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# Sulfites

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# 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 ($Na_2S_2O_5$, $K_2S_2O_5$), 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 30 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]. It is now apparent that sulfite sensitivity affects only a small subgroup of the asthmatic population [6–8]. But, concerns remain because sulfite-induced asthma can be severe—even life-threatening—in some sensitive individuals. Accordingly, the use of sulfites in foods and drugs has changed considerably over the years. Sulfites have been replaced in some products, levels have been reduced in others, and the search for effective alternatives continues. Federal regulations have restricted the use of sulfites in certain food products in the United States.

**Clinical manifestations of sulfite sensitivity**

A host of adverse reactions have been attributed to sulfiting agents, including asthma, anaphylaxis, urticaria, diarrhea, abdominal pain and cramping, nausea and vomiting, pruritis, localized angioedema, difficulty in swallowing, faintness, headache, chest pain, loss of consciousness, "change in body temperature," "change in heart rate," and nonspecific rashes. With the notable exception of the role of sulfites in asthma, the causative role for sulfites in these conditions has not been fully confirmed. 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 [9].

***Nonasthmatic responses on oral exposure to sulfites***

Various authors have suggested adverse reactions involving several organ systems following oral exposure to sulfites, but for the most part these effects have not been substantiated by double-blind, placebo-controlled (DBPC) provocation studies. In a preliminary report, Flaherty et al. [10] presented a patient who appeared to have hepatotoxicity as manifested by changes in liver function tests following challenge with potassium metabisulfite. Meggs et al. [11] failed to demonstrate any role for sulfites among eight individuals with systemic mastocytosis. Schwartz [12] described two nonasthmatic subjects who developed abdominal distress and hypotension associated with oral challenge with potassium metabisulfite. Placebo-controlled challenges proved negative, however.

Sulfites have also been implicated as possible causative factors in persistent rhinitis [13]. 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, rhinorrhea) and subject (nasal blockage and itching) symptoms in six of 20 individuals who reported improvement in rhinitis on the additive-free diet [13]. A reduction of ≥ 20% in nasal peak inspiratory flow rate was also observed in these six subjects [13].

Cutaneous adverse reactions suggestive of hypersensitivity responses have been observed but confirmed by challenge in only a few isolated individual cases. Epstein [14] described a patient who developed contact sensitivity, as confirmed by appropriate patch testing, through exposure to sulfiting agents used in a restaurant. Subsequently, several

other cases of occupational contact sensitivity of sulfites have been described [15, 16]. The ingestion of sulfites has been reported to elicit urticaria in a very few cases as confirmed by DBPC challenges [17], single-blind challenges [18, 19], or open challenges [20]; in other cases, urticarial responses were not confirmed by oral challenge [21]. 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 [20]. Wuthrich [18] conducted single-blind, placebo-controlled challenges with sodium bisulfite in 245 patients with suspected sulfite sensitivity. Fifty-seven (15%) of the challenges were positive, including 17 patients with urticaria/angioedema, seven patients with rhinitis, and five patients with local anesthetic reactions. Wuthrich et al. [19] reported a case of acute intermittent urticaria with an associated vasculitis due to sulfites based on a placebo-controlled, single-blind challenge. Huang and Fraser [22] presented an individual who developed palmar and plantar pruritis, 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 pruritis but no generalized urticaria. Yao and Bloomberg [23] identified a single patient with urticaria occurring a few hours after oral challenge with a cumulative dose of 390 mg of sodium metabisulfite. Sulfites have also been occasionally implicated in exacerbation of chronic urticaria with the largest trial involving 36 subjects [24]. However, studies of chronic urticaria are often complicated by the underlying condition and breakthrough urticaria occurring if medications are withheld during challenges. 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 performed only in some instances. Prenner and Stevens [25] described a nonasthmatic individual who developed urticaria, pruritis, 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 [26] 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 Hydick [27] 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. [28] 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.

Studies have been undertaken to determine whether sulfiting agent sensitivity frequently causes idiopathic anaphylaxis or chronic idiopathic urticaria [11, 29–31]. Sonin and Patterson [29] 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. [11] 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 [30]. Using a rigorous blinded, placebo-controlled trial and objective criteria for positive reactions, Simon [31] was unable to demonstrate 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 nonasthmatic subject. Properly performed DBPC challenges are necessary to confirm whether sulfite sensitivity was responsible for suspected adverse reactions.

