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Short Review of Sulphites as Food Additives

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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ABSTRACT

Sulphites or sulphiting agents refer to sodium hydrogen sulphite, sodium metabisulphite, potassium metabisulphite, calcium sulphite, calcium hydrogen sulphite, and potassium hydrogen sulphite. As food additives, they are widely used by the food industry with a variety of commercial uses in food and beverages. Sulphites are effective bleaching agents, antimicrobials, oxygen scavengers, reducing agents, and enzyme inhibitors. Wine, beer, dehydrated fruits and vegetables, jam, juice, sugar, processed potatoes, seafood, meat and baked products are some of the food categories in which sulphites are added. Sulphites have been implicated in various health related issues. Asthmatic reactions and some antinutritional consequences such the degradation of thiamine (vitamin B_1) are adverse reactions associated with sulphites. In many countries, sulphites have been regulated. Sulphites are generally recognized as safe in the USA with some exceptions when using in raw fruits and vegetables. In the European Union sulphites are also controlled, and the permitted amount varies according to the food product.

Keywords: Food additives; sulphites; sulphiting agents; legal status; toxicity.

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1. INTRODUCTION

Sulphites or sulphiting agents are a group of sulphur-based compounds that are capable to release sulphur dioxide SO_2, which is the active component that helps to preserve food [1,2]. Sulphites have been added to foods as preservative agents and other purposes for centuries [2]. Sulphites were used by many ancient cultures such as Romans and Greeks to reduce or prevent spoilage and discoloration of foods, to sanitize wine vessels or as a purifier and disinfectant [1,3]. Furthermore, naturally occurring sulphites exist especially in fermented products, such as beer and wine. They are produced by yeasts during the fermentation process [1].

Sulphites have many functional uses in food. They are effective bleaching agents, antimicrobials, oxygen scavengers, reducing agents, and enzyme inhibitors. Their primary function is to act as a preservative or antioxidant to prevent or reduce/retard spoilage and browning during the preparation, storage, and distribution of many foods [2,4]. Additionally, sulphites are utilized to stabilize product colour and inhibit discoloration, as well as to improve flavour of many foods [5]. Sulphites are also used in the pharmaceutical and cosmetics industries as preservatives of the active ingredient. Thus, in addition to being cheap and convenient, sulphites are extremely versatile, and in many products, serve more than one purpose [3].

Despite all uses of sulphites in the food industry, sulphites have been related to asthmatic reactions in a small subset of sensitive individuals of the asthmatic population [2]. They have also been related with some anti-nutritional consequences such as degradation of thiamine (vitamin B_1) [5].

This short review presents the available data published regarding sulphites, their uses, related health problems, and the actual legislation around these food additives.

2. CHEMISTRY OF SULPHITES

Sulphites are a group of compounds characterized by the presence of the sulphite ion SO_3^{2-} [1]. The term sulphites is commonly used to describe the oxo species of sulphur oxidation state that include the ionic and non-ionic forms: SO_2, HSO_3^{-}, SO_3^{2-}, and $S_2O_5^{2-}$ [6]. The concentration of free sulphites in foods correlates with the preservative activity, with sulphite levels in foods and drinks usually expressed as theoretical yields or 'equivalents' of SO_2 [3]. The term S(IV) is used to refer to any of the four oxo species of sulphur oxidation (Fig. 1) [6,7]. The most common sulphites used by food industry are described in Table 1.

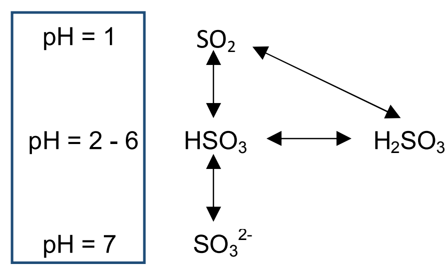

Fig. 1. Sulphites chemistry equilibrium, modified from Vally et al. [3]

A distinction is often made between free and bound S(IV) which forms reversible interaction products. The former refers to all the species of the additive which may rapidly and quantitatively be converted to SO_2, thereby acidifying a treated food. The latter represents hydroxysulphonate adducts formed by reaction of carbonyl groups with HSO_3^{-}. In fact, according to the nature of food, the type and extent of the technological processes, and the conditions and time of storage, sulphites react with reducing sugars, aldehydes, ketones, proteins to form combined compounds [6-8].

