

Sulfites

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KEY CONCEPTS

- Sulfites are frequently used food and drug additives.
- Ingestion of sulfite residues has been documented to trigger asthmatic reactions in sensitive individuals.
- Sulfite-induced asthma occurs in less than 5% of asthmatic individuals and those with severe, persistent asthma are at greatest risk.
- The diagnosis of sulfite-induced asthma is best made by blinded oral challenge with assessment of lung function.
- Labeling regulations in the United States alert sulfite-sensitive individuals to the presence of sulfites in foods which must then be avoided.

Introduction

Sulfites or sulfiting agents include sulfur dioxide (SO_2), sulfurous acid (H_2SO_3), and any of several inorganic sulfite salts that may liberate SO_2 under their conditions of use. The inorganic sulfite salts include sodium and potassium metabisulfite ($\text{Na}_2\text{S}_2\text{O}_5$, $\text{K}_2\text{S}_2\text{O}_5$), sodium and potassium bisulfite (NaHSO_3 , KHSO_3), and sodium and potassium sulfite (Na_2SO_3 , K_2SO_3). Sulfites have a long history of use as food ingredients, although potassium sulfite and sulfurous acid are not permitted for use in foods in the United States [1]. Sulfites occur naturally in many foods, especially fermented foods such as wines [1]. In addition, sulfites have long been used as ingredients in pharmaceuticals [2,3].

Over the past 25 years, questions have arisen about the safety of the continued use of sulfites in foods and drugs. These concerns were first voiced following the independent observations in 1981 by David Allen in Australia and Donald Stevenson and Ronald Simon in the United States of the role of sulfites in triggering asthmatic reactions in some sensitive individuals [4–6]. While it is now apparent that sulfite sensitivity affects only a small subgroup of the asthmatic population [6,7], concerns remain because sulfite-induced asthma can be severe – even life threatening – in some sensitive individuals.

As a consequence of the concerns related to sulfite-induced asthma, the use of sulfites in foods and drugs has changed

considerably over the years. Sulfites have been replaced in some products; and the search for effective alternatives continues; in addition, levels of sulfites used have been reduced in other products. Federal regulations have further restricted the use of sulfites in certain food products in the United States. Nevertheless, the sulfite-sensitive individual must stay alert to avoid inadvertent exposure to sulfites.

Clinical manifestations of sulfite sensitivity

A host of adverse reactions have been attributed to sulfiting agents, including asthma, diarrhea, abdominal pain and cramping, nausea and vomiting, urticaria, pruritus, localized angioedema, difficulty in swallowing, faintness, headache, chest pain, loss of consciousness, “change in body temperature,” “change in heart rate,” and non-specific rashes. With the notable exception of the role of sulfites in asthma, diagnostic challenges were not undertaken to confirm the causative role for sulfites in the reported adverse reactions. For normal individuals, exposure to sulfiting agents appears to pose little risk. Toxicity studies in normal volunteers showed that ingestion of 400 mg of sulfite daily for 25 days had no adverse effect [8].

Non-asthmatic responses on oral exposure to sulfites

Various authors have suggested adverse reactions involving several organ systems, but for the most part these effects have not been substantiated by double-blind, placebo-controlled (DBPC) provocation studies. Schmidt *et al.* [9] posited that sulfiting agents may have caused the appearance of a cardiac

arrhythmia in a patient given intravenous dexamethasone. This relationship was never confirmed by appropriate challenge. Hallaby and Maddocks [10] attributed central nervous system toxicity to the absorption of sodium bisulfite from peritoneal dialysis solutions. Wang *et al.* [11] described eight patients who developed chronic neurological defects after receiving an epidural anesthetic agent that contained sodium bisulfite as a preservative. Using an animal model, they demonstrated that the sulfiting agent produced a similar defect. Whether the clinical manifestation in humans was directly attributable to the sodium bisulfite is unknown. In a preliminary report, Flaherty *et al.* [12] presented a patient who appeared to have hepatotoxicity as manifested by changes in liver function tests following challenge with potassium metabisulfite. Meggs *et al.* [13] failed to demonstrate any role for sulfites among eight individuals with systemic mastocytosis. Schwartz [14] described two non-asthmatic subjects who developed abdominal distress and hypotension associated with oral challenge with potassium metabisulfite. Placebo-controlled challenges proved negative, however.

Cutaneous adverse reactions suggestive of hypersensitivity responses have been observed in a few individuals. Cutaneous exposure to sulfites can on rare occasions, apparently elicit contact sensitivity reactions [15]. Epstein [15] described a patient who developed contact sensitivity, as confirmed by appropriate patch testing, through exposure to sulfiting agents used in a restaurant. The ingestion of sulfites has been reported to elicit urticaria in a very few cases as confirmed by DBPC challenges [16], single-blind challenges [17,18], or open challenges [19]; in other cases, an urticarial response was not confirmed by oral challenge [20]. Angioedema attributable to the ingestion of sulfiting agents was reported in two of these patients, but only urticaria was confirmed by open challenge with potassium metabisulfite [19]. Wuthrich [17] conducted single-blind, placebo-controlled challenges with sodium bisulfite in 245 patients with suspected sulfite sensitivity. Fifty-seven of the challenges were positive including 17 patients with urticaria/angioedema, 7 patients with rhinitis, and 5 patients with local anesthetic reactions. Wuthrich *et al.* [18] reported a case of acute intermittent urticaria with an associated vasculitis due to sulfites, based on a placebo-controlled, single-blind challenge. Huang and Frazier [21] presented an individual who developed palmar and plantar pruritus, generalized urticaria, laryngeal edema, and severe abdominal pain with fulminant diarrhea after ingesting sulfiting agents. In a controlled challenge with a local anesthetic containing 0.9 µg of sodium metabisulfite, the patient experienced palmar pruritus but no generalized urticaria. The toxicological mechanism involved in these cutaneous reactions has not been elucidated.

Anaphylaxis-like events have been described in several individuals, although appropriate confirmatory testing was only performed in some instances. Prenner and Stevens [22] described a non-asthmatic individual who developed urticaria, pruritus, and angioedema after eating sulfited foods

in a restaurant. A single-blind challenge with no placebo controls was conducted with sodium metabisulfite. Some of the symptoms (nausea, coughing, erythema of the patient's skin) were reproduced by this challenge. Clayton and Busse [23] reported a patient who developed anaphylaxis after ingesting wine. An open challenge with wine reproduced the patient's symptoms of urticaria, angioedema, and hypotension. While this patient represents a possible case of sulfite sensitivity, specific testing with sulfites was not conducted, nor was any association with sulfiting agents in wine recognized at that time.

Sokol and Hydock [24] identified a single case of sulfite-induced anaphylaxis presenting with urticaria, angioedema, nasal congestion, and nasal polyp swelling that was later confirmed by multiple, single-blind, placebo-controlled oral challenge trials. The patient, who had a history of similar food-related reactions, also produced a positive skin test to sulfite, and histamine could be released from her basophils following incubation with sulfites. Yang *et al.* [25] described three patients with systemic anaphylactic symptoms (rhinorrhea with asthma in one; urticaria with asthma in the second; asthma only in the third) confirmed by sulfite challenge. These three patients had positive skin tests to sulfites and two of the three had positive Prausnitz-Küstner (PK) tests. One individual subsequently died, allegedly after ingestion of sulfited food.

Sulfites have also been implicated as possible causative factors in persistent rhinitis [26]. The role of sulfites was evaluated in a group of 226 patients with persistent rhinitis using DBPC challenges after 1 month on an additive-free diet. Challenges with up to 20 mg of sodium metabisulfite elicited both objective (sneezing and rhinorrhea) and subject (nasal blockage and itching) symptoms in 6 of 20 individuals who reported improvement in rhinitis on the additive-free diet [26]. A reduction of greater than or equal to 20% in nasal peak inspiratory flow rate was also observed in these six subjects [26].

