 2%.

Several studies have utilized an elimination diet approach in their evaluation of food-additive contributions to chronic urticaria. Unfortunately, no blind or placebo studies of this

type have been reported. The Ros study [14] reported an additive-free diet to be “completely helpful” in 24% of patients with chronic urticaria. Another 57% of patients were “much improved,” 19% were “slightly better” or had experienced “no change.” Rudzki [22] observed clinical response to a diet free of salicylates, benzoates, and azo dyes in 50 of 158 patients. These studies did not investigate which particular additive was potentially inducing or exacerbating the urticaria.

Gibson and Clancy [23] reported the use of an elimination diet in 69 patients with chronic idiopathic urticaria (symptoms present for greater than 3 months; physical urticarias excluded). They found that 54 of the patients experienced complete remission within 2–4 weeks of beginning the diet. Challenge studies using multiple additives revealed that 34% reacted to benzoates. An initial placebo tablet was utilized in the challenges; blinding was not mentioned. Twelve patients agreed to re-challenge after remaining in complete remission for 1 year on the elimination diet. Three of the four in this group who had initially reacted to benzoates remained positive to benzoate challenge at 1 year. None of the three patients who had reacted initially to tartrazine remained positive at 1 year.

Ehlers *et al.* [24] evaluated the response to an elimination diet in 16 children with chronic urticaria (at least 3 months duration). Nine of the 16 children were free of symptoms within 10 days of beginning the diet. An additional 3 patients “improved considerably.” Six of the patients who responded to the diet were challenged in a double-blind, placebo-controlled fashion. Details of the challenge protocol and criteria for positive reactions were not discussed. Five of the 6 patients reacted to at least one of the additives. Four of them reacted to multiple additives (three or more). Parabens elicited reactions in 3 of the 6. Benzoic acid caused a reaction in 1 of the 6. The authors suggested that additives appear to play a significant role in pediatric chronic urticaria, a relatively uncommon condition.

Malanin and Kalimo [25] evaluated the utility of skin testing with additives in chronic urticaria patients. Ninety-one subjects were skin tested with 18 food additives. Twenty-four subjects had at least one histamine equivalent positive food-additive skin test. Ten of the 24 participants with a positive skin test underwent oral food-additive challenges with the suspected additive(s). Only one had a positive challenge (benzoic acid). Overall, significantly more patients with positive skin tests responded to an elimination diet (16 of 18 with positive skin tests versus 17 of 42 with negative skin tests.) The authors proposed non-IgE-mediated skin hyperreactivity as the mechanism for skin test positive reactions. The pathogenesis of additive reactions is presently unknown.

In summary, oral challenge studies with food additives in the setting of chronic urticaria–angioedema present many design challenges. Meticulously designed studies which utilize double-blind, placebo-controlled challenges such as the

Ortalan study and the Simon study suggest that benzoates and parabens are uncommon provoking or exacerbating factors. In selected patients, a trial of an additive-free diet may be warranted followed by systematic reintroduction of additive-containing foods if significant clinical improvement was observed. Double-blind, placebo-controlled additive challenges could then be utilized to diagnose the particular additive sensitivity if clinically appropriate.

## **Benzoates, parabens, and associations with asthma**

The prevalence of asthmatic reactions to food additives in the general population or select groups such as atopic asthmatics has not been definitively defined. Nevertheless, several studies suggest that such reactions are unusual. Weber and colleagues evaluated aspirin and additive sensitivity in a group of 43 patients with moderate to severe persistent asthma. [26] In the initial single-blind challenges, two showed a positive response (decrease in FEV1 of 25% or more from baseline) to benzoates and parabens. Only one (2%) of the patients remained positive during double-blind testing. The prevalence of tartrazine sensitivity in this study was 16% during initial open challenges. This fell to 0% during subsequent double-blind challenges. Of note, bronchodilator medication was not withheld in the majority of patients because a number of apparent false-positive reactions had been obtained earlier in the study when these medications were withheld. This study emphasizes the importance of the double-blind challenge and observing a relatively stable baseline FEV1 prior to the initiation of challenges in patients with persistent asthma.

Tarlo and Broder found only one patient with sodium benzoate hypersensitivity (FEV1 fall of more than 20% from baseline) among 28 patients with persistent asthma. [27] The protocol utilized a double-blind, placebo-controlled design and medications were not withheld. Of note, clinical improvement of this patient’s asthma was not observed when benzoates were removed from the diet. Osterballe *et al.* performed initial open multiple additive challenges in 46 children with persistent asthma [28]. Eleven of the 46 showed positive reactions (FEV1 decrease greater than 20% of baseline). Confirmatory double-blind, placebo-controlled challenges gave only three positive responders.