Table 1. Most common sulphites used by food industry

Name	E-number	Chemical formula
Sulphur dioxide	E-220	SO_2
Sodium sulphite	E-221	Na_2SO_3
Sodium hydrogen sulphite (Sodium bisulphite)	E-222	$NaHSO_3$
Sodium metabisulphite	E-223	$Na_2O_5S_2$
Potassium metabisulphite	E-224	$K_2O_5S_2$
Calcium sulphite	E-226	$CaSO_3$
Calcium hydrogen sulphite	E-227	$Ca(HSO_3)_2$
Potassium hydrogen sulphite	E-228	$KHSO_3$

In the digestive tract, the free and reversibly bound S(IV) species can be liberated [9]. The useful properties of sulphiting agents are generally due to the nucleophilicity of the sulphite ion that may react by addition to carbonyl groups, carbon-carbon double bonds, quinones, heterocyclic nitrogen compounds [6-8]. The most common reactions of S(IV) are the result of oxidation by molecular oxygen catalysed by transition metal ions [10].

3. SULPHITES AS FOOD ADDITIVE

3.1 Uses and Reactions in Food

Sulphites are used in a wide variety of food products such as beverages, dried fruits, jams, seafood, meat, sugar, and others (Table 2) [3]. In wine, the aim of adding sulphite is to prevent microbial growth and oxidation of volatile odorous compounds which may develop during fermentation [9].

Table 2. Major type of foods that may contain sulphiting agents [11,12]

Food category	Examples
Drinks	Bottled soft drinks and fruit juice, cordials, cider, beer, wine (including sparkling wine)
Processed fruits	Dried apricots, fruit bars, maraschino cherries, canned, bottled, or frozen fruit juices, commercial preparations of citrus fruit beverage mixes.
Processed vegetables	Canned vegetables (including potatoes), pickled vegetables (including sauerkraut), dried vegetables, instant mashed potatoes, frozen potatoes, potato salad
Fish and crustaceans	Canned clams; fresh, frozen, canned, or dried shrimp; frozen lobster; scallops; dried cod
Other commercial foods	Gravies, sauces and fruit toppings, maple syrup, jams, jellies, biscuits, bread, pie and pizza dough, gelatine, coconut, vinegar, beef stew.

Sulphites are the most effective and cheapest antibrowning agents [13,14]. Sulphites reduce quinones produced by catalysis of polyphenol oxidase to less reactive, and colourless compounds, thereby preventing pigmentation [15]. The quantity of sulphites necessary to prevent enzymatic browning varies according to the concentration and the nature of the substrate, the level of activity exhibited by the polyphenoloxidase, the desired period of control and the presence of other inhibitors [1].

Besides anti-browning and anti-microbial functions, sulphites are used as dough conditioners in bakery industry, especially in frozen pizza dough and pie crusts. They are also used in biscuits, tortilla shells, cookies and crackers. The level of sulphites required for dough conditioners are relatively low. Sulphites act by breaking the cysteine disulphide bonds that are present in the gluten fraction of the dough [1]. Cleavage of thiamine (vitamin B_1) in stored food [4], and destruction of cyanocobalamin (vitamin B_{12}) are undesired reactions of sulphites in foods [16].

3.2 Legal Status

In the European Union sulphiting agents are regulated by Regulation 1333/2008 of the European Parliament and of the Council on food additives. According with Annex II of this Regulation, sulphiting agents are considered food additives other than sweeteners or colorants. The name of the most commonly used authorized compounds and their E-number are shown in Table 1 [17].

