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LRA by ELISA/ACT® CLINICAL UPDATE #12

Sulfites

What are sulfites, and why are they used?

Sulfites or sulfiting (whitening) agents describe a group of sulfur-based chemicals including sulfur dioxide (SO_2), sulfurous acid (H_2SO_3), and inorganic salts of sulfur that are able to release SO_2. The most common sulfur salts are sodium and potassium **metabisulfate** ($Na_2S_2O_5$ and $K_2S_2O_5$), sodium and potassium **bisulfite** ($NaHSO_3$ and $KHSO_3$), and sodium and potassium **sulfite** (Na_2SO_3 and K_2SO_3)[11,19,21].

Sulfites can occur naturally in foods, especially fermented foods such as wine, but they are usually chemically tied up. Sulfites are also added to foods and drugs; the added sulfites are of primary health concern. Sulfites are commonly used to inhibit enzymatic and nonenzymatic browning (oxidizing) of foods such as shrimp, potatoes, fresh fruits and vegetables, guacamole, and dried fruits. Sulfiting agents are also used in frozen pie and pizza crusts as a dough conditioner, in wines and corn syrup to inhibit bacterial growth, in foods as bleaching and stabilizing agents, and for disinfecting food containers[20,21].

In 1958, the FDA approved a Food Additives Amendment to the Federal Food, Drug, and Cosmetic Act of 1938 prohibiting the use of food additives until they were proven safe. However, the law exempted substances "generally recognized as safe" (GRAS) based on prolonged use and no compelling evidence of harmful effects. Sulfites were among those substances grandfathered on the "GRAS" list, and thus never went through rigorous testing to exclude the occurrence of adverse health effects. Most recently Congress abolished the GRAS list and has directed FDA to study the possible health benefits of healthy antioxidants and the health risks of immunotoxins (like sulfite).

What are the health consequences of sulfites, and who is at risk?

Although sulfites are not a health hazard for the general population, certain individuals are sulfite-sensitive. Ingestion, inhalation, or injection of sulfiting agents can cause moderate to severe reactions, including death. Between 1985 and 1987, adverse reactions had been reported by over 1,400 people, and between 1985 and 1990, 27 persons had died of sulfite-induced anaphylactic reactions[11]. In most cases, foods and beverages were implicated by the complainants: 48% of the complaints were associated with sulfites on fruits and vegetables in salad bars at restaurants, and 12% of the complaints were related to sulfites used on potatoes. It is currently believed that many of the deaths were due to sulfites on potatoes.

The primary symptom associated with sulfites is asthma, or difficulty breathing[19]. However, vomiting, nausea, diarrhea, cramps, hives, abdominal pain, unconsciousness, and eczematous reactions have also been reported[18,20]. Other sulfite-induced symptoms include pruritus, difficulty swallowing, localized angioedema, hypotension, and chest pain[19,20]. Moreover, sulfites have been reported to induced contact dermatitis[13] and acute urticaria with vasculitis[4,25] in a number of patients. Thus, the range of symptoms is broad, a reality that has made identification of sensitive persons extremely difficult.

The epidemiology of sulfite sensitivity has been hampered because of difficulties in achieving a true diagnosis. Nonetheless, populations at risk have been identified. At greatest risk are individuals with asthma, especially asthmatics who are steroid-dependent[20]. the prevalence in adult asthmatics has been reported to be between 4%[20] and 8.2%[16]. In the largest study to date, Bush et al estimated a prevalence of 3.9% in the general asthmatic population and 8.4% in those who were steroid-dependent[5].

Fewer studies have been carried out in children, but current estimates indicate a

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prevalence of between 20%[8,15] and 66%[22] for children 5.5 to 14 years of age with moderate to severe asthma. Vandenbossche et al[23] recently examined the relationship between bronchial responsiveness to metabisulfite and age of children with moderately severe asthma. They found that 71% of the children over 10 were sensitive whereas only 31% of children 10 and under exhibited signs of sulfite sensitivity. They concluded that sensitivity to sulfites increases with age. This possibility will require confirmation given the implications of the findings and the increasing number of children with asthma.