Genton and associates found 1 of 17 asthmatic patients who reacted to sodium benzoate in a single-blind, randomized placebo-controlled study [16]. Garcia *et al.* reported no reactions to sodium benzoate among 62 patients with steroid-dependent asthma [29]. Not surprisingly, other less rigorously controlled studies have reported more widely varying rates of asthmatic reactions to food additives [30,31].

Similar to chronic urticaria, some authors have suggested an additive-free diet is useful in selected persistent asthmatic patients [32]. This approach has not been evaluated in published controlled trials.

## Benzoates, parabens, and anaphylaxis

Relatively few reports of possible anaphylactic/anaphylactoid reactions have appeared in the medical literature. Given the widespread consumption of these preservatives, one can conclude that such reactions are exceedingly rare. In 1944, Kinsey and Wright reported an “anaphylactoid-type” reaction in an individual 4 hours after he had received a 6-g oral dose of sodium benzoate to evaluate liver function [33]. The following day identical symptoms of “shock” developed within 4 hours of another 6-g sodium benzoate dose. Michels *et al.* reported the case of a young woman who developed “flush, angioedema, and severe hypotension (systolic blood pressure under 50 mm Hg)” 30 minutes after eating a meal containing sodium benzoate as a food preservative [34]. One week earlier she had experienced “generalized itching” after eating cheese, which also contained benzoates. A placebo-controlled challenge with 20 mg of oral sodium benzoate produced urticaria confined to her arms and generalized pruritus. A second challenge, apparently several days later after treatment of a sinus infection, resulted in only “mild localized itching” after ingestion of 160 mg of sodium benzoate. Neither of the above cases provides conclusive evidence of systemic anaphylaxis related to ingested benzoates.

Orally ingested parabens have not been reported to cause systemic anaphylaxis. Nagel *et al.* did report a case of bronchospasm and generalized pruritus associated with administration of intravenous steroids containing parabens in an asthmatic child [35]. Intravenous steroids without paraben preservatives did not induce any symptoms. Skin testing to individual parabens as well as passive transfer tests were positive. Skin testing with the steroid preparations with and without parabens provided further evidence of a hypersensitivity reaction induced by the paraben preservatives. Carr [36] reported two cases of hypotension and diffuse macular rash potentially associated with paraben preservatives contained in a topical lignocaine preparation used for intraurethral anesthesia prior to cystoscopy. One of the patients tolerated a preservative-free topical lignocaine preparation 2 months after his initial reaction. No mention was made concerning whether or not the second patient was able to tolerate a preservative-free preparation.

## Benzoates, parabens, and dermatitis

The development of contact dermatitis associated with topical parabens used in cosmetics and other skin-care products has been reported extensively in the literature dating back to 1940 [5]. A loosely controlled study by Veien *et al.* [37], evaluated the possibility of oral paraben ingestion as an exacerbating factor in patients with chronic “dermatitis” and contact paraben sensitivity diagnosed by patch testing. Two of 14 patients reported flares of their “usual dermatitis”

within 24 hours of ingesting parabens, placebo challenges were negative. These two patients were subsequently followed on an elimination diet for 1–2 months. Neither the patients nor the physicians noted any significant improvement. Perioral contact urticaria has been reported in association with sodium benzoate in a toothpaste [38]. Overall, reported contact reactions to benzoates are rare in comparison to the parabens.

The potential role of ingested benzoates or parabens in atopic dermatitis has received limited attention in the medical literature. Van Bever *et al.* [39], investigated the role of food and food additives in 25 children with severe atopic dermatitis. All of the children were hospitalized and received an elemental diet by nasogastric tube. Topical therapy was continued in the hospital setting. All children were reported to be “almost free of active eczema” after 1–2 weeks of the elemental diet and topical therapy. Selective double-blind, placebo-controlled food and food-additive challenges were performed after 1 week of the observed clinical improvement. Six of the children were challenged with sodium benzoate and three “reacted.” The reactions consisted of “pruritus and redness of the skin” which had apparently resolved within the 4-hour period of observation post-challenge since no “late reactions” were seen. Exacerbations of underlying atopic dermatitis related to challenges were not reported. Any skin findings lasting more than 4 hours were not observed after any food or food-additive challenge. Nevertheless, the authors reported that 24 of the 25 children “reacted” to one or more foods and all children who were challenged with additives “reacted” to at least one. Clearly, reaction criteria were among the major flaws of the study. This study has also been criticized because no placebo reactions occurred after 132 placebo challenges. Hannuksela and Lahti had observed equivalent reaction rates between placebo and active substances in patients with chronic urticaria and atopic dermatitis in an earlier study [18].