Studies have been undertaken to determine whether sulfiting agent sensitivity frequently causes idiopathic anaphylaxis or chronic idiopathic urticaria (CIU) [13,27–29]. Sonin and Patterson [27] conducted sodium metabisulfite challenges on 12 individuals with idiopathic anaphylaxis, nine of whom reported episodes associated with restaurant meals. None of the patients responded to the challenge. One additional patient with CIU and restaurant-associated symptoms was also challenged; this individual also failed to react to the challenge. Meggs *et al.* [13] studied 25 patients with idiopathic anaphylaxis. Two of the individuals reacted on single-blind challenge; after repeating the sulfite and placebo challenge, one of these patients was subsequently found not to be sulfite sensitive. Another individual appeared to react on repeated challenge and not to placebo. However, institution of a sulfite-free diet had no effect on this patient's subsequent episodes. In a preliminary report on 65 adults

with CIU, none reacted to sulfites when appropriately challenged [28]. Using a rigorous blinded, placebo-controlled trial and objective criteria for positive reactions, Simon [29] was unable to demonstrate a positive reaction to encapsulated metabisulfite (200 mg maximum dose) in 75 patients with chronic urticaria and/or anaphylaxis with a history suggestive of sulfite sensitivity.

Thus, although many adverse reactions have been ascribed to sulfiting agents, the risk appears to be rather low for the non-asthmatic subject. Properly performed DBPC challenges are necessary to confirm whether sulfite sensitivity was responsible for suspected adverse reactions.

Adverse reactions to sulfites on inhalation or intravenous exposures

In addition, systemic adverse reactions have been attributed to intravenous and inhalation administration of sulfiting agents contained in pharmaceutical products. While receiving bronchodilator therapy with isoetharine, an asthmatic subject developed acute respiratory failure that required mechanical ventilation [30]. The patient subsequently experienced erythematous flushing with urticaria upon intravenous administration of metaclopramide that contained a sulfiting agent. In placebo-controlled oral provocation with sodium metabisulfite, this patient developed flushing without urticaria, as well as a significant decrease in pulmonary function. Jamieson *et al.* [31] performed inhalation challenge in a patient with presumed sulfite sensitivity. This individual experienced intense pruritus, tingling of the mouth, nausea, chest tightness, and a feeling of impending doom. No placebo challenge was undertaken, however.

Asthmatic responses on oral exposure to sulfites

Although sulfiting agents play a very limited and somewhat controversial role in the causation of non-asthmatic adverse reactions, their role in the causation of bronchospasm and severe asthma is better established. Kochen [32] was among the first to suggest that ingestion of sulfited food can cause bronchospasm. He described a child with mild asthma who repeatedly experienced coughing, shortness of breath, and wheezing when exposed to dehydrated fruits treated with sulfur dioxide that were packaged in hermetically sealed plastic bags. No direct challenge studies were conducted to confirm this observation. Single-dose, open challenges without placebo control performed in a group of asthmatics by Freedman [33,34] suggested that sulfiting agents could trigger asthma. Eight of 14 subjects with a history of wheezing following consumption of sulfited orange drinks were shown to experience changes in pulmonary function upon administration of an acidic solution containing 100 ppm (100 mg/l) of sodium metabisulfite.

The role of sulfite sensitivity in asthma became more widely recognized after reports of Stevenson and Simon [5] and Baker *et al.* [4]. The initial studies of Stevenson and Simon [5] demonstrated that placebo-controlled oral challenges with potassium metabisulfite could produce significant changes in pulmonary function in certain asthmatics. Their first subjects had severe persistent asthma. In addition to their asthmatic response, these individuals experienced flushing, tingling, and faintness following sulfite challenges. Baker *et al.* [4] showed that oral ingestion and intravenous administration of sulfites could cause significant bronchoconstriction to the point of respiratory arrest in two individuals with severe, persistent asthma. Exposure to sulfiting agents may occur through ingestion and other routes. Sulfur dioxide generated from sulfited foods and drugs may be inhaled. Werth [35] described an asthmatic individual who developed wheezing, flushing, and diaphoresis upon inhaling the vapors released from a bag of dried apricots. The patient did not respond to ingested metabisulfite in capsule form, but reacted to inhalation of nebulized metabisulfite in distilled water. Reports have described several patients who suffered paradoxical responses to the inhalation of bronchodilator solutions. Koepke *et al.* [36,37] demonstrated that sodium bisulfite used as a preservative in bronchodilator solutions was capable of producing bronchoconstriction. Other studies from this group [38] confirmed that the concentration of metabisulfite contained in bronchodilator solutions could potentially generate 0.8–1.2 ppm of sulfur dioxide. Four of 10 subjects who tested negative to a capsule challenge with metabisulfite reacted upon inhalation, whereas 10 non-asthmatic controls did not respond.

In addition to sulfiting agents administered intravenously, orally, or via inhalation, patients may respond to the topical application of sulfiting agents. Schwartz and Sher [39] reported an individual who experienced a 25% decrease in forced expiratory volume in one second (FEV₁) after application of one drop of a 0.75-mg/ml potassium metabisulfite solution to the eye. This patient had previously experienced episodes of bronchoconstriction from the use of eye drops containing sulfite preservatives for the treatment of glaucoma.

Asthmatic subjects may develop bronchoconstriction in response to a wide variety of stimuli. Interestingly, a patient has been described [40] who failed to respond to typical triggers of bronchoconstriction, including inhalation of methacholine and cold air hyperventilation, but who nevertheless experienced increased airway resistance and decreased specific airway conductance following oral challenge with potassium metabisulfite. The significance of this response remains unknown, as no changes in other parameters of pulmonary function, including FEV₁, were observed.

The potential for fatal reactions from sulfite exposure has been confirmed [25,41]. In many instances, individuals who supposedly died from an adverse reaction to sulfite had not undergone appropriate diagnostic challenges. Nonetheless,

competent investigators observed that severe bronchoconstriction, hypotension, and loss of consciousness can occur, demonstrating the potential for fatal reactions in some subjects – particularly those with severe, persistent asthma.

Prevalence

Adult populations

The prevalence of adverse reactions to sulfiting agents is not precisely known. Although attempts have been made to establish the prevalence of sulfite sensitivity in asthmatic subjects, the nature of the population studied and use of several different challenge methods in these studies have resulted in some uncertainty regarding the prevalence estimates. Simon *et al.* [42] examined the prevalence of sensitivity to ingested metabisulfite in a group of 61 adult asthmatics. None indicated a history of sulfite sensitivity. After challenges were conducted with potassium metabisulfite capsules and solutions, a placebo-controlled challenge was used to confirm positive responses. Five of 61 patients (8.2%) experienced a 25% or greater decline in FEV1 upon challenge.

Koepke and Selner [43] conducted open challenges with sodium metabisulfite in 15 adults with a history of asthma after ingestion of sulfited foods and beverages. One of 15 patients (7%) showed a 28% decline in FEV1; no confirmatory challenge was conducted. In a larger study by Buckley *et al.* [44], 134 patients underwent single-blind challenges with potassium metabisulfite capsules. Of these subjects, 4.6% were suspected of having sulfite sensitivity. In these three studies, the population consisted of a large proportion of severe, persistent asthma patients requiring oral steroids for therapy and who were being treated at major referral centers, although sulfite sensitivity was diagnosed in several mild asthmatics as well [6]. Thus, the prevalence estimated from these studies may not be applicable to the asthma population as a whole. Wuthrich [17] challenge 87 suspected, sulfite-sensitive asthmatics with capsules containing sodium bisulfite (5–200mg doses). Fifteen of 87 asthmatics (17.2%) reacted to these sulfite challenges, but the proportion of patients with severe, persistent asthma in this study population was not determined. Because subjects were selected for suspected sulfite sensitivity, the results of this study cannot be used to assess the prevalence of sulfite sensitivity in the overall population of asthmatics.