This Regulation 1333/2008 allows the use of sulphiting agents in both food products and with other food additives, enzymes, flavourings and nutrients [18]. The permitted amounts vary depending of the food as listed in the Annex II [19] or the form of the ingredient in which they are added as listed in the Annex III [18]. The range goes from 10 mg/kg (e.g. table grapes) to 10,000 mg/kg in papain in solid form [17-19].

With introduction of the legislative Package on Food Improvement Agents in December 2008, the regulation of food additives in the European Union was reformed. Regulation 1333/2008 of the European Parliament and the Council, introduced one regime for the use of food additives in the Union, food colours sweeteners and the remaining food additives that until then were regulated in separate Directives (respectively Directive 94/36/EC, Directive 94/35/EC and Directive 95/2/EC).Apart from consolidating the regulation of food additives, Regulation 1333/2008 also started a process of re-evaluation of all food additives authorized for use in the Union prior to 20 January 2009. Based on the re-evaluation carried out by EFSA, the Commission will revise the list of food additives and the conditions of use specified therein. Hereby sulphites will be revised within the food additives other than colours and sweeteners category on 31 December 2018 [20].

In the USA, since 1959 sulphiting agents have been listed as generally recognised as safe (GRAS) when used in accordance with good manufacturing practice, except in meats or in foods recognised as a source of thiamine (vitamin B_1) [8]. However, in 1986 the practice of adding sulphites to fruits and vegetables that are to be sold or served raw to the public was banned by revocation of the GRAS status [2,5,21]. Also, any food containing more than 10 ppm of a sulphiting agent must have a label declaration [22].

4. BIOLOGICAL DATA

4.1 Absorption, Distribution, Metabolism and Excretion

Sulphites are readily absorbed from the digestive tract [23]. Normally, human serum has a sulphite concentration in the range 0–10 μM [24]. Sulphite is oxidized *in vivo* to sulphate by sulphite oxidase, a molybdenum containing enzyme, located in the intra-membrane space of mitochondria [25]. Sulphite oxidase is present in mammalian tissues and organs, mainly in liver, heart and kidney and very low amounts may be found in spleen, brain, skeletal muscle, and blood [26,27]. In humans, sulphite oxidase activity varies from slightly to substantially less than in other mammals and some individuals present levels well below the normal range [4]. During the oxidation of sulphite to sulphate in mitochondria, cytochrome c transfers the electrons produced to the electron transport chain, allowing generation of ATP in oxidative phosphorylation [24].

Metabolism of sulphites by sulphate oxidase has been shown to be rapid. Therefore, sulphite does not accumulate in the tissues on chronic administration. Sulphate, which represents the normal non-toxic sulphite metabolite, is excreted rapidly through the urine [31]. In several species, less than 10% of the dose administered appeared in the urine as sulphite [16]. A proportion of the sulphite absorbed is converted to thiosulfate. When elevated levels of thiosulfate in body fluids are observed it may be due to sulphite oxidase deficiency [28].

4.2 Adverse Reactions

Sulphites have been implicated as initiators of asthmatic reactions in a small subset of sensitive individuals of the asthmatic population [2]. Adverse reactions, including anaphylactic reactions, dermatitis, urticaria, flushing, hypotension, abdominal pain and diarrhoea, have been reported in those individuals [29]. The mechanism of action of sulphites in asthmatic reactions is not established, and various studies have proposed different possible mechanisms.

One study suggests that the reaction of nitric oxide and its carriers with sulphites may be a major source of sulphites' biological toxicity by affecting the pathway of the drugs used to treat asthma [30]. Another study provided evidence that this response may be mediated through stimulation of an oro-bronchial reflex by sulphur dioxide vapour released from foods, rather than by an immunological mechanism [31]. A third study says that partial sulphite oxidase deficiency is a possible mechanism involved in sulphite sensitivity due to alterations in drug metabolizing enzymes that can contribute to the varying susceptibility and response of sulphite-sensitive individuals to different drugs and/or therapeutics used for treatments.