Worm *et al.* have performed two carefully designed studies that provide evidence of a link between food additives and atopic dermatitis. In the initial study [40], 50 patients with atopic dermatitis were monitored while eating their usual diet for 4 weeks. Baseline atopic dermatitis skin status scores using a variation of the Costa method were obtained. In phase two, 41 of the patients followed an elimination diet for 6 weeks. At the end of the dietary intervention phase, 26 of the 41 patients showed an improvement in their skin status scores of greater than 35%. Open oral provocation tests with an additive-rich diet given over a period of 2 days were performed in 24 of the 26 responders (two refused). The open diet challenge resulted in positive reactions (worsening of Costa score above 10 points within 48 hours) in 19 of the 24 patients. The authors reported no immediate reactions but rather solely late-phase reactions typically occurring between 24 and 48 hours. Ten patients who had not responded to the dietary intervention also underwent

the open challenge as a control group. None of the control patients reacted. In 15 of the 19 patients reacting to the open challenge, double-blind, placebo-controlled oral food-additive challenges were performed. The additives given together in a single capsule included sodium benzoate, *p*-hydroxybenzoate, azo-dyes, BHA/BHT, and others. Six of 15 patients reacted to the additive challenge given as a single dose followed by a 48-hour observation period. One patient reacted to placebo. Additives were not tested individually.

In the second study [41], the authors set out to determine food-additive-induced sulfidoleukotriene production by leukocytes isolated from the peripheral blood of the group of patients who had positive double-blind, placebo-controlled oral food-additive challenges and to compare these values with both atopic and non-atopic controls. Cysteinyl leukotrienes are potent inflammatory mediators and studies have shown biologically active amounts of leukotrienes present in the skin of atopic dermatitis patients [42]. The study evaluated three groups of patients. Group A ( $n = 10$ ) included non-atopic donors whereas groups B and C included patients suffering from atopic dermatitis. Group B patients ( $n = 9$ ) were those who had improved Costa skin scores after following an elimination diet for 6 weeks but who did not show a positive response to double-blind, placebo-controlled food challenge with food additives. The group C patients ( $n = 9$ ) included patients similar to group B except who did react to double-blind, placebo-controlled food challenge with food additives. Peripheral leukocytes were obtained from each patient of the three groups and incubated with the food additives (food color mix, tartrazine, nitrite, benzoate, metabisulfite, and salicylate) after priming with IL-3. The authors found that baseline sulfidoleukotriene production in the non-atopic group A was significantly lower than that of the atopic groups B and C. No significant baseline differences were noted between atopic groups in this measure. None of the non-atopic group A controls showed increased sulfidoleukotriene production in the presence of any of the food additives used. However, in atopic dermatitis patients with negative food challenges (group B), a modest induction of sulfidoleukotriene production was determined in 1 patient using tartrazine and 2 patients using nitrites. Group C patients (atopic dermatitis with positive food challenge) showed 7 of the 9 patients with increased sulfidoleukotriene production in the presence of different food additives, the most frequent additives implicated being nitrite (5 of 9 patients), benzoate (4 of 9 patients), and tartrazine (3 of 9 patients).

### Miscellaneous reactions

Isolated case reports appear in the literature suggesting symptoms ranging from depression to rhinitis may be related to benzoate ingestion in certain individuals [45]. A study by Pacor *et al.* [43] enrolled 226 patients with

persistent rhinitis categorized as moderate to severe (symptoms present more than 4 days a week and longer than 4 weeks). Patients with asthma, positive skin prick results, history of smoking, recent corticosteroid use, and other medical conditions were excluded. Each patient underwent a 30-day additive-free diet and recorded daily rhinitis symptom scores. At the end of the diet, each patient was reintroduced to a food-additive-rich diet for 15 days, again with daily recording of rhinitis symptom scores. Finally, each patient then underwent a double-blind, placebo-controlled food-additive challenge with three different doses of each additive including tartrazine, erythrosine, monosodium benzoate, *p*-hydroxybenzoate, sodium metabisulfite, and monosodium glutamate. Evaluation of the food-additive challenge was performed subjectively by patient report of rhinitis symptoms and objectively by nasal peak inspiratory flow rate, where decline of 20% in the flow rate was considered positive. Twenty patients (8.8%) reported statistically significant improvement in their daily rhinitis symptom scores while on the food-additive elimination diet, with 6 of these patients (2.6%) reporting no symptoms at all. The same 20 patients showed a positive double-blind, placebo-controlled food challenge with monosodium benzoate as evidenced by reduction in nasal peak inspiratory flow rate by at least 20%. In this study, monosodium benzoate was the only food additive tested that was found to result in a positive oral challenge. All 20 subjects documented return of their rhinitis symptoms during the food-additive-rich diet.

