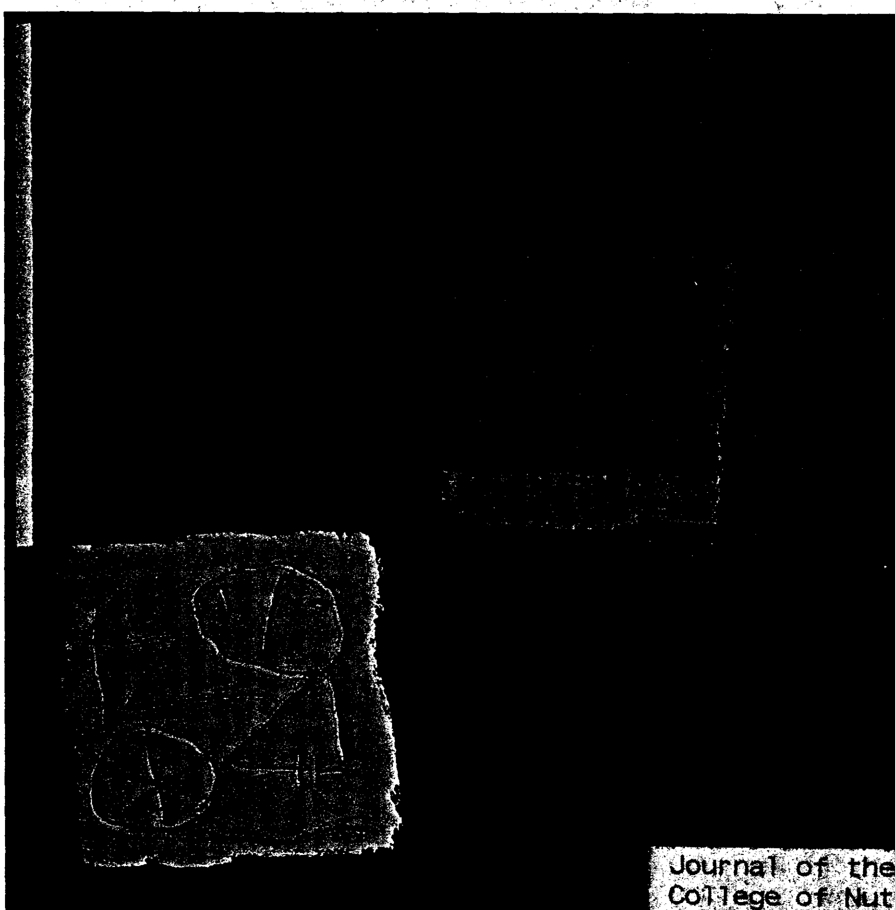
JOURNAL OF THE AMERICAN COLLEGE OF

NUTRITION

VOLUME 14 • NUMBER 3 • JUNE 1995



Journal of the American College of Nutrition

Volume 14, Number 3, June 1995

EDITORIALS

REVIEW ARTICLES

ORIGINAL PAPERS

(continued)

Journal of the American College of Nutrition (ISSN 0731-5724) is published bimonthly by the American College of Nutrition, c/o Hospital for Joint Diseases, 301 E. 17th St., New York, NY 10003. **POSTMASTER:** Send address changes to *Journal of the American College of Nutrition*, P.O. Box 3000, Denville, NJ 07834. Postage paid at New York, NY and at additional mailing offices. Subscription price; $40 annually for members (allocated from dues), $75 for nonmember individuals, and $150 for institutions. Add $40 for postage if outside the US. Indexed in Index Medicus, Excerpta Medica, Science Citation Index, Current Contents/Life Sciences, SciSearch,

Review Article

Sulfite Sensitivity: Significance in Human Health

Mitchell R. Lester, MD

Department of Pediatrics, Children's Hospital, Boston, Massachusetts

Key words: sulfite, food additive, sulfite sensitivity, sulfite reactions

Endogenous sulfite is generated as a consequence of the body's normal processing of sulfur-containing amino acids. Sulfites occur as a consequence of fermentation and also occur naturally in a number of foods and beverages. As food additives, sulfiting agents were first used in 1664 and approved in the United States as long ago as the 1800s. With such long experience with their use, it is easy to understand why these substances have been regarded as safe. They are currently used for a variety of preservative properties, including controlling microbial growth, preventing browning and spoilage, and bleaching some foods.