Another group that appears to be sensitive to sulfites is persons with fibromyalgia (FM). A recent evaluation of 41 patients with FM uncovered 9 (22%) with sensitivity to sulfite. Removal of this food additive resulted in significant improvement in their overall symptomatology. Thus, although the population prevalence of sulfite sensitivity is probably extremely low, the severity of the reactions among those who are sensitive has captured the attention of many.

What are the proposed mechanisms of sulfite sensitivity?

The mechanisms of sulfite action are uncertain, but several hypotheses have been proposed. Immunologic mechanisms, including both immediate and delayed hypersensitivity reactions, have been implicated in many cases[26]. Although Type I or immediate hypersensitivity Ig-E mediated reactions have been proposed to explain sulfite-induced responses in some individuals, specific Ig-E antibodies to sulfites and conjugated sulfite have not been found in sera of sulfite-sensitive individuals[19]. Positive skin prick tests to sulfites have, however, been documented[13,19]. Delayed hypersensitivity, or Type II to IV reactions have been suggested based on the finding of contact dermatitis in some patients[20]. However, the presence of antibodies to sulfites or alterations in complement activity have not been demonstrated. More recently, it has been shown that sulfite in low concentrations stimulates neutrophils to produce superoxide anions[3]; this finding provides indirect evidence of a delayed mechanism. it is possible that sulfite inducedenhancement of neutrophils to produce more free radicals may amplify inflammatory responses, but this has not bee confirmed.

Non-immunologic mechanisms have also been proposed. For example, inhalation of SO_2 and/or local formation of SO_2 from bisulfite appears to activate sensory nerves in the bronchial wall which causes bronchoconstriction via both cholinergic and noncholinergic mechanisms[23]. Approximately 1% of healthy normal subjects have significantly increased pulmonary impedance at only 1 ppm SO_2. Once in contact with the lower airways, SO_2 gas will form sulfurous acid, which can result in pulmonary edema. However, this is clearly no the only mechanism causing reactions to sulfites.

Finally, sulfite oxidase deficiency has also been proposed. This enzyme is responsible for metabolizing sulfites and sulfated amino acids; a reduced amount or activity of sulfite oxidase could, in theory, result in excessive accumulation of sulfites. This hypothesis was proposed based on the findings of a partial sulfite deficiency in skin fibroblasts of sulfite-sensitive individuals[4,20], but further study will be required to confirm this possibility.

In sum, it is likely that several different mechanisms may be responsible for reactions to sulfites. Importantly, repeated sulfite exposure may impair the immune system through an underlying, persistent Type IV response, which in turn could cause sensitization and finally, anaphylaxis. Standardized methodologies for diagnosing this sensitivity are being developed, and until they are used, we will continue to witness untoward reactions and potentially death from sensitive individuals.

Where are sulfites found?

Sulfites are a part of most people's lives unless labels are read and precautions are taken. These agents are used in a variety of prescription and over-the-counter medications, including injectables, inhalants, oral liquid, and oral solid preparations. They are used primarily as antioxidants, but sulfites have also been used to prepare water-soluble derivatives of some insoluble drugs. The sulfite concentrations typically range from 0.01 to 1.0%[6]. In a review of 1,467 frequently prescribed medications, sulfites were used in 3,8%[9]. In particular, sulfiting agents are found in a variety of parenteral emergency drugs and local anesthetics (Table 1). At the recommended dosages, injections can provide from 0.5 to 3 mg of sulfite per mL[17]. In addition to medications, bisulfites are present in many parenteral amino acid solutions to ensure nutrient stability during and after sterilization[10]. Such formulations are routinely used in neonatal, pediatric, and adult populations who require intravenous nutrient alimentation. Luckily, drug-related sulfite reactions are less common than food-induced reactions; nonetheless, numerous adverse reactions have been reported with drug administration[17]. Clearly, physicians and dentists must be notified when an individual is sulfite sensitive so that sulfite-free preparations can be used[18].