In the largest study conducted to date, Bush *et al.* [7] conducted capsule and neutral solution sulfite challenges in 203 adult asthmatics. None was selected based on a history of sulfite sensitivity. Of these patients, 120 were not receiving oral corticosteroids, while 83 were. Of the patients not receiving oral steroids, only one experienced a 20% or greater decline in FEV1 after single-blind and confirmatory double-blind challenge. The patients receiving oral steroids had a higher response rate, estimated at approximately 8.4%. The prevalence in the asthmatic population as a whole was

less than 3.9%, with patients with severe, persistent asthma appearing to face the greatest risk.

Pediatric population

Limited studies have been conducted in children. Towns and Mellis [45] evaluated 29 children, aged 5.5–14 years, with moderate to severe asthma. Seven subjects had a history suggestive of sulfite sensitivity. Challenges were conducted with placebo on the first day and with sequential administration of sodium metabisulfite in capsule and solution form on a second day. Nineteen of 29 subjects showed a decrease in the peak expiratory flow rate varying from 23% to 72%, while peak expiratory flow rates with placebo were either unaffected or dropped 19%. When a 20% decline in peak expiratory flow rate was viewed as a positive response, 66% of these children were considered to be sulfite sensitive. Subsequently, the patients were instructed to avoid sulfited food for 3 months. No overall significant improvement appeared in the patients' asthma as a result of this avoidance diet.

Friedman and Easton [46] studied 51 children, aged 5–17 years. Eighteen of 51 (36%) showed a 20% or greater decrease in FEV1 when provoked with potassium metabisulfite in an acidic solution, although placebo challenges in these individuals showed only one responder. The severity of asthma was not apparently correlated with the likelihood of a positive sulfite challenge. Steinman *et al.* [47] evaluated 37 asthmatic children and determined that 8 (22%) responded to double-blind challenges of sulfited apple juice with a 20% or greater decline in FEV1. An additional 8 children were considered to experience a reaction to sulfite when the criterion for a positive reaction was changed to a 10% or greater decrease in FEV1. In contrast, a study by Boner *et al.* [48] determined that only 4 of 56 asthmatic children (7%) responded to single-blind challenges with sulfite in capsules and/or solutions. Furthermore, the sulfite-sensitive individuals displayed no additional change in bronchial reactivity as assessed by methacholine challenges conducted after sulfite reactions. In this study, a positive response was defined as a 20% decline in FEV1.

Whether sulfite sensitivity really occurs more frequently in children has yet to be definitively established. Differences in challenge procedures (capsule versus acidic beverage solutions) may account for the apparent observation of a higher prevalence in asthmatic children. Nonetheless, the overall prevalence of sulfite sensitivity – particularly in adult asthmatics – is small but significant. Severe, persistent asthmatics, particularly adult asthmatics, appear to be at greatest risk.

Mechanisms

The mechanisms of sulfite sensitivity remain unknown. Depending on the route of exposure, a number of possible

mechanisms have been hypothesized. Asthmatics are known to respond with significant bronchoconstriction upon inhalation of less than 1.0ppm of sulfur dioxide [49]. Fine and co-workers [50] demonstrated that bronchoconstriction developed in asthmatics who inhaled sulfur dioxide and bisulfite (HSO_3^-), but not sulfite (SO_3^{2-}). Alteration of airway pH itself did not cause bronchoconstriction. Thus, asthmatics may respond differently to various ionic forms of sulfite that are dependent on pH. Some asthmatics also respond to either oral or inhalation challenge with sulfite, although inhalation appears more apt to produce a bronchoconstrictive response [51]. However, the inhalation of sulfur dioxide or various sulfites may not be the total explanation. Field *et al.* [52] challenged 15 individuals with increasing concentrations of SO_2 gas or a metabisulfite solution. All 15 subjects reacted to the metabisulfite solution, and 14 of the 15 reacted to inhaled SO_2 with a 20% or greater drop in FEV1. These investigators concluded that the generation of SO_2 gas cannot fully explain sulfite-induced asthma [52].

Considerable variability has been noted in the response to capsule and acidic beverage challenges with sulfiting agents [53]. When challenged on repeated occasions, the same group of individuals may not consistently experience bronchoconstriction. This variability may provide some clues to understanding of the mechanism of sulfite-induced asthma.

Inhalation during swallowing

In a study of 10 sulfite-sensitive asthmatic subjects, Delohery *et al.* [54] demonstrated that all of the subjects reacted to an acidic metabisulfite solution when it was administered as a mouthwash or swallowed. However, none of these subjects reacted when the metabisulfite was instilled through a nasogastric tube. These same individuals did not respond with changes in pulmonary function when they held their breath while swallowing the solution. A control group of 10 non-sulfite-sensitive asthmatics showed no response to the mouthwash or swallowing challenge. Delohery *et al.* [54] hypothesized that some individuals respond to these forms of challenge because they inhale sulfur dioxide during the swallowing process.

Linkage with airway hyperreactivity

Because asthmatics respond to various stimuli (airway irritants) at concentrations lower than normal individuals (i.e. they exhibit airway hyperresponsiveness), attempts have been made to link sulfite sensitivity with airway responsiveness to histamine and methacholine. Such an association has not been established [48,54]. For example, Australian investigators [54] were unable to demonstrate a relationship between the degree of airway responsiveness to inhaled histamine and the presence of sulfite sensitivity.

In human studies, attempts to block the effect of metabisulfite by agents such as inhaled lysine aspirin, inhaled indomethacin, and inhaled sodium salicylate demonstrated

a slight protective effect, suggesting a possible role of prostaglandins in the mechanism of sulfite sensitivity [55]. Further, leukotriene receptor antagonists attenuate SO_2 -induced bronchoconstriction, implying that leukotriene release may also be involved [56]. Administration of the neutral endopeptidase inhibitor, thiorphan, was shown to enhance the airway response to inhaled sodium metabisulfite challenge in normal individuals [57]. This study suggests that tachykinins may play a role in metabisulfite-induced bronchoconstriction [57]. This mechanism was also supported by observations in guinea pigs that capsaicin-sensitive sensory nerves are involved in sulfite-induced bronchoconstriction [58]. Inhaled magnesium sulfate also has been shown to mildly inhibit inhaled metabisulfite-induced bronchoconstriction, but the mechanism is not known [59].

Refractoriness has been demonstrated to a number of indirect bronchoconstrictor stimuli including metabisulfite. The generation of nitric oxide (NO) as a possible explanation for the refractoriness has been investigated in asthmatic subjects undergoing inhaled metabisulfite challenge [60]. Blockage of NO had no effect either on the response to metabisulfite *per se* or the refractory process, suggesting that NO is not involved in metabisulfite-induced bronchoconstriction.

Animal models demonstrated that application of sodium metabisulfite to the trachea of anesthetized sheep increased local blood flow and vascular permeability and induced epithelial damage [61]. Sulfite-induced bronchoconstriction in sheep may also involve stimulation of bradykinin B_2 -receptors which may subsequently activate cholinergic reflex mechanisms [62].

Our group attempted to induce sulfite sensitivity in a group of 16 asthmatic subjects (unpublished). After the provocative dose of methacholine producing a 20% decrease in FEV1 was established, a sulfite challenge using an acidic sulfite solution was instigated to identify any sulfite sensitivity. Three of the 16 subjects reacted to the sulfiting agent with a 20% or greater decrease in FEV1. One week after this challenge, the patients underwent bronchial challenge with an antigen to which they exhibited sensitivity. The following day, the patients returned for a repeat methacholine challenge, followed by a second sulfite challenge 24 hours later. After the antigen challenge, only one additional subject showed a response to sulfiting agent that had not been present before antigen challenge. No significant increase was observed in airway response to methacholine. Thus, this study did not link airway hyperreactivity and sulfite sensitivity. Similar negative results were obtained in a study of asthmatic children [48].

