THE REEXAMINATION OF THE GRAS STATUS OF SULFITING AGENTS

January 1985

Prepared for

CENTER FOR FOOD SAFETY AND APPLIED NUTRITION
FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20204

under

Task Order #5
Contract No. FDA 223-83-2020
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LIFE SCIENCES RESEARCH OFFICE
FEDERATION OF AMERICAN SOCIETIES
FOR EXPERIMENTAL BIOLOGY
9650 Rockville Pike
Bethesda, Maryland 20814
NOTICE

The Life Sciences Research Office (LSRO), Federation of American Societies for Experimental Biology (FASEB), provides scientific assessments on topics in the biomedical sciences. Reports are based upon comprehensive literature reviews and the scientific opinions of knowledgeable investigators engaged in work in relevant areas of biology and medicine.

This report was developed for the Center for Food Safety and Applied Nutrition, Food and Drug Administration (FDA) in accordance with the provisions of Task Order #5 of Contract No. 223-83-2020. FASEB recognizes that the safety of Generally Recognized as Safe (GRAS) substances is of national significance and that its resources are particularly suited to marshaling the opinions of knowledgeable scientists to assist in this reexamination of the GRAS status of sulfiting agents.

During the course of the evaluation of the GRAS substances by the Select Committee on GRAS Substances (SCOGS) (1972–1982), FASEB and FDA agreed that when additional information and data became available subsequent to completion of an evaluation report, the FDA could request review and evaluation of the supplemental information and data. Based upon the evaluation of all available data, the Select Committee would prepare a supplemental report. While the Select Committee on GRAS Substances was terminated in 1982, similar mechanisms for review and evaluation have been maintained in FASEB by the LSRO.

This report was prepared by an ad hoc Review Panel on Reexamination of the GRAS Status of Sulfiting Agents. Members of the Panel and others who assisted in preparation of the report are identified in Section VIII. The scientists selected as members of the Panel were chosen for their qualifications, experience, and judgment with due consideration for balance and breadth in the appropriate professional disciplines. Certain members of the Panel were formerly members of the Select Committee on GRAS Substances and participated in the review of several hundred GRAS substances including sulfiting agents. The review of the sulfiting agents resulted in publication of the report, "Evaluation of the Health Aspects of Sulfiting Agents as Food Ingredients" (SCOGS, 1976).

The ad hoc Review Panel's evaluation of currently available information and data has been made independently of FDA or any other group, governmental or nongovernmental. The ad hoc Panel, as consultants to LSRO, and the LSRO accept responsibility for the contents of the report.
The ad hoc Review Panel issued a tentative report on October 15, 1984. The tentative report was made available to the public for review in the Dockets Management Branch (HFA-305), FDA, Room 4-62, 5600 Fishers Lane, Rockville, Maryland 20857, and at the LSRO at the address appearing on the title page. As announced by FASEB, and by FDA in the Federal Register, an opportunity (open meeting) was provided for any interested person to appear before the ad hoc Review Panel on Reexamination of the GRAS Status of Sulfiting Agents to make oral presentation of data, information, and views on the substances covered by the tentative report. The data, information, and views presented at the open meeting were considered by the ad hoc Panel in reaching its final conclusions.

The final report was approved by the ad hoc Review Panel and the Director of LSRO, and subsequently reviewed and approved by the LSRO Advisory Committee (which consists of representatives of each constituent society of FASEB) under authority delegated by the Executive Committee of the Federation Board. Upon completion of these review procedures, the report was approved and transmitted to FDA by the Executive Director of FASEB.

While this is a report prepared by a Panel convened by an office of the Federation of American Societies for Experimental Biology, it does not necessarily reflect the opinion of FASEB, its constituent societies, or the individual members of each constituent society.

January 23, 1985
(date)

Kenneth D. Fisher, Ph.D.
Director
Life Sciences Research Office
FASEB
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I. INTRODUCTION

This reexamination of the health aspects of using sulfiting agents as food ingredients is based partly on the information contained in a scientific literature review (monograph) furnished by the Food and Drug Administration (FDA) (The Franklin Institute Research Laboratories, 1972), which summarized the world's scientific literature from 1920 through 1972*, and the assessment of this information by the Select Committee on GRAS Substances (SCOGS) in 1976*. In its 1976 report on the evaluation of the health aspects of sulfiting agents (potassium bisulfite, potassium metabisulfite, sodium bisulfite, sodium metabisulfite, sodium sulfite, and sulfur dioxide) used as food ingredients, the Select Committee (SCOGS, 1976) concluded that:

There is no evidence in the available information on potassium bisulfite, potassium metabisulfite, sodium bisulfite, sodium metabisulfite, sodium sulfite, and sulfur dioxide that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when they are used at levels that are now current and in the manner now practiced. However, it is not possible to determine, without additional data, whether a significant increase in consumption would constitute a dietary hazard.

Based in part upon the report of the Select Committee, the FDA, in the Federal Register of July 9, 1982, proposed to affirm the use of four sulfiting agents (potassium metabisulfite, sodium bisulfite, sodium metabisulfite, and sulfur dioxide) as GRAS (FDA, 1982). At the same time, FDA proposed not to affirm the use of potassium bisulfite and sodium sulfite as GRAS. Subsequent to the completion of the Select Committee's report and the publication of the FDA proposal, additional information and data on uses of sulfiting agents in foods as well as reports of health effects possibly associated with sulfiting agents have become available.

* These documents (PB-221 217 and PB-265 508, respectively) are available from the National Technical Information Service, 5285 Port Royal Road, Springfield, Virginia 22161.
Early in 1984, the FDA requested that the Federation of American Societies for Experimental Biology (FASEB), through its Life Sciences Research Office (LSRO), convene an ad hoc Panel on Reexamination of the GRAS Status of Sulfiting Agents to consider the recent scientific publications and new information submitted to FDA in response to its 1982 proposal on the affirmation of the GRAS status of sulfiting agents. The ad hoc Panel was asked to address the following question:

"In view of the currently available information relevant to the use and safety of sulfiting agents, which of the five types of conclusions* for the appraisal of GRAS substances that were developed by the Select Committee now applies to the use of sulfiting agents? The conclusion which is reached should be supported by a discussion of the rationale behind that conclusion."

To insure completeness and currency as of the date of this report, the information and data received from FDA have been supplemented by searches of scientific and statistical reference sources and compendia that are generally available; use of new, relevant books and reviews and the literature citations contained in them; consideration of current literature citations obtained through computer retrieval systems of the National Library of Medicine; searches for relevant data in the files of FDA; inquiry of leading investigators in the field and the combined knowledge and experience of members of the ad hoc Review Panel and the LSRO staff. In addition, the Federal Register of July 9, 1984 (FDA, 1984a) announced the opportunity for all interested parties to submit information, data, and reports on the health effects of sulfiting agents. The Panel made its tentative report on the health