***Adverse reactions to sulfites from exposures via other routes***

In addition, systemic adverse reactions have been attributed to intravenous, inhalation, and other routes of 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 [32]. The patient subsequently experienced erythematous flushing with urticaria upon IV 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. [33] performed inhalation challenge in a patient with presumed sulfite sensitivity. This individual experienced intense pruritis, tingling of the mouth, nausea, chest tightness, and a feeling of impending doom. No placebo challenge was undertaken, however. Cutaneous exposure to sulfites can, on rare occasions, apparently elicit contact sensitivity reactions [14–16]. Schmidt et al. [34] 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, however. Hallaby and Mattocks [35] attributed central nervous system toxicity to the absorption of sodium bisulfite from peritoneal dialysis solutions. Wang et al. [36] 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.

***Asthmatic responses on exposure to sulfites through foods and drugs***

Although sulfiting agents play a very limited and somewhat controversial role in the causation of nonasthmatic adverse reactions, their role in the causation of bronchospasm and severe asthma is better established. Kochen [37] 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, however. Single-dose, open challenges without placebo control performed in a group of asthmatics by Freedman [38, 39] 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 [40] 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. [41, 42] demonstrated that sodium bisulfite used as a preservative in bronchodilator solutions was capable of producing bronchoconstriction. Other studies from this group [43] 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 nonasthmatic 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 [44] reported an individual who experienced a 25% decrease in $FEV_1$ 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 [45] 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 $FEV_1$, were observed.

The potential for fatal reactions from sulfite exposure has been confirmed [28, 46]. In many instances, individuals who supposedly died from an adverse reactions 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 has resulted in some uncertainty regarding the prevalence estimates. Current estimates range from 3% to 10% of asthmatics [7]. Simon et al. [47] 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 $FEV_1$ upon challenge.

Koepke and Selner [48] 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 $FEV^1$; no confirmatory challenge was conducted. In a larger study by Buckley et al. [49], 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 [18] challenged 87 suspected, sulfite-sensitive asthmatics (SSAs) with capsules containing sodium bisulfite (5–200 mg 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 $FEV_1$ 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 [50] 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 one 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 [51] studied 51 children, aged 5–17 years. Eighteen of 51 (36%) showed a 20% or greater decrease in $FEV_1$ 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. [52] evaluated 37 asthmatic children and determined that eight (22%) responded to double-blind challenges of sulfited apple juice with a 20% or greater decline in $FEV_1$. An additional eight 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 $FEV_1$. In contrast, a study by Boner et al. [53] determined that only four 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 $FEV_1$.

Whether sulfite sensitivity really occurs more frequently in children has yet to be definitively established. Differences in challenge procedures (capsule vs. 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 upon 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 ppm of sulfur dioxide [54]. Fine and coworkers [55] demonstrated that bronchoconstriction developed in asthmatics who inhaled sulfur dioxide and bisulfite ($HSO_3^-$) but not sulfite ($SO_3^=$). Alteration of airway pH itself did not cause bronchoconstriction. Thus, asthmatics may respond differently to various ionic forms of sulfite that are dependent upon pH. Some asthmatics also respond to either oral or inhalation challenge with sulfite, although

inhalation appears more apt to produce a bronchoconstrictive response [56]. However, the inhalation of sulfur dioxide or various sulfites may not be the total explanation. Field et al. [57] 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 $FEV_1$. These investigators concluded that the generation of $SO_2$ gas cannot fully explain sulfite-induced asthma [57].

Considerable variability has been noted in the response to capsule and acidic beverage challenges with sulfiting agents [58]. 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 sulfiteinduced asthma.

***Inhalation during swallowing***

In a study of 10 SSA subjects, Delohery et al. [59] 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-SSAs showed no response to the mouthwash or swallowing challenge. Delohery et al. [59] 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 [59, 60]. For example, Australian investigators [57] 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 [61]. Further, leukotriene receptor antagonists attenuate $SO_2$-induced bronchoconstriction, implying that leukotriene release may also be involved [62]. Administration of the neutral endopeptidase inhibitor, thiorphan, was shown to enhance the airway response to inhaled sodium metabisulfite challenge in normal individuals [63]. This study suggests that tachykinins may play a role in metabisulfite-induced bronchoconstriction [63]. This mechanism was also supported by observations in guinea pigs that capsaicin-sensitive sensory nerves are involved in sulfite-induced bronchoconstriction [64]. Inhaled magnesium sulfate also has been shown to mildly inhibit inhaled metabisulfite-induced bronchoconstriction, but the mechanism is not known [65].