Cholinergic reflux

Because sulfur dioxide may produce bronchoconstriction through cholinergic reflex mechanisms, preliminary studies have examined the effect of atropine and other anticholinergic agents [63]. Inhalation of atropine blocked the airway response to sulfiting agents in three of five subjects

and partially inhibited the response in the other two subjects. Doxepin, which possesses both anticholinergic and antihistaminic properties, had protective effects in three of five individuals. In a study on sheep, inhaled metabisulfite-induced bronchoconstriction that could be prevented by pretreatment with either ipratropium bromide or nedocromil sodium, but not by chlorpheniramine [62]. Sulfite-induced bronchoconstriction in these sheep was also associated with a 9-fold increase in immunoreactive kinins. Consequently, Mansour *et al.* [62] concluded that sulfite-induced bronchoconstriction in sheep involves stimulation of bradykinin B₂-receptors with subsequent activation of cholinergic mechanisms. Studies in guinea pigs suggest that capsaicin-sensitive sensory nerves may play a role in sulfite-induced bronchoconstriction [58].

Possible IgE-mediated reactions

Adverse reactions to sulfites appear most commonly in atopic individuals, and studies have attempted to identify an immunological basis for these reactions. Several reports have demonstrated positive skin tests to solutions of sulfiting agents in some sensitive patients. The positive skin tests and other related evidence may point to the existence of an IgE-mediated mechanism in at least some sulfite-sensitive individuals.

Prenner and Stevens [22] observed a positive scratch skin test to an aqueous solution of sodium bisulfite at 10mg/ml in a patient. This patient also exhibited a dramatic response to intradermal testing at the same concentration. Three non-sensitive control subjects had negative skin tests. The patient of Twarog and Leung [30] also showed a positive intradermal skin test response to an aqueous solution of bisulfite at 0.1 mg/ml, whereas controls were negative with concentrations up to 1.0mg/ml of the solution. Yang *et al.* [25] also identified several asthmatic subjects with either positive prick or intradermal skin test to sulfites. Boxer *et al.* [64] identified two additional cases with positive skin tests that also had positive oral challenges to sulfiting agents. Selner *et al.* [65] reported positive intradermal and skin prick tests with 0.1- and 10-mg/ml potassium metabisulfite solutions, respectively, in an SSA subject. This patient also had a positive intradermal test with a 0.1-mg/ml solution of acetaldehyde hydroxysulfonate, a major bound form of sulfite in wine and other foods [65]. Control subjects had negative skin tests.

Further evidence for an IgE mechanism can be found in positive passive transfer tests (PK transfer). Several investigators have successfully transferred skin test reactivity to non-sensitized subjects with sera from sulfite-sensitive individuals [22,25,66]. The effect can be abolished by heating sera to 56°C for 30 minutes [66]. These observations suggest the presence of a serum factor (IgE). However, specific IgE antibodies to sulfiting agents have not been demonstrated [64,66].

Sulfiting agents can induce mediator release from human mast cells (MCs) and basophils obtained from some sensitive individuals. Histamine release has been demonstrated in mixed peripheral blood leukocyte studies in sulfite-sensitive individuals [24,30]. Similarly, Meggs *et al.* [13] noted a significant rise in plasma histamine levels in two of seven subjects with systemic mastocytosis undergoing a sulfite challenge. No clinical response was observed in these patients, however. In a skin test-positive exposure demonstrated increased histamine levels in nasal lavage fluid 7.5 minutes after challenge [67]. Similar results were obtained in chronic rhinitis control subjects, although the histamine levels generally fell below those found in patients with sulfite sensitivity [67]. In contrast, other investigators have not been successful or noted inconsistent results in attempting to demonstrate histamine release from the MCs or basophils among sulfite-sensitive individuals [5,14,68,69]. Histamine, *per se*, may not play a significant role in sulfite-induced airflow obstruction since H₁-receptor antagonists fail to block the response [56].

Indirect evidence for the role of MC mediators in the production of bronchoconstriction due to sulfiting agents has also been found. Friedman [34] mentions that inhaled sodium cromolyn prevented the asthmatic response. In preliminary studies, Simon *et al.* [63] found that inhaled cromolyn inhibited sulfite-induced asthma in four of six subjects and partially inhibited the response in two other subjects. Schwartz [70] reported that oral cromolyn at a dose of 200 mg blocked an asthmatic response to oral sulfite challenge in a single individual.

Sulfite oxidase deficiency

Other possible mechanisms for sulfite sensitivity have also been suggested. Simon [68] proposed that a deficiency in sulfite oxidase, an enzyme that metabolizes sulfite to sulfate, may promote the adverse reactions. The skin fibroblasts of six sulfite-sensitive subjects exhibited less sulfite oxidase activity than normal controls. However, the major source of sulfite oxidase activity in humans resides in the liver. Further investigation will be needed to determine the importance of this suggested mechanism.

Diagnosis

The diagnosis of sulfite sensitivity cannot be established by the patient's history alone. Our group [7] was unable to correlate the presence of a positive sulfite challenge with the patient's history, and vice versa. The diagnosis of sulfite sensitivity should, therefore, be made only in individuals who demonstrate an objective response upon appropriate challenge.

Skin testing – by both prick and scratch methods – has identified some individuals with positive responses [25,64]. In contrast, some individuals who have equally severe bronchospasm or other reactions had negative skin tests.

Table 29.1 Capsule and neutral solution metabisulfite challenge**Preparing the patient and collecting preliminary data*

- Withhold short-acting aerosol sympathomimetics and cromolyn/nedocromil sodium for 8 hours and short-acting antihistamines for 24–48 hours before pulmonary function testing.
- Measure pulmonary function: FEV1 must be greater than or equal to 70% of predicted normal value and greater than or equal to 1.5 L in adults. (Test contraindicated in patients with an FEV1 below those levels. Standards for children have not been defined.)

Performing the single-blind challenge

- Administer placebo (powdered sucrose) in capsule form. Measure FEV1.
- Administer capsules containing 1, 5, 25, 50, 100, and 200 mg of potassium metabisulfite at 30-minute intervals. Measure FEV1 30 minutes after administering each dose and if the patient becomes symptomatic.
- If no response, administer 1, 10, and 25 mg of potassium metabisulfite in water–sucrose solution at 30-minute intervals. Measure FEV1 30 minutes after each dose and if symptoms occur. Positive response is indicated by a decrease in FEV1 of 20% or more.

Performing the double-blind challenge

- Perform challenge and placebo procedures on separate days, in random order.
- Placebo day: Administer only sucrose in capsules and solution. Measure FEV1 30 minutes after each dose and if patient becomes symptomatic.
- Challenge day: Same protocol as single-blind challenge day.

*Protocol used in the University of Wisconsin prevalence study [7]. Perform this test only where the capability for managing severe asthmatic reactions exists. Stop challenge sequence after a positive response is obtained.
(Reproduced from Bush RK [71], with permission.)

Diagnostic challenges

Because diagnostic challenges represent the only effective confirmatory technique, and because such challenges may pose significant risk to sensitive subjects, patients must be informed of the risks involved. Physicians instituting such provocation procedures should have available all equipment necessary for the treatment of severe bronchospasm or anaphylaxis, including airway intubation and mechanical ventilation. The end point for objective assessment of reactivity should be ascertained before the challenge begins. Such measures might include changes in airway function in asthmatics or the appearance of urticaria in patients with this type of response. Patients may be challenged with capsules, neutral solutions, or acidic solutions of metabisulfite. Some protocols reported in the literature are shown in Tables 29.1 and 29.2 [71]. Currently, a capsule challenge is the preferred option, as most sulfite exposure is likely to involve bound forms of sulfites in foods rather than solutions.