It is estimated that up to 500,000 (<.05% of the population) sulfite-sensitive individuals live in the United States. Sulfite sensitivity occurs most often in asthmatic adults—predominantly women; it is uncommonly reported in preschool children. Adverse reactions to sulfites in nonasthmatics are extremely rare. Asthmatics who are steroid-dependent or who have a higher degree of airway hyperreactivity may be at greater risk of experiencing a reaction to sulfite-containing foods.

Even within this limited population, sulfite sensitivity reactions vary widely, ranging from no reaction to severe. The majority of reactions are mild. These manifestations may include dermatologic, respiratory, or gastrointestinal signs and symptoms. Severe nonspecific signs and symptoms occur less commonly. Bronchoconstriction is the most common sensitivity response in asthmatics.

The precise mechanisms of the sensitivity responses have not been completely elucidated. Inhalation of sulfur dioxide (SO_2) generated in the stomach following ingestion of sulfite-containing foods or beverages, a deficiency in a mitochondrial enzyme, and an IgE-mediated immune response have all been implicated.

The FDA requires labeling of foods containing 10 ppm or more of sulfites. Most sulfite-sensitive individuals will react to ingested sulfite in quantities ranging from 20 mg to 50 mg. Avoidance should be advised in known sensitive or high-risk individuals. Sulfiting agents are thought to pose no risk to the majority of the population.

Key teaching points:

- A small percentage of individuals, primarily adult asthmatics, experience mild, moderate, or severe dermatological, respiratory, or gastrointestinal reactions to sulfites.
- Sulfite-sensitive individuals may react to ingested sulfites found in food or beverages, or inhaled SO_2 from pharmaceutical agents or polluted air.
- Ingested sulfites may provoke reactions in sensitive individuals in quantities ranging from 20 to 50 mg.
- Explanations posited for sulfite reactions include sensitivity to inhaled SO_2 generated in the stomach following ingestion of sulfite-containing foods or beverages; inefficient production of the mitochondrial enzyme sulfite oxidase, which promotes oxidation of sulfite to sulfate; and IgE-mediated mechanisms.

INTRODUCTION

Sulfiting agents have been used for many years by many people and for many purposes. The ancient Greeks used SO_2 to fumigate their homes, and the Romans and Egyptians used it to cleanse wine receptables [1]. As food additives, sulfiting agents were first used in 1664 and approved in the United States as long ago as the 1800s. With such long experience with their use, it is easy to understand why these substances have been regarded as safe. They are currently used for a variety of preservative properties, including controlling microbial growth, preventing browning and spoilage, bleaching some foods, such

Reprints not available from author.

Journal of the American College of Nutrition, Vol. 14, No. 3, 229–232 (1995)
Published by the American College of Nutrition

as maraschino cherries, and modifying the texture of some types of dough [2].

However, during the past decade, questions have arisen concerning the safety of these substances as food additives, particularly with respect to potential adverse effects reported among at-risk individuals [3].

Moreover, some studies have failed to clarify the issue of risk. This article, therefore, will examine basic information about these chemicals, identifying where they exist in the environment; evaluating the risk these chemicals pose for the general public, based on a review of the literature; and exploring the possibility of adverse effects in those persons most at risk, asthmatic patients.

SULFITE SENSITIVITY: PREVALENCE AND EXPOSURE

Given the ubiquity of sulfites in our environment, it is important to examine the manifestations of sulfite sensitivity and to attempt to identify who is at risk for such reactions and who is not at risk. Determining the prevalence of sulfite sensitivity has been problematic.