Foods actually are a far greater concern than medications when it comes to sulfites. As can be seen in Table 2, the list of foods containing sulfites is long; few processed foods are exempt from this additive. The World Health Organization has recommended that the Acceptable Daily Intake (ADI) of sulfites (as SO_2) be set at 0.7 mg/kg/day[24] or less than 35 and 50 mg/day for 50 and 70 kg persons, respectively. However, their recommendation is not based on any clinical studies. In 1975 an Expert Panel on Food Safety and Nutrition concluded that most Americans consume no more than 15 mg/day[21], and recent studies in France indicate an

average daily intake of 20mg/day[14]. Both values are below the ADI, but heavy consumers of alcoholic beverages may need to be concerned about exceeding the ADI. A hypothetical meal of 250 mL of wine, a restaurant salad, and a 25 g serving of dried apricots alone would provide approximately 160 mg of SO_2. Clearly the usual intake of 10 to 20 mg can easily be exceeded.

Sulfites are commonly added to potatoes, fresh seafood, and meats to prevent discoloration and for antimicrobial activity. Analysis of potatoes at processing plants prior to freezing indicate sulfite residues ranging from 14 to 1,282 ppm SO_2 equivalents[12]. Death from sulfites has been noted with only 96 ppm[12]. Sulfites are also routinely added to shrimp but the FDA has established a limit of 100 ppm as the allowable level of total SO_2 equivalents. Washing shrimp will reduce the levels, but shrimp treated abusively can have residual levels well above the 100 ppm limit[19]. Thus, all shrimps should be viewed as sulfite treated. Recent analyses of fresh and cooked hamburger meat in Europe indicate levels can be quite high. Although sulfite levels are decreased by cooking, many restaurant hamburgers provide amounts approaching the tolerable weekly consumption levels[1]. Eating one or two hamburgers would impose considerable risk to asthmatics. Fortunately, some countries (including the United States) have prohibited the use of sulfites in meat because of its damaging effect on thiamine.

Based on the large number of complaints associated with sulfites in 1980's, the FDA initiated investigations which ultimately led to a number of regulatory actions. Some of these actions include:

- In July 1986 the FDA prohibited the use of sulfites on raw fruits and vegetables served or sold to consumers.
- In July 1986 the FDA required that any food containing as much as 10 ppm or more of sulfites must be labeled.
- In June 1987 the FDA required manufacturers of prescription drugs containing sulfites to include statements so indicating on the label.
- In January 1988 the Bureau of Alcohol, Tobacco and firearms required that all alcoholic beverages containing 10 ppm or more of sulfites to be labelled.
- In March 1990 the FDA revoked the GRAS status of sulfites on fresh, raw or cooked potatoes that are not canned, frozen or dehydrated.

The number of sulfite-induced adverse reactions has declined significantly since implementation of these regulation, but this may also reflect a greater awareness on the part of the consumer. The adage "Consumer Beware" remains in effect despite the legislation already put forward.

How can an individual be tested for sensitivity to sulfites?

The only treatment for sulfite sensitivity is avoidance; thus, identifying those who are at risk is critical. A variety of tests for sulfites have been available for years, but many have both low sensitivity and specificity. Moreover, several of the tess are only useful if the sensitivity is due exclusively to an immediate allergic response. We know from our work and our study of patients with fibromyalgia that delayed responses are more the rule than the exception.

The one test that can diagnose delayed hypersensitivity to sulfite is the Lymphocyte Response Assay (LRA) by ELISA/ACT®. Sulfites are one of the many antigens tested as part of the complete LRA by ELISA/ACT profile. Our testing of healthy subjects has demonstrated that 14% of the population may be sensitive to sulfites. This is truly not surprising given their ubiquitous nature and our sustained exposure over the years. To find out more about testing for sulfite sensitivities in your patients, call EAB at (800) 553-5472 or (703) 450-2980. We have helped many difficult patients regain their health by identifying a sulfite sensitivity and then showing them how to actually avoid these food additives. We believe you can help many of your patients with the LRA by ELISA/ACT tests and treatment program.