When conducting challenges in a single-blind fashion, positive results should be confirmed via a double-blind procedure. Moreover, if a placebo day and an active challenge

Table 29.2 Acid solution metabisulfite challenge¹*Preparing the patient and collecting preliminary data*

- Withhold aerosol sympathomimetics and cromolyn sodium for 8 hours and antihistamines for 24–48 hours before pulmonary function testing.
- Measure pulmonary function: FEV1 must be greater than or equal to 70% of predicted normal value and greater than or equal to 1.5 L in adults. (Test contraindicated in patients with an FEV1 below those levels. Standards for children have not been defined.)

Performing the bisulfite challenge

- Dissolve 0.1 mg of potassium metabisulfite in 20 ml of a sulfite-free lemonade crystal solution. Have the patient swish the solution around for 10–15 seconds, then swallow.
- Measure FEV1 10 minutes after the first dose. Then, administer 0.5, 1, 5, 10, 15, 25, 50, 75, 100, 150,² and 200² mg per 20 ml of the solution at 10-minute intervals. Measure FEV1 10 minutes after each incremental increase in dose. Positive response is signified by a decrease in FEV1 of 20% or more.

¹ Protocol investigated by the Bronchoprovocation Committee–American Academy of Allergy, Asthma and Immunology. Perform this test only where the capability for managing severe asthmatic reactions exists. Stop challenge sequence after a positive response [71].

² Doses in excess of 100 mg are likely to produce non-specific bronchial reactions in asthmatics due to the high levels of free SO₂ that are generated.

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day are conducted on two separate occasions, the possibility of order effects on the results must be considered. For example, if a patient receives placebo on the first day and experiences no response, he or she may experience a reaction on the subsequent challenge day regardless of whether placebo or active challenge with sulfite is administered, because of increased anxiety. To overcome this possibility, the order of administration of active and placebo challenges should be randomized and a third challenge day, either active or placebo, potentially instituted.

Treatment

Avoidance of sulfited foods and drugs

Sulfite-sensitive individuals should avoid sulfite-treated foods [72,73] and drugs [71,74] that have been shown to trigger the response. Because individuals may vary in their sensitivity to sulfited foods, it may be necessary to perform challenges with foods containing sulfites to determine which ones the patient can tolerate.

Some bronchodilator solutions, subcutaneous lidocaine, intravenous corticosteroids, and intravenous metaclopramide may pose a risk for sensitive subjects. Many pharmaceutical companies are aware of this possibility, however, and are taking steps to eliminate sulfiting agents from their products.

Table 29.3 Some anti-asthma preparations that may contain sulfites

Epinephrine	Adrenaline, Monarch
	Twinject™, versus Pharmaceuticals
	Epi-Pen™, Dey Laboratories
	Epinephrine, Lypomed
	Epinephrine, America Reagent
Isoproterenol solutions	Isoproteranol, Elkins-Sinn
	Isuprel™, Sanofi-Winthrop
Ingestible corticosteroid	Decadron™, Merck
	Dexamethasone, Elkins-Sinn
	Dexamethasone, Abbott Laboratories

A partial list of sulfited medications appears in Table 29.3. Package inserts for suspect medications should be consulted for the latest information.

Use of injectable epinephrine

Although some forms of epinephrine contain sulfite used as a preservative, administration of this drug has not been shown to cause a reaction in sulfite-sensitive individuals. Apparently, epinephrine’s action overcomes any adverse effects attributable to the preservative. Thus, patients who are inadvertently exposed to sulfites typically find self-administration of epinephrine useful.

Use of blocking agents

Limited studies have been conducted with a variety of agents that may block the responses to sulfite, including cromolyn sodium, atropine, doxepin, and vitamin B₁₂ [63,75]. Although these treatments have demonstrated beneficial effects in limited numbers of patients, they remain investigational and cannot be recommended for standard use.

Use of sulfite test strips

Chemically treated strips to test foods for sulfite content have been available in the past. Both false-positive and false-negative reactions have been encountered using these devices, so they are not reliable [76].

A better understanding of the mechanisms involved in sulfite sensitivity would allow for more specific interventions to treat and perhaps prevent these reactions.

Food and drug uses

Food

Sulfiting agents are added to many different types of foods for several distinct technical purposes (Table 29.4). The key technical attributes of sulfites in foods include the inhibition of enzymatic browning, antimicrobial actions, dough conditioning effects, antioxidant purposes, bleaching applications, and a host of other uses characterized as processing aids [1]. Some uses of sulfites have now been restricted by federal regulatory actions in the United States. In many food products, sulfites serve multiple purposes. In white wines, for example,

Table 29.4 Technical attributes of sulfites in foods

Technical attribute	Examples of specific food applications
Inhibition of enzymatic browning	Fresh fruits and vegetables*
	Salads*
	Guacamole*
	Shrimp (black spot formation)
Inhibition of non-enzymatic browning	Pre-peeled raw potatoes
	Dehydrated potatoes
	Other dehydrated vegetables
	Dried fruits
Antimicrobial actions	Wines
	Corn wet-milling to make cornstarch, corn syrup
Dough conditioning	Frozen pie crust
	Frozen pizza crust
Antioxidant action	No major US applications
Bleaching effect	Maraschino cherries
	Hominy

*No longer allowed by US Food and Drug Administration.

their primary function is to prevent bacterial growth and acetic acid formation; an important secondary effect is to prevent browning [1]. Because of their important technical attributes, sulfites are utilized in an enormous number of specific applications in a wide variety of foods [1,77].

Given the wide variety of applications for sulfites, a broad range of use levels and residual sulfite concentrations can be found in foods (Table 29.5). Residual sulfite concentrations in foods can range from undetectable (less than 10ppm) to more than 2000ppm (mg SO₂ equivalents per kg of food). Although SSAs vary in their degree of sensitivity to ingested sulfites, all such individuals can tolerate some sulfite. Certainly, the more highly sulfited foods pose the greatest hazard to SSAs.

Inhibition of enzymatic browning and other enzymatic reactions

Sulfites can inhibit numerous enzymatic reactions, including those involving polyphenoloxidase, ascorbate oxidase, lipoxygenase, peroxidase, and thiamine-dependent enzymes [1]. The inhibition of polyphenoloxidase helps to control enzymatic browning, which occurs to varying degrees and at variable rates on the surfaces of cut fruits (especially apples and pears) and vegetables (especially potatoes), at the edges of shredded lettuce, and in guacamole. In the presence of oxygen, polyphenoloxidase catalyzes the oxidation of mono- and ortho-diphenols in these fruits and vegetables to quinones. The quinones can cyclize, undergo further oxidation, and condense to form brown pigments. Black spot formation in shrimp comprises a similar type of reaction, in which tyrosinase (a type of polyphenoloxidase) catalyzes the oxidation of the amino acid, tyrosine, in the shrimp tissue.

Table 29.5 Estimated total SO₂ level as consumed for some sulfited foods*

<i>>100 ppm</i>	
Dried fruit (excluding dark raisins and prunes)	
Lemon juice (non-frozen)	
Lime juice (non-frozen)	
Wine	
Molasses	
Sauerkraut juice	
Grape juice (white, white sparkling, pink sparkling, red sparkling)	
Pickled cocktail onions	
<i>50–99.9 ppm</i>	
Dried potatoes	
Wine vinegar	
Gravies, sauces	
Fruit topping	
Maraschino cherries	
<i>10.1–49.9 ppm</i>	
Pectin	
Shrimp (fresh)	
Corn syrup	
Sauerkraut	
Pickled peppers	
Pickles/relishes	
Corn starch	
Hominy	
Frozen potatoes	
Maple syrup	
Imported jams and jellies	
Fresh mushrooms	
<i><10 ppm</i>	
Malt vinegar	Sugar (especially beet sugar)
Dried cod	Gelatin
Canned potatoes	Coconut
Beer	Fresh fruit salad
Dry soup mix	Domestic jams and jellies
Soft drinks	Crackers
Instant tea	Cookies
Pizza dough (frozen)	Grapes
Pie dough	High fructose corn syrup

*Adapted from the re-examination of the GRAS status of sulfiting agents. Life Science Research Office, Federation of American Societies for Experimental Biology, January, 1985.