Sensitivity to sulphites can develop at any time during a person's lifespan, with some initial reactions not showing up until a person has reached their forties or fifties [11]. Dose-related respiratory hyper-reactivity has also been documented in a small number of individuals following consumption of potassium bisulphite-treated red wine and wine which contained smaller amounts of sulphites formed naturally as products of fermentation [32]. The most sensitive patients have reacted to a dose of 5 mg sodium bisulphite [33].

On the other hand, gastric lesions had been induced in rats by sodium metabisulphite [34]. Furthermore, gastro-intestinal reactions are also known to occur in man; with very high doses of sulphites, abdominal pain and vomiting have been observed in human volunteers [32].

5. TOXICOLOGICAL DATA

5.1 Acute, Sub-chronic and Chronic Toxicity

The acute toxicity of free sulphites is low with a LD50 of 1000-2000 mg/kg bw. The acute toxicity of bound sulphites may even be lower with a LD50 that exceeds 5000 mg/kg bw [35].

Til et al. studied the toxicity of sulphite in newly weaned Wistar rats. 120 males and 120 females, were divided into six groups each of 20 males and 20 females. The groups were maintained on the stock diet containing 0.0 (control), 0.125, 0.25, 0.5, 1.0 or 2.0% sodium metabisulphite for periods up to 2 years and over three generations. A level of 2% sulphite caused slight growth retardation in two generation of rats, however it was no significant. Blood was present in the faeces in groups given 1% sulphite or more. Pathological examination revealed hyperplastic changes in both the fore- and glandular stomach with levels of 1 and 2% sulphite in each of the three generations. Also, it was perfomed a series of short-term studies in 10 male and 10 female rats on high sulphite levels (0–8%) for 10–56 days. Diets containing 6% sulphite caused considerable growth depression and reduced food intake and food efficiency. Anaemia occurred at 2% and above. Increase in weight of the spleen occurred with levels of 4% and above. The most sensitive criteria of sulphite damage in the present studies was the presence of blood in the faeces and changes in gastric morphology. The dietary level of sulphite that did not show any significant adverse effect was 0.25% in the diet, which is equivalent to 72 mg SO_2/kg of body weight after conversion and correction for sulphite losses [36].

The same research group examined sub-chronic and chronic oral toxicity of sodium metabisulphite. 20 male and 20 female pigs were fed with diets at levels of 0.0, 0.125, 0.25, 0.5, 1.0 or 2.0% of $Na_2S_2O_5$. After 15 weeks, 14 males and 14 females from each group were killed. The six males and six females remaining in each group were kept on the same diets for up to 48 weeks. The concentrations of sulphite still present in the various experimental diets when they were consumed by the pigs were calculated to be on average 0.06, 0.16, 0.35, 0.83 and 1.72% respectively. Organ-to-body weight ratios of the liver, kidneys, heart and spleen were significantly increased with dietary levels of 1.72%, after both 15 and 48 weeks; and with dietary levels of 0.83% only after 48 weeks. The no-effect level established in this study was 0.35% $Na_2S_2O_5$ in the diet of pigs for 48 weeks [37].

More recently, Kadi et al. determined the sodium metabisulphite sub-chronic toxicity on 24 female Wistar rats divided in four groups treated with 0.0, 0.25, 1 and 4% of sodium metabisulphite in their drinking water for 90 days. Administration of $Na_2S_2O_5$ at 1% and 4% had significant effects on body weight, food and water consumed. There was an increase in biochemical parameters (calcium, urea, creatinine, uric acid, transaminases) and decrease immunoglobulin levels. The hematology revealed a decrease in red blood cells and hemoglobin, as well as leucocytosis. They concluded that sub-chronic intake of $Na_2S_2O_5$ 1% and 4% seems to alter immune function, biochemical, hematological and physiological parameters in Wistar rats [38].