While approximately 10% of the population is asthmatic, based on experimental evidence, only 2% to 5% of asthmatics are estimated to be sulfite-sensitive (approximately 500,000 individuals). Not all sulfite-sensitive individuals are asthmatic, but asthmatics represent most of the significant sensitivity reactions to ingested sulfites. The subgroup of greatest concern, therefore, is the sulfite-sensitive asthmatic population, and most of these individuals are aware of the need to avoid sulfite-containing substances.

According to Bush and colleagues, "in spite of a great deal of attention in the popular media and anecdotal reports, adverse reactions to sulfites in nonasthmatics are extremely rare" [1]. It is the asthmatic patient who appears at greatest risk of experiencing sulfite sensitivity reactions. Asthmatics who are steroid-dependent or who have a higher degree of airway hyperreactivity may be at greater risk of experiencing a reaction to sulfited foods. However, it should be noted that numerous studies have also noted a great variability of reactions even in these high-risk populations, ranging from no reaction to mild, moderate, or severe reactions. In all of the studies reported in the literature, the investigators call for more research to identify the precise mechanisms of the sensitivity responses and to account for the variability among sensitive patients.

The average age of the individual who experiences sulfite-sensitivity asthma is 40 years; sensitivity occurs predominantly in women [4,5]. It is uncommonly reported in preschool children, perhaps because their diets include fewer foods with high sulfite content and they do not drink beer or wine.

The amount of sulfite required to produce a response also varies. For example, 1 to 5 mg ingested potassium metabisulfite provoked a reaction in a sulfite-sensitive person [6]. According to Simon, most sulfite-sensitive individuals will react to ingested metabisulfite in quantities ranging from 20 to 50 mg [5]. In addition to the problem of identifying the precise prevalence of sulfite sensitivity, it is also difficult to measure sulfites in foods and beverages accurately. According to Bush et al, the amount of sulfite added to foods does not reflect the residual levels after processing, storage, and preparation [1].

Estimates of the average daily sulfite consumption in the United States range from 7 to 19 mg of sulfur dioxide equivalents (SDE). However, the actual consumption may vary widely based on individual patterns of ingestion. For example, one report estimated that an average restaurant meal can contain 25 to 100 mg of sulfites [5]. Another study reported the per capita intake of sulfite in the 99th percentile of the population to be 163 mg of SDE [4]. As a working framework, the average consumption is <20 mg of SDE per day. The Food and Drug Administration (FDA) requires that foods containing ≥10 ppm include sulfite in the ingredient label and has also banned the use of sulfiting agents on fresh fruits and vegetables. Levels <10 ppm cannot be measured and foods that contain <10 ppm are not regarded as posing any risk even to the most highly sensitive individuals [5].

The manifestations of sulfite sensitivity are diverse. In the majority of instances, the reactions are mild. These manifestations may include dermatologic symptoms such as urticaria, angioedema, hives and pruritus, flushing, tingling, and swelling; respiratory symptoms including dyspnea, wheezing, and bronchoconstriction; and gastrointestinal symptoms such as nausea and stomach cramps. However, less common but more severe nonspecific signs and symptoms, such as hypotension, cyanosis, diaphoresis, shock, and loss of consciousness have been reported. Bronchoconstriction is a common feature of the sensitivity responses in asthmatics, particularly in steroid-dependent asthmatics.

SOURCES OF SULFITES

The principal substances that will be discussed are SO_2 and five sulfite salts (Table 1). In addition to their use as additives, these substances occur naturally, in varying quantities, as a consequence of fermentation, and are, therefore, found in foods and beverages such as wine and beer (Table 2).