TABLE 1. Selected Drugs Containing Sulfites

Dobutamine	**Aminophyline**	**Dexamethasone**
Dopamine	**Epinephrine**	**Hydrocortisone**
Phenylephrine	**IV Corticosteroids**	**IV Lidocaine**
Procainamide	**Isoetharine HCL**	**Isoproterenol**
Norepinephrine	**Antibiotics**	**Vitamins**
Physostigmine	**Dextrose Solutions**	**Anticoagulants**
Nasal Sprays	**Vaginal Suppositories**	**Opthalmic Solutions**
Ascorbic Acid Injections	**Codeine Injections**	**Dextrose/Electrolyte Injections**

TABLE 2: FDA INFORMATION ON COMMON FOODS WITH SULFITES

Food Category	Types of Foods
Alcoholic beverages	Wine, beer, cocktail mixes, wine coolers
Baked goods	Cookies, crackers, mixes with dried fruits or vegetables, pie crust, pizza crust, quick crust, flour tortillas
Beverage bases	Dried citrus fruit base, bottled beverages, mixes, cider, root beer
Condiments and relishes	Horseradish, onion and pickle relishes, pickles, olives, salad dressing mixes, wine vinegar
Confections and frostings	Brown, raw powdered, or white sugar derived from sugar beets
Dairy product analogs	Filled milk (skim milk enriched in fat content by addition of vegetable oils)
Fish and shellfish	Canned clams; fresh, frozen, canned or dried shrimp; frozen lobster, scallops; dried cod
Processed fruits	Canned, bottled, or frozen fruit juices (including lemon, lime, grape, apple); dried fruit; canned, bottled or frozen dietetic fruit or fruit juices; maraschino cherries; glazed fruit; shredded coconut
Processed vegetables	Vegetable juices; canned vegetables (including potatoes); pickled vegetables (including sauerkraut, cauliflower, and peppers); dried vegetables; instant mashed potatoes; frozen potatoes; potato salad
Gelatins, puddings, fillings	Fruit fillings, flavored and unflavored gelatin, pectin, jelling agents
Grain products and pasta	Cornstarch, modified food starch, spinach pasta, gravies, hominy, breading, batters, noodle/rice mixes
Jams and jellies	Jams and jellies
Plant protein products	Soy protein products
Snack foods	Dried fruit snacks, trail mixes, filled crackers
Soups and soup mixes	Canned soups, dried soup mixes
Sweet sauces, toppings, syrups	Corn syrup, maple syrup, fruit toppings, high-fructose corn syrup, pancake syrup, molasses
Tea	Instant tea, liquid tea concentrates

Note: Not all manufacturers of these foods use sulfites, and the amounts used may vary. Information from this list should be supplemented by reading the labels of packaged foods.

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References

1. Armentia-Alvarez A, Fernandez-Casero A, Garcia-Moreno C, and Pena-Egido MJ. Residual Levels of Free and Total sulfite in fresh and cooked burgers. *Food Additives Contaminants* 1993;10: 157-165.

2. Atkinson DA, Sim TC, and Grant JA. Sodium metabisulfite and SO_2 release: An under-recognized hazard among shrimp fishermen. *Ann Allergy* 1993; 71:563-566.

3. Beck-Speier I, Liese JG, Belohradsky BH, and Godleski JJ. Sulfite stimulates NADPH Oxidase of human neutrophils to produce active oxygen radicals via protein kinase C and Ca^{2+}/Calmodulin pathways. *Free Radical Biol Med* 1993;14: 661-668.