Refractoriness has been demonstrated to a number of indirect bronchoconstrictor stimuli including metabisulfite. The generation of nitric oxide as a possible explanation for the refractoriness has been investigated in asthmatic subjects undergoing inhaled metabisulfite challenge [66]. Blockage of nitric oxide (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.

Other animal models demonstrated that application of sodium metabisulfite to trachea of anesthetized sheep increased local blood flow and vascular permeability and induced epithelial damage [67]. Sulfite-induced bronchoconstriction in sheep may also involve stimulation of bradykinin $B_2$ receptors which may subsequently activate cholinergic reflex mechanisms [68].

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 $FEV_1$ 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 $FEV_1$. 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 [60].

***Cholinergic reflux***

Because sulfur dioxide may produce bronchoconstriction through cholinergic reflex mechanisms, preliminary studies have examined the effect of atropine and other anticholinergic agents [69]. 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 [68]. Sulfite-induced bronchoconstriction in these sheep was also associated with a nine-fold increase in immunoreactive kinins. Consequently, Mansour et al. [68] concluded that sulfite-induced bronchoconstriction in sheep involves stimulation of bradykinin $B_2$ 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 [64].

***Possible IgE-mediated reactions***

Adverse reactions to sulfites appear most commonly in atopic individuals, and studies have attempted to identify an immunologic 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 [25] observed a positive scratch skin test to an aqueous solution of sodium bisulfite at 10 mg/ml in a patient. This patient also exhibited a dramatic response to intradermal testing at the same concentration. Three nonsensitive control subjects had

negative skin tests. The patient of Twarog and Leung [32] 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 mg/ml of the solution. Yang et al. [28] also identified several asthmatic subjects with either positive prick or intradermal skin test to sulfites. Boxer et al. [70] identified two additional cases with positive skin tests who also had positive oral challenges to sulfiting agents. Selner et al. [71] reported positive intradermal and skin prick tests with 0.1 mg/ml 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 [71]. 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 nonsensitized subjects with sera from sulfite-sensitive individuals [25, 28, 72]. The effect can be abolished by heating sera to 56°C for 30 minutes [71]. These observations suggest the presence of a serum factor (IgE). However, specific IgE antibodies to sulfiting agents have not been demonstrated [70, 72].

In vitro activation of basophils by metabisulfites has been reported [73]. Sulfiting agents can induce mediator release from human MCs and basophils obtained from some sensitive individuals. Histamine release has been demonstrated in mixed peripheral blood leukocyte studies in sulfite-sensitive individuals [27, 32]. Similarly, Meggs et al. [11] 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 individual, sulfite exposure resulted in increased histamine levels in nasal lavage fluid 7.5 minutes after challenge [74]. Similar results were obtained in chronic rhinitis control subjects, although the histamine levels generally fell below those found in patients with sulfite sensitivity [74]. In contrast, other investigators have not been successful or noted inconsistent results in attempting to demonstrate histamine release from the MCs or basophils among sulfitesensitive individuals [5, 12, 74, 75]. Histamine, per se, may not play a significant role in sulfite-induced airflow obstruction since $H_1$ receptor antagonists fail to block the response [62].

Indirect evidence for the role of MC mediators in the production of bronchoconstriction due to sulfiting agents has also been found. Freedman [39] mentions that inhaled sodium cromolyn prevented the asthmatic response. In preliminary studies, Simon et al. [69] found that inhaled cromolyn inhibited sulfite-induced asthma in four of six subjects and partially inhibited the response in two other subjects. Schwartz [76] 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***

Simon [75] proposed that a deficiency in sulfite oxidase, an enzyme that metabolizes sulfite to sulfate, may promote sulfite-induced 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. In addition,

congenital sulfite oxidase deficiency in humans is not associated with asthma [77]. 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 [28, 70]. Basophil activation tests may eventually prove useful [73]. In contrast, some individuals who have equally severe bronchospasm or other reactions had negative skin tests.

### *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 previously reported in the literature are shown in Tables 1 and 2 [78]. 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.

**Table 1.** Capsule and neutral-solution metabisulfite challenge[a]

**Preparing the patient and collecting preliminary data**

- Withhold short-acting aerosol sympathomimetics and cromolyn/nedocromil sodium for 8 h and short-acting antihistamines for 24–48 h before pulmonary function testing.
- Measure pulmonary function: forced expiratory volume in 1 s ($FEV_1$) 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 $FEV_1$ below those levels. Standards for children have not been defined).