The mechanism of action of sulfites in inhibition of enzymatic browning appears to be complex [1]. Sulfites may directly inhibit the polyphenoloxidase [1]. They may also react with intermediate products, especially the quinones, formed during the browning reaction, thereby preventing the ultimate formation of the brown pigments [1]. Sulfites also act as reducing agents that promote the conversion of the quinones back to the original phenols.

The amount of sulfites necessary to prevent enzymatic browning varies according to the level of activity exhibited by the polyphenoloxidase, the nature and concentration of the substrate, the desired period of control, and the presence of other inhibitors or controlling factors. When only monophenols such as tyrosine are present, fairly low levels of sulfite can produce an effect (as in potatoes and shrimp). When diphenols are present (as in guacamole and cut fruit), much higher concentrations of sulfites may be necessary. The concentrations of these phenolic substrates in fruits and vegetables vary widely, with high levels found in guacamole and rather low levels present in lettuce. Sulfites do not irreversibly inhibit enzymatic browning, so the required concentrations of sulfites remain dependent on the length of time that the reaction must be inhibited.

The US Food and Drug Administration (FDA) has prohibited many of the uses of sulfites for the control of enzymatic browning. Several alternatives exist for the control of enzymatic browning [1]. Because polyphenoloxidase is dependent on oxygen, exclusion of oxygen through modified atmosphere packaging is a viable alternative. The use of acidulents (e.g. citric, acetic, or erythorbic acids) to slow the activity of the enzyme and the addition of reducing agents (e.g. ascorbic acid) to convert the quinones back to phenols are the most common alternatives; these techniques are often used in combination. Blanching of fruits or vegetables can also inactivate the enzyme – but then the products are no longer fresh. Freezing slows the activity of polyphenoloxidase markedly. For this reason, frozen potatoes do not require the addition of appreciable levels of sulfites, unlike fresh or refrigerated potatoes. This freezing effect also avoids the necessity of adding sulfites to other fruits and vegetables. Alternatives to sulfites for pre-peeled raw potatoes and shrimp have proved difficult to develop due to the level of activity of the enzymes, the long period of inhibition desired, and especially the ability of sulfite to penetrate into subsurface tissue. 4-Hexylresorcinol has been identified as an effective alternative in shrimp and other foods [78,79], although its application remains rather limited.

Inhibition of non-enzymatic browning

Non-enzymatic browning is a term used to describe a family of diverse reactions that commonly involve the formation of carbonyl intermediates and, ultimately, brown polymeric pigments. The final pigments closely resemble those produced by enzymatic browning. The key difference is the lack of any enzyme to catalyze these reactions. Examples of non-enzymatic browning include the reaction between amino acids and reducing sugars and the caramelization of sugar. Specific food applications in which sulfites are used to control nonenzymatic browning include dehydrated potatoes, other dehydrated vegetables, dried fruits, white wines, white grape juice, non-frozen lemon and lime juices, grated coconut, pectin, and some varieties of vinegar.

Sulfites control non-enzymatic browning by reacting with any of the carbonyl intermediates or substrates for this reaction [1,80]. Once bound to sulfites, the carbonyls can no longer condense to form the brown pigments. The stability of the carbonyl-sulfite reaction products varies widely, ranging from virtually irreversible to readily reversible. The sulfite level necessary to control non-enzymatic browning likewise varies with the nature of the carbonyls formed and the stability of the carbonyl-sulfite reaction products. Where unstable products result, more sulfite is needed.

No effective alternatives to sulfite for the inhibition of non-enzymatic browning have been identified despite intensive efforts [1]. The removal of sugars by fermentation, application of glucose oxidase, changes in formulation, and leaching can produce the desired effect, but have obvious limitations because the resulting products would be dramatically altered. Acids can slow, but not stop, non-enzymatic browning. Acidification has limitations as well because of the long shelf life of some of the affected products.

Antimicrobial actions

Sulfites are not widely used in foods for their antimicrobial actions. In a few food processes, however, sulfites play a crucial role in the inhibition of undesirable bacteria [1,81]. In wine-making, sulfites allow the yeast to ferment sugar to ethanol while preventing the growth of undesirable bacteria that would lead to the formation of acetic acid. In corn wet-milling, the corn kernels are soaked in sulfited steep liquor. The sulfite dissociates interactions between corn germ proteins and the starchy endosperm, thereby facilitating the removal of the starch. Another extraordinarily important function of the sulfites in corn wet-milling is the prevention of bacterial growth in the steep liquor. In addition, SO₂ is widely used during the transport and storage of table grapes to prevent mold growth [82]. In general, sulfites work much more effectively against bacteria and molds than they do against yeasts.

The mechanism of antimicrobial action of sulfites is not well understood [1]. Acidic pHs enhance the antimicrobial activity of sulfites, suggesting that H₂SO₃ may be the active sulfite form in producing the antimicrobial effects. The amount of sulfites necessary to prevent undesirable microbial growth depends on the nature of the substrate, the length of time that growth inhibition is required, and the degree of binding between sulfites and other food components. Certain wine components (such as acetaldehyde and pyruvate) bind strongly to sulfites, and these bound forms of sulfite do not provide effective antimicrobial properties. Thus, sufficient sulfite must be added to wines to preserve enough free sulfite to prevent bacterial growth. In corn wet-milling, the sulfite concentrations in the steep liquor are relatively high, but nearly all of the sulfite is removed following further purification of corn starch and corn syrup. With table grapes, distribution of the fruit is not

allowed unless residual sulfites have dissipated to undetectable levels.

While sulfites have few applications in foods for antimicrobial purposes, suitable alternatives have proven difficult to find. The wide spectrum of antimicrobial activity is appealing in both corn wet-milling and wine-making. Other antimicrobial agents approved for use in foods have a narrower spectrum of activity and represent ineffective replacements for sulfites. In table grapes, the gaseous nature of SO₂ is indispensable and replacement is, therefore, unlikely.

Dough conditioning

Sulfites were widely used as dough conditioners in the baking industry, especially in frozen pizza doughs and pie crusts [1]. Most of these uses of sulfites has now been discontinued. Occasionally, these substances are used in crackers, cookies, biscuits, and tortilla shells. Sulfites act by breaking the cysteine disulfide bonds that are prevalent in the gluten fraction of the dough [83]. The levels of sulfites required for dough conditioning are relatively low. Some dough formulations do not require sulfite, and such options are growing in favor.

Antioxidant uses

Sulfites are not used in the United States to prevent oxidative rancidity of fats because other additives are favored for this application. Sulfites are used for this purpose in other countries, especially in meat products. In contrast, it is illegal to add sulfites to meats in the United States. (The ability of sulfites to inhibit enzymatic and non-enzymatic browning might also be described as an antioxidative effect.) At one time, sulfites were routinely added to beer to prevent undesirable, oxidative flavor changes [81], but they are no longer used in US beers.

Bleaching actions

Sulfites have major applications in the bleaching of cherries for the production of maraschino cherries and glace fruit and the bleaching of hominy [1]. Other minor bleaching uses include the bleaching of pectins and the development of translucency in orange, lemon, grapefruit, and citron peel [1]. In other products, their bleaching effects are considered detrimental to quality. Relatively high concentrations of sulfites are necessary to produce the bleaching effect, although further processing removes much of the sulfite from these products. Consequently, exposure to sulfites from these foods is minimal. No alternative bleaching agents have been identified.