4. Belchi-Hernandez J, Florido-Lopez F, Estrada-Rodriguez JL, Martinez-Alzamora F, Lopez-Serrano C, and Ojeda-Casas J. Sulfite-induced urticaria. *Ann Allergy* 1993;71: 230-232.

5. Bush RK, Taylor SL, Holen K, Nordlee JA, and Busse WW. The prevalence of sensitivity to sulfiting agents in asthmatics. *Am J Med* 1986; 81: 816-820.

6. Dalton-Bunnow MF. Sulfite content of drug products. *Am J Hosp Pharmacy* 1985; 42: 2196-2201.

7. Foulke JE. A Menu of modern safety standards. *FDA Consumer* April 1994; 7-9.

8. Friedman ME and Easton JG. Prevalence of positive metabisulfite challenges in children with asthma. Pediatr *Asthma Allergy Immunol* 1987; 1: 53-59.

9. Kolly M, Pecond A, and Frei PC. Additives contained in drug formations most frequently prescribed in Switzerland. *Ann Allergy* 1989; 62: 21.

10. Lavoie JC and Chessex P. Biologic effects of parenteral bisulfite on human vascular tissue. *Pediatric Res* 1993; 33: 347-351.

11. Lecos CW. Sulfites: FDA limits uses, broadens labeling. *FDA Consumer* October 1986;11-13.

12. Lecos CW. An order of fries - Hold the sulfites. *FDA Consumer* March 1988; 9-11.

13. Lodi A, Chiarelli G, Mancini LL, and Crost C. Contact allergy to sodium sulfite contained in an antifungal preparation. *Contact Dermatitis* 1993; 29: 97.

14. Mareschi JP, Francois-Collange M, and Suschetet M. Estimation of sulfites in food in France. *Food Additives Contaminants* 1992; 9: 541-549.

15. Sanz J, Martorell A, Torro I, Cerda JC, and Alvarez V. Intolerance to sodium metabisulfite in children with steroid-dependent asthma. *J Invest Allerg Clinl Immunology* 1992; 2: 36-38.

16. Simon RA, Green L, and Stevenson DD. The incidence of ingested metabisulfite sensitivity in an asthmatic population. *J Allerg Clin Immunol* 1982; 69: 188.

17. Smolinske SC. Review of parenteral sulfite reactions. *Clinical Toxicol* 1992; 30: 597-606.

18. Sticco SL. Anesthetic management of a patient with sulfite sensitivity. *CRNA The Clinical Forum for Nurse Anesthetists* 1993; 4: 203-206.

19. Taylor SL, Nordlee JA. Chemical additives in seafood products. *Clinical Rev Allergy* 1993;11: 261-291.

20. Taylor SL, Higley NA, Bush RK, Nordlee JA. Sulfites. Blackwell Scientific Publications. *Adverse Reactions to Food and Food Additives* 1991; 239-260.

21. Taylor SL, Higley NA, Bush RK. Sulfites in foods: Uses, analytical methods, residues, fate, exposure assessment, metabolism, toxicity, and hypersensitivity. *Advances in Food Research* 1986; 30: 1-76.

22. Towns SJ and Mellis CM. Role of acetyl salicylic acid and sodium metabisulfite in chronic childhood asthma. *Pediatrics* 1984; 73: 631-637.

23. VandenbosscheLEG, Hop WCJ, de Jongste JC. Bronchial responsiveness to inhaled metabisulfite in asthmatic children increases with age. *Pediatric Pulmonology* 1993; 16: 236-242.

24. WHO, 1985; *GEMS Guidelines for the study of dietary intakes of chemical contaminants*. WHO Offset Publication No. 87 (Geneva: World Health Organization).

25. Wuthrich B, Kagi MK, and Hafner J. Disulfite-induced acute intermittent urticaria with vasculitis. *Dermatology: Int J Clin Invest Derm* 1993; 187: 290-292.

26. Wuthrich B. Adverse reactions to food additives. *Ann Allergy* 1993; 71: 379-384.

Contact

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