Cutaneous vasculitis has been reported occasionally in association with sodium benzoate ingestion [44–46]. In two of these reports the patients also had microhematuria. Challenge tests were reported to be associated with cutaneous vasculitic lesions and the patients improved with dietary intervention. A study by Lunardi *et al.* evaluated the effects of an elimination diet in 5 patients with biopsy-proven leukocytoclastic cutaneous vasculitis [46]. Evidence for an associated autoimmune disorder, infection, or neoplastic disease was not found. All patients improved on the elimination diet; four showed complete resolution of their skin lesions. All patients “reacted” to at least one food or food additive. Patients were asked to record skin scores on a daily diary. One of the patients reacted to benzoates. The authors reported that with elimination of the offending foods and/or food additives, no relapses were seen in 2 years of follow-up.

The Melkersson–Rosenthal syndrome is a rare disorder characterized by recurrent or persistent orofacial edema, which typically involves the lips, variable facial paralysis, and lingua plicata (fissuring of the tongue) [47]. The syndrome's etiology is unknown but is reported to be more common in atopic individuals. A few reports have suggested that food additives, including benzoates, may play a role [47–51]. However, another investigation using double-blind, placebo-controlled challenges in six patients found no evidence of food or food-additive sensitivity [52].

There has been some interest in linking the prevalence of hyperactivity in children to food-additive intolerance. The initial reports linked hyperactivity to artificial food flavors and colors [53]. Recently, a large study of 3-year old children from the Isle of Wight, UK attempted to address the possible link between food additives and hyperactivity in children in a population-based study [54]. The study was designed to test the hypothesis that food additives have a pharmacological effect on behavior that is irrespective of other characteristics of the child, specifically hyperactivity at baseline and atopy. Bateman *et al.* attempted to enroll all children resident on the Isle of Wight with birth dates in a specified date range who were registered with a general practitioner. Phase 1 of the trial involved screening with a behavioral questionnaire and was followed by skin prick testing for atopy (phase 2). A total of 397 children were selected to enter the challenge stage of the trial, phase 3. Based on results of the behavior questionnaire and skin prick testing, the children were divided into four groups: hyperactive/atopic, non-hyperactive/atopic, hyperactive/non-atopic, and non-hyperactive/non-atopic. After assessment, each group was subjected to a diet eliminating artificial colorings and benzoate preservatives for 1 week. In the subsequent 3 weeks the subjects underwent a double-blind crossover study where they received periods of dietary challenge with a drink containing artificial colorings and sodium benzoate or a placebo mixture. Behavior was then assessed by a tester blind to the subjects' dietary status and by parent's ratings. The study found significant reductions in hyperactive behavior during the additive-free diet phase by parental report. There were also significantly greater increases in hyperactive behavior during the additive versus placebo period based on parental reports. There was no correlation with presence or absence of hyperactivity neither at baseline nor by the presence of atopy. The authors concluded that there is a general adverse effect of artificial food coloring and benzoate preservatives on the behavior of 3-year old children. However, there are aspects of the study that make it difficult to interpret. There were a significant number of dietary mistakes reported where children consumed products that contained preservatives and/or artificial colorings. Also, research psychologists using validated tests were unable to associate the subjects' hyperactivity with consumption of the additive drink versus placebo. Further study of the relationship between childhood hyperactivity and food additives needs to be carried out before any firm conclusions can be made.

## Summary and conclusions

Benzoates and parabens are used extensively as chemical preservatives in foods and beverages in the United States and throughout much of the developed world. These compounds have essentially no toxicity at approved concentrations and

considering their widespread consumption, are extremely well tolerated. Benzoates and parabens have been investigated frequently in association with chronic urticaria–angioedema. Many studies with less stringent design criteria have implicated these agents, particularly the benzoates, as relatively frequent exacerbating factors. On the other hand, more rigorously designed protocols suggest that these chemicals are unusual provoking or exacerbating agents among urticaria patients.

Asthmatic reactions have also been reported and investigated in association with food additives including benzoates and parabens. Well-designed trials have not provided a conclusive link between persistent asthma and benzoates or parabens.

The association of atopic dermatitis with food additives has received relatively limited attention in the medical literature. No well-designed study has implicated benzoates or parabens individually as pathogenic factors. Studies by Worm *et al.* using multiple food additives including benzoates provide evidence that at least some of these substances may be provoking factors in a minority of patients and a potential mechanism may be increased production of leukotrienes.

Rarely, anaphylactic-type reactions have been reported with ingested benzoates but definitive evidence of systemic anaphylaxis is lacking. Oral parabens have not been reported as potential causes of anaphylaxis. However, parabens have been implicated in systemic reactions related to their use in pharmaceutical agents, particularly local anesthetic preparations. Other miscellaneous reports have appeared suggesting benzoates as occasional inciting agents in cutaneous vasculitis.

Reports of hyperactivity in children induced by food additives have been present in the literature for several decades, but further study is needed to confirm this association.

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