Sulfite salts and SO_2 are water-soluble. Sulfite is a strong nucleophilic anion that is capable of reacting with a variety of

Table 1. Sulfate Salts

Name	Chemical formula
Potassium metabisulfite	$K_2S_2O_3$
Sodium metabisulfite	$Na_2S_2O_3$
Potassium bisulfite	$KHSO_3$
Sodium bisulfite	$NaHSO_3$
Sodium sulfite	Na_2SO_3

Table 2. Estimated Total SO_2 Level as Consumed for Some Sulfited Food

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

immunologic components that may potentially lead to toxicity [4]. It is important to remember, however, that endogenous sulfite is also generated as a consequence of the body's normal processing of sulfur-containing amino acids. Cysteine and methionine are the amino acids that produce sulfite in the body. In normal individuals, endogenous sulfite is maintained at a very low, steady-state level. A mitochondrial enzyme, sulfite oxidase, is believed responsible for maintaining this level, and for promoting the oxidation of sulfite to sulfate, which is excreted in urine [1,2,4]. Because the generation of sulfite from dietary cysteine or methionine involves a series of physiologic processes, manifestations of endogenous sulfite sensitivity may occur more slowly than manifestations that may be associated with the direct ingestion of exogenous sulfite [4]. Many investigators have suggested that a defect in this enzymatic oxidative process may account for sulfite sensitivity in some individuals in whom ingested and absorbed sulfites increase demand on sulfite oxidase and overwhelm its capacity to metabolize sulfite to sulfate. In addition, ingested sulfites are converted to SO_2 by the acidic gastric environment. Thus, SO_2 may be inhaled after burping and cause bronchoconstriction in people with airway hyperreactivity.

As noted, sulfites occur naturally in the body and are also added to foods as preservatives. Sulfur dioxide is found in ambient air, particularly in areas with high levels of pollution. While the adverse health effects of inhaling polluted air are well documented, inhalation of atmospheric SO_2 poses little risk of sulfite sensitivity in the normal individual. However, in the sulfite-sensitive person—particularly one with hyperreactive airways—such inhalation can provoke a serious bronchospastic response. The degree of reactivity is dependent upon exercise rate, concentration, and the cooling or drying factor of the airways.

Finally, sulfites are added to some parenteral and aerosolized pharmaceutical agents, notably antibiotics and antioxidants. They are no longer used in bronchodilators. In sensitive individuals, worsening of FEV_1 (forced expiratory volume [in one second]) and other pulmonary function parameters has been noted.

MECHANISMS OF SULFITE SENSITIVITY

Understanding the possible pathogenic mechanisms may help explain the variability among sulfite-sensitive patients. Three major theories have been advanced to explain the adverse effects associated with sulfites in the asthmatic population. The most widely held theory is that reactions occur as a result of inhalation of SO_2 generated in the stomach following ingestion of sulfite-containing foods or beverages. Simon noted that when sulfites are placed in solution, SO_2 is produced, and this production is enhanced in a higher temperature and lower pH. The warm, acidic environment of the mouth and stomach are prime conditions for the production of SO_2 (Fig. 1) [5]. It is well known that asthmatics, particularly steroid-dependent asthmatics, have hyperreactive airways and will be more sensitive to this circumstance than other individuals.

Anibarro and colleagues, as well as Belchi-Hernandez et al, have examined the cholinergic pathway in triggering bronchospasm in asthmatics [7,8]. Gunnison and Jacobsen summarize the data concerning stimulation of the parasympathetic nervous system suggested to be operative in the sulfite-sensitive individual [4]. Studies showing the full or partial blockade of sulfite-induced bronchoconstriction with atropine support the

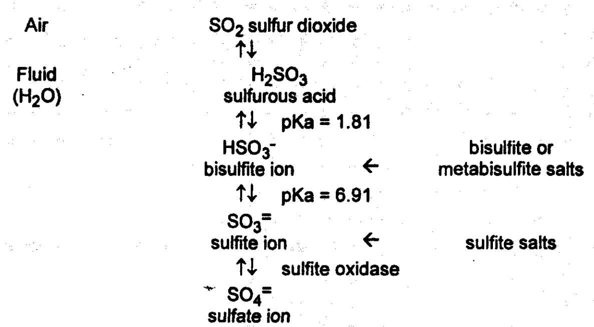


Fig. 1. Chemical reactions of sulfites in solution [1].

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.

WHAT WILL YOU BUILD? | sales@docketalarm.com | 1-866-77-FASTCASE

fastcase® Smarter legal research.