**Performing the single-blind challenge**

- Administer placebo (powdered sucrose) in capsule form. Measure $FEV_1$.
- Administer capsules containing 1, 5, 25, 50, 100, and 200 mg of potassium metabisulfite at 30-min intervals. Measure $FEV_1$ 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-min intervals. Measure $FEV_1$ 30 min after each dose and if symptoms occur. Positive response is indicated by a decrease in $FEV_1$ 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 $FEV_1$ 30 min after each dose and if patient becomes symptomatic.
- Challenge day: same protocol as single-blind challenge day.

**Source:** From Reference 78.

[a]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.

**Table 2.** Acid-solution metabisulfite challenge[a]

**Preparing the patient and collecting preliminary data**

- Withhold aerosol sympathomimetics and cromolyn sodium for 8 h and antihistamines for 24–48 h before pulmonary function testing.
- Measure pulmonary function: forced expiratory volume in 1 s ($FEV_1$) 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 $FEV_1$ 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 s, then swallow.
- Measure $FEV_1$ 10 minutes after the first dose. Then, administer 0.5, 1, 5, 10, 15, 25, 50, 75, 100, 150[b], and 200[b] mg per 20 ml of the solution at 10-min intervals. Measure $FEV_1$ 10 min after each incremental increase in dose. Positive response is signified by a decrease in $FEV_1$ of 20% or more.

**Source:** From Reference 78.

[a]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 [78].

[b]Doses in excess of 100 mg are likely to produce nonspecific bronchial reactions in asthmatics due to the high levels of free $SO_2$ that are generated.

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 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 [79, 80] and drugs [78, 81] 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. A partial list of sulfited medications appears in Table 3. Package inserts for suspect medications should be consulted for the latest information.

**Table 3.** Some antiasthma preparations containing sulfites

| | |
|---|---|
| Epinephrine | Adrenalin, Monarch<br>TwinJect™, versus Pharmaceuticals Epi-Pen™, Dey Laboratories<br>Multiple manufacturers |
| Isoproterenol solutions | Isuprel™, Sanofi-Winthrop<br>Isoproterenol, Elkins-Sinn |
| Injectable corticosteroid | Decadron™, Merck Dexamethasone, multiple manufacturers |

### *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. Self-injection with an automatic dispenser of epinephrine, delivering 0.3 ml of a 1:1000 solution (0.3 mg) for adults, is available (Epi-Pen, Dey Inc., Napa, California). A similar device available for children delivers 0.15 ml of a 1:1000 solution of epinephrine.

### *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, vitamin $B_{12}$, inhaled furosemide

and leukotriene receptor antagonists [8, 69, 82]. Although these treatments have demonstrated beneficial effects in limited numbers of patients, they remain investigational and cannot be recommended for standard use.

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**

Sulfiting agents are added to many different types of foods for several distinct technical purposes (Table 4). The key technical attributes of sulfites in foods include the inhibition of enzymatic and nonenzymatic 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, such as their application to fresh fruits and vegetables (except potatoes) to inhibit enzymatic browning, have now been restricted by federal regulatory actions in the United States, as will be described later in this chapter. Because of their important technical attributes, sulfites are utilized in an enormous number of specific applications in a wide variety of foods, as reviewed elsewhere [1, 83].

**Table 4.** Technical attributes of sulfites in foods

| Technical Attribute | Examples of Specific Food Applications |
|---|---|
| Inhibition of enzymatic browning | Fresh fruits and vegetables[a]<br>Salads[a]<br>Guacamole[a]<br>Shrimp (black spot formation)<br>Pre-peeled raw potatoes |
| Inhibition of nonenzymatic browning | Dehydrated potatoes<br>Other dehydrated vegetables<br>Dried fruits |
| Antimicrobial actions | Wines<br>Corn wet milling to make cornstarch, corn syrup |
| Dough conditioning | Frozen pie crust<br>Frozen pizza crust |
| Antioxidant action | No major U.S. applications |
| Bleaching effect | Maraschino cherries<br>Hominy |

[a]No longer allowed by the U.S. Food and Drug Administration

Given the wide variety of applications for sulfites in foods, a broad range of use levels and residual sulfite concentrations can be found in foods (Table 5). Residual sulfite concentrations in foods can range from undetectable (less than 10 ppm) to more than 2000 ppm (mg $SO_2$ 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.