Drugs

Sulfites are added to many pharmaceutical products [2,3]. Table 29.3 contains a list of drugs intended for asthmatics that may contain sulfites. With the increased concern over sulfite-induced asthma, these substances have been removed from some drugs in recent years, especially from

drugs intended for asthmatics. Sulfites are used in drugs intended for oral, topical, respiratory, and internal use.

Sulfites have two primary functions as drug ingredients. First, they act as antioxidants, typically preventing the oxidation of one or more of the active drug ingredients. Second, they prevent non-enzymatic browning, which involves the reactions of reducing sugars with amino acids or amines. The addition of sulfites prevents those reactions, which can occur in enteral feeding solutions and dextrose solutions. The latter stages of the non-enzymatic browning reaction involve the condensation of quinones. Epinephrine can undergo a similar reaction that diminishes its potency. Consequently, sulfites are routinely added to epinephrine to prevent such condensation reactions.

The usage levels of sulfites in pharmaceutical products vary from 0.1% to 1.0%, although a few products may contain higher concentrations. Exposure to sulfites via drugs can be high but would be sporadic in most cases. The active ingredients of the drug may, in a few cases, counteract the effects of sulfite in sulfite-sensitive individuals. Until recently, sulfites were common additives in certain bronchodilators but, except in a few rare cases [36], the bronchodilating effect of the active ingredient overwhelms the bronchoconstricting effect of sulfite. As noted earlier, epinephrine easily overwhelms the bronchoconstricting effects of sulfites. Thus, sulfite-containing epinephrine should never be denied to or avoided by a sulfite-sensitive asthmatic because it can act as a life-saving antidote [2,84].

Many existing alternatives could replace sulfites as antioxidants in pharmaceutical products. These alternative formulations have been widely adopted in drugs commonly used by asthmatics. On the other hand, alternatives do not exist for sulfite for the prevention of non-enzymatic browning. The development of effective alternatives for this purpose will be extremely difficult. Sulfite-sensitive individuals should stay alert to the possible presence of sulfites in medications and seek out alternative formulations. Epinephrine is the exception. Epinephrine can be administered, if necessary, to sulfite-sensitive individuals.

Fate of sulfites in foods

SO₂ and its sulfite salts are extremely reactive in food systems. The wide range of technical attributes of sulfites in foods is a direct result of this reactivity. Thus, these substances often react with a variety of food components. A dynamic equilibrium exists between free sulfites and the many bound forms of sulfite [1]. Thus, the fate of these food additives will vary widely, depending on the nature of each individual food.

SO₂ and the sulfite salts readily dissolve in water and, depending on the pH of the medium, can exist as sulfurous acid (H₂SO₃), bisulfite ion (HSO₃⁻), or sulfite ion (SO₃⁻) [74]. All of these forms react with a variety of food components

with the extent and reversibility of these reactions relating to pH. At acidic pHs (pH of less than 4.0), SO₂ can be released as a gas from a sulfite-containing food or solution. Thus, sulfites can actually be lost from foods, albeit only under acidic conditions.

Sulfites react readily with food constituents including aldehydes, ketones, reducing sugars, proteins, amino acids, vitamins, nucleic acids, fatty acids, and pigments [1]. The extent of any reaction between sulfite and some food component is dependent on the pH, temperature, sulfite concentration, and reactive components present in the food matrix. Equilibrium always exists between free and bound sulfites, although the reversibility of the reactions varies over a wide range [1,77]. Some reactions, such as between acetaldehyde and sulfite to form acetaldehyde hydroxysulfonate, are virtually irreversible. Other reactions, such as between the anthocyanin pigments of fruits and sulfite, reverse readily. The binding of sulfite by various food constituents diminishes the concentration of free sulfite in the food. While the dissociable, bound forms of sulfite can serve as reservoirs of free sulfite in the food, irreversible reactions tend to remove sulfite permanently from the pool of free sulfite. The desirable actions of sulfites in foods frequently depend on free sulfite, so the concentration of the pool of free sulfite represents a critically important factor in technical effectiveness. Therefore, treatment levels for specific food applications aim to provide an active, residual level of free sulfite throughout the shelf life of the product.

In lettuce, high concentrations of sulfite (500–1000 ppm) were once used to prevent enzymatic browning. Because lettuce consists mostly of cellulose and water, the sulfite had few components with which to react. Consequently, most of the sulfite added to lettuce lingered in the form of free inorganic sulfite [85]. Lettuce is unique in this regard, as most foods contain substances that readily react with sulfites. In most foods, therefore, the bound forms of sulfite predominate.

A comprehensive discussion of the possible reactions between sulfites and food constituents lies beyond the scope of this chapter. An entire book has been written on the subject of the chemistry of sulfites in foods [77]. Suffice it to say that the fate of sulfite in individual food products is dynamic, extraordinarily complex, and difficult to predict with any degree of precision.

Likelihood of reactions to sulfited foods

Few trials have attempted to evaluate the sensitivity of SSAs to sulfited foods. Based on the suspected mechanisms of sulfite-induced asthma, one might predict that acidic foods and beverages capable of generating SO₂ gas would be more hazardous than other forms of sulfited foods. Clinical challenges with acidic solutions of sulfite in lemon juice or some other vehicle appear to support this conclusion [54,84]. In all

foods, the fate of sulfite may be an important determinant of the degree of hazard faced by the sulfite-sensitive consumer. Little evidence currently exists, however, regarding the hazard levels posed by the various forms of foodborne sulfite. The overall concentration of residual sulfite in the food also represents an important determinant of the likelihood of a reaction.

Clinical challenges have documented several features of sulfite-induced asthma. First, all SSAs exhibit some tolerance for ingested sulfite. The threshold levels vary from one patient to another, ranging from approximately 0.6 mg of SO₂ equivalents (1 mg of K₂S₂O₅) to levels greater than 120 mg of SO₂ equivalents (200 mg of K₂S₂O₅). Second, clinical challenges have confirmed that free, inorganic sulfite presents a hazard to SSAs. Third, more asthmatics will respond to inhalation of SO₂ or ingestion of acidic sulfite solutions than to ingestion of sulfite in capsules.

From these facts, several predictions can be made about the likelihood of reactions to sulfited foods among SSAs. First, reactions will be more likely and probably more severe to highly sulfited foods such as lettuce, dried fruit, and wines. Certainly, no evidence exists to implicate foods with low levels of residual sulfite (less than 10–50 ppm) in adverse reactions in sensitive individuals [86]. Second, foods containing a higher proportion of free inorganic sulfite may offer greater risks than foods in which the bound forms of sulfite predominate. Sulfited lettuce is certainly the best example of a food with a high proportion of free inorganic sulfite [85]. This prediction assumes, however, that the bound forms of sulfite are less hazardous than free inorganic sulfite – an assumption that has not been clinically established. Finally, one might predict that acidic foods or beverages containing sulfites would pose greater danger than other sulfited foods. Examples of these hazardous foods would include wines, white grape juice, non-frozen lemon and lime juices, and perhaps lettuce treated with an acidic salad freshener solution. These predictions appear to match the practical experiences of SSAs.

Few experiments have been conducted to test these predictions. Halpern *et al.* [87] tested 25 non-selected asthmatics with 4 oz of white wine containing 160 mg of SO₂ equivalents per liter. Because patients were not pre-screened for sulfite sensitivity, the results of this clinical trial are difficult to evaluate. Only 1 (4%) of the 25 patients exhibited reproducible symptoms with the wine challenge, however.

Howland and Simon [88] conclusively demonstrated that sulfited lettuce can trigger asthmatic reactions in confirmed SSAs. The five patients in this trial were exposed to 3 oz of lettuce containing 500 ppm of SO₂ equivalents. All of these patients had documented reactions to sulfite ingested in capsule form. Taylor *et al.* [72] confirmed the reactivity of sulfite-sensitive asthmatics to ingestion of sulfited lettuce, including one subject who responded to only acidic solution challenges of sulfite.