5.2 Genotoxicity and Carcinogenicity

Sulphites are capable of inducing mutations in yeast, *E. coli* and *Vicia faba*, but only at high concentrations (0.2 – 3 M) and pH values in the range of 5 – 5.6 [39]. Hayatsu and Miura described the mutagenic activity of sodium bisulphite on *E. coli* K12 after a treatment with a solution of 3 M $NaHSO_3$and pH of 5.6 during 1.5 hours. Sodium bisulphite caused mutations by modification of cytosine [40]. Similarly, Mukai et al. showed that a concentration of 1 M sodium bisulphite solution at pH 5.2 in *E. coli*K12is specific for cytosine-guanine mutants [41].

In a study *in vitro*, sodium bisulphite at low concentrations (0.05, 0.1, 0.5, 1.0, and $2.0x10^{-3}$ M) induced chromatid-type aberrations, but not chromosome-type aberrations in human blood lymphocytes; high concentrations induced both chromatid- and chromosome-type aberrations. The authors concluded that sulphur dioxide is a clastogenic and genotoxic agent [42].

Til et al. however, did not find any carcinogenic effect in Wistar rats on the stock diet containing 0.0 (control), 0.125, 0.25, 0.5, 1.0 or 2.0% sodium metabisulphite for periods up to 2 years and over three generations [36].

Tanaka et al. examined the carcinogenicity of potassium metabisulphite in ICR/JCL mice. Three groups of 50 male and 50 female mice each received 0, 1, and 2% potassium metabisulphite solution in distilled water for 24 months. There was no significant difference in tumor incidence between the two experimental groups and the control group, suggesting that potassium metabisulphite is not carcinogenic in mice [43].

In summary, sulphites has been shown genotoxicity *in vitro* but not *in vivo* [44]. Furthermore, sulphites has a number of reactions with nucleic acids, and cellular molecules, but no harm has been yet been demonstrated in laboratory animals, generally rats or mice, to sulphite levels of 50 or 100 times in excess of the usual maximum human environmental exposure [45].

5.3 Acceptable Daily Intakes (ADI's)

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) established an ADI of 0 –0.7 mg/kg-bw in 1974 [46], which was maintained in its latest evaluation in the 51st report about evaluation of certain food additives. This ADI is for use with all the sulphiting agents presented in Table 1.The ADI was based on long-term studies in rats with a NOEL of 2.5 g/kg (0.25%) sodium metabisulphite in the diet, equivalent to 70 mg/kg of body weight per day of sulphur dioxide equivalents [44].

In the EU, the Scientific Committee for Food (SCF) in its 35th report established an ADI of 0 – 0.7 mg/kg of body weight in accordance to the established by the JECFA [32].

Surveys on sulphite content in food and intake, carried out in different countries, showed that the acceptable daily intake (ADI) for this additive is likely to be exceeded [4]. Nonetheless, a study performed in Belgium found that the intake of sulphites in the Belgian adult population is likely to be below the acceptable daily intake (ADI) with the possible exception for some high consumers of wines with high sulphite levels. Further, it was shown that for several food groups, actual use levels of sulphites are much lower than the maximum levels set in legislation [9].

6. CONCLUSIONS

Sulphites are well known food additives that constitute an important and versatile category within the food additives. They are widely used in food industry and they have some applications in other industries. Besides their functions, sulphites constitute a very cheap food additive.

Sulphites are associated with some adverse reactions such as asthmatic and anaphylactic episodes in some sensitive individuals. However, there is no data that suggests the present Acceptable Dietary Intake levels have any adverse reactions in the normal population. Only caution should be taken in cases with sulphite oxidase deficiency, which is the main enzyme that degrades sulphites into sulphate.

Overall, the available data suggests that sulphites can be used safely as a food additive. Therefore, EFSA's re-evaluation on food additives is opportune and its Opinion will be relevant to future uses of sulphites within the food industry.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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