**Table 5.** Estimated total $SO_2$ level as consumed for some sulfited foods

| | |
|---|---|
| **> 100 ppm** | |
| Dried fruit (excluding dark raisins and prunes) | Molasses |
| Lemon juice (nonfrozen) | Sauerkraut juice |
| Lime juice (nonfrozen) | Pickled cocktail onions |
| Wine | Grape juice (white, white sparkling, pink sparkling, red sparkling) |
| **50–99.9 ppm** | |
| Dried potatoes | Fruit topping |
| Wine vinegar | Maraschino cherries |
| Gravies, sauces | |
| **10.1–49.9 ppm** | |
| Pectin | Corn starch |
| Shrimp (fresh) | Hominy |
| Corn syrup | Frozen potatoes |
| Sauerkraut | Maple syrup |
| Pickled peppers | Imported jams and jellies |
| Pickles/relishes | Fresh mushrooms |
| **< 10 ppm** | |
| Malt vinegar | Sugar (esp. 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 |

**Source:** Adapted from *The Reexamination of the GRAS Status of Sulfiting Agents*. Life Science Research Office, Federation of American Societies for Experimental Biology, January 1985.

Sulfites are added to many pharmaceutical products [2, 3]. Table 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: to prevent the oxidation of active drug ingredients and to prevent nonenzymatic browning, which involves the reactions of reducing sugars with amino acids or amines that can occur in enteral feeding solutions and dextrose solutions. The latter stages of the nonenzymatic 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%, 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 [41], 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 an SSA because it can act as a life-saving antidote [2, 84].

**Fate of sulfites in foods**

$SO_2$ 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.

$SO_2$ and the sulfite salts readily dissolve in water and, depending upon the pH of the medium, can exist as sulfurous acid ($H_2SO_3$), bisulfite ion ($HSO_3^-$), or sulfite ion ($SO_3^=$) [81]. 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), $SO_2$ 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, to name but a few [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. An equilibrium always exists between free and bound sulfites, although the reversibility of the reactions varies over a wide range [1, 83]. Some reactions, such as the one 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 would 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 [83]. Suffice it to say that the fate of sulfites 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 $SO_2$ 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 [59, 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 food-borne 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 $SO_2$ equivalents (1 mg of $K_2S_2O_5$) to levels greater than 120 mg of $SO_2$ equivalents (200 mg of $K_2S_2O_5$). Second, clinical challenges have confirmed that free, inorganic sulfite presents a hazard to SSAs. Third, more asthmatics will respond to inhalation of $SO_2$ 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 (from less than 10 ppm to 50 ppm) in adverse reactions in sensitive individuals [86, 87]. 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, nonfrozen 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 nonselected asthmatics with 4 oz of white wine containing 160 mg of $SO_2$ equivalents per liter. Because patients were not prescreened for sulfite sensitivity, the results of this clinical trial are difficult to evaluate. Only one (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 $SO_2$ equivalents. All of these patients had documented reactions to sulfite ingested in capsule form. Taylor et al. [79] confirmed the reactivity of

SSAs to ingestion of sulfited lettuce, including one subject who responded to only acidic solution challenges of sulfite.

In their study, Taylor et al. [79] assessed the sensitivity of eight SSAs to a variety of sulfited foods, including lettuce, shrimp, dried apricots, white grape juice, dehydrated potatoes, and mushrooms. Sulfite sensitivity was 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, her 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, 79]. In dehydrated potatoes, the sulfite level is intermediate, the food is not acidic, and sulfite is typically bound to starch [1, 79]. 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, 79]. 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 [79].

**Avoidance diets**

As noted earlier, 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 SSAs should be instructed to avoid the more highly sulfited foods, which are defined as having in excess of 100 ppm of SO2 equivalents (Table 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 10 ppm 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 10 ppm 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 have disappeared. The major continuing problem is sulfited potatoes. SSAs should be instructed to avoid all potatoes products in restaurants except baked potatoes with the skins intact.

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 10 ppm; similar regulations were enacted with wines. The 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. Since the FDA has taken these regulatory actions on sulfites, the number of sulfite-induced reactions reported to the FDA has decreased. 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 in some instances. 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.

SSAs should be instructed to avoid highly sulfited foods. The FDA and other US federal regulatory agencies have moved to protect SSAs 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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