In their study, Taylor *et al.* [72] assessed the sensitivity of eight SSAs to a variety of sulfited foods, including lettuce, shrimp, dried apricots, white grape juice, dehydrated potatoes, and mushrooms. Results were confirmed by double-blind, capsule-beverage challenges. Despite the positive double-blind challenges, four of these patients failed to respond to any of the sulfited foods or beverages. The other four patients experienced bronchoconstriction after ingesting sulfited lettuce, although this test was the only positive food challenge for the acidic beverage reactor. Curiously, this patient did not react adversely to a challenge with white grape juice, which is an acidic, sulfited beverage. Two of the remaining three patients also reacted to dried apricots and white grape juice; the third patient did not complete these challenges. Only one of the three patients reacted to challenges with dehydrated potatoes and mushrooms; in the case of dehydrated potatoes, however, the response to multiple double-blind challenges with dehydrated potatoes was not consistent. None of these patients responded to sulfited shrimp.

While these results were somewhat confusing, they illustrated that SSAs will not react equivalently to the ingestion of all sulfited foods. The likelihood of a response could not be predicted on the basis of the dose of residual SO₂ equivalents in the sulfited foods. The nature of the sulfite present in these foods varied widely. In lettuce, the sulfite level is high and free inorganic sulfite predominates [85]. In white grape juice, and especially dried apricots, the sulfite level is high, the foods are acidic, and sulfite may be bound to reducing sugars [1,72]. In dehydrated potatoes, the sulfite level is intermediate, the food is not acidic, and sulfite is typically bound to starch [1,72]. In mushrooms, the sulfite level is low and variable, but the form of sulfite remains unknown. In shrimp, the sulfite level is intermediate, the food is not acidic, and sulfite is probably bound to protein [1,72]. The likelihood of a reaction to a sulfited food depends on several factors: the nature of the food, the level of residual sulfite, the sensitivity of the patient, and (perhaps) the form of residual sulfite and the mechanism of sulfite-induced asthma [72].

Detection of sulfited foods

A comprehensive discussion of the methods for the detection of sulfite residues in foods lies beyond the scope of this chapter, although the subject has been extensively reviewed elsewhere [1,77]. The numerous procedures available include distillation–titration, ion chromatography, polarography, enzymatic oxidation with sulfite oxidase, gas chromatography, and enzyme-linked immunosorbent assay [1,77]. These procedures are highly specialized and should be undertaken only by skilled analytical chemists. One of these procedures, the Monier-Williams distillation–titration procedure, probably represents the method of choice because

it has been officially sanctioned by the Association of Official Analytical Chemists [89]. None of the available methods has the ability to measure all forms of sulfite in foods, including free inorganic sulfite plus the many bound forms of sulfite [1]. Most of these methods aim to detect free sulfite plus some of the reversibly bound forms of sulfite. While they are termed methods for measuring total SO_2 , they actually measure “sub-total SO_2 .” A few procedures intended to measure only free inorganic sulfite in foods are used on rare occasions [1,89]. Because clinicians do not know which forms of sulfites in foods pose hazards to sulfite-sensitive asthmatics, it would be impossible to develop a procedure that would detect only clinically relevant forms of sulfite. Instead, in the absence of information on hazardous forms of sulfite, the focus has been on measuring as much of the residual sulfite – both free and bound – as possible.

Avoidance diets

As noted, the most common treatment for individuals with sulfite-induced asthma is the avoidance of sulfite in the diet. Of course, asthmatics with a low threshold for sulfites must take greater care to avoid these substances than individuals with higher thresholds. Certainly, all sulfite-sensitive asthmatics should be instructed to avoid the more highly sulfited foods, which are defined as having in excess of 100ppm of SO_2 equivalents (Table 29.5). Individuals with lower thresholds for sulfite might be advised to remove all sulfited foods from their diets, although adherence to such diets can prove difficult. Packaged foods containing more than 10ppm residual SO_2 equivalents must declare the presence of sulfites or one of the specific sulfiting agents on their labels. Thus, sulfite-sensitive consumers should be able to avoid significantly sulfited foods by careful perusal of labels. They must also be instructed that the terms sulfur dioxide, sodium or potassium bisulfite, sodium or potassium metabisulfite, and sodium sulfite indicate the presence of sulfites or sulfiting agents. Some sulfite-sensitive individuals may know that they can safely consume certain foods declaring sulfite on the labels because the amount of available sulfite in that particular food falls below their threshold doses. Such patients should be warned that the concentration of residual sulfite in any specific food is variable and that continued consumption might occasionally elicit an adverse reaction. No absolute evidence exists to suggest that sulfite-sensitive individuals need to avoid foods having less than 10ppm residual SO_2 equivalents.

While the avoidance of sulfited packaged foods is relatively straightforward, restaurant foods pose a more difficult challenge. The FDA has banned sulfite from fresh fruits and vegetables in restaurants, but other sulfited foods in restaurants remain unlabeled. With the banning of sulfites from salad bar items, many of the problems with sulfite-induced asthma in restaurants disappeared. The major continuing

problem is sulfited potatoes. SSAs should be instructed to avoid all potato products in restaurants except baked potatoes with the skins intact.

Regulatory restrictions

The US regulatory agencies have moved to regulate certain uses of sulfites following the discovery of sulfite-sensitive asthma. The FDA initially moved to require the declaration of sulfites on the label of foods when sulfite residues exceeded 10ppm; similar regulations were enacted with wines. FDA then banned the use of sulfites from fresh fruits and vegetables other than potatoes. This ban affected lettuce, cut fruits, guacamole, mushrooms, and many other applications, especially the once-common practice of sulfiting fresh fruits and vegetables placed in salad bars. Potatoes remain the sole exception to the ban of sulfite use on fresh fruits and vegetables. In these actions, FDA has not distinguished between uses that result in low levels of residual sulfite and uses that create much higher levels. Under Environmental Protection Agency restrictions, imported table grapes must be detained at their port of entry until sulfite residues can no longer be detected. FDA has also enacted a regulation specifying the allowable sulfite residue levels in shrimp.

Since FDA has taken these regulatory actions on sulfites, fewer reports of sulfite-induced reactions have been reported to FDA [90]. From 1996 through 1999, FDA processed a total of 59 market withdrawals (recalls) of foods due to undeclared sulfites at levels above 10ppm [90]. FDA's actions seem to be effective in reducing sulfite-related incidents associated with foods.

While FDA actions have helped to protect sulfite-sensitive individuals from the hazards associated with sulfited foods, FDA has taken no action to limit the use of sulfites in drugs. However, voluntary removal of sulfites from certain drugs has occurred. Certainly, any regulation is only as effective as its enforcement, so sulfite-sensitive individuals and their physicians should remain alert to avoid inadvertent exposures from both foods and drugs.

Conclusion

Sulfite sensitivity primarily affects a relatively small subgroup of the asthmatic population. The symptoms of sulfite-induced asthma can, on occasion, prove quite severe and even life threatening. Sulfite sensitivity should ideally be diagnosed with an oral double-blind challenge protocol. Many unknowns remain regarding sulfite-induced asthma, including the mechanism of the illness and the likelihood of reactions to specific sulfited foods. Reactions to sulfited foods certainly derive in part from the concentration of residual sulfite in the food and the degree of sensitivity exhibited by the individual patient. In addition, the form of

sulfite in the food and the mechanism of the sulfite-induced reaction may affect the likelihood of a response to a specific sulfited food.

Sulfite-sensitive asthmatics should be instructed to avoid highly sulfited foods. The FDA and other US federal regulatory agencies have moved to protect sulfite-sensitive asthmatics from unlabeled uses of sulfites in foods. Nevertheless, sulfites continue to be used in many foods and drugs, and sensitive individuals must be cautious to avoid inadvertent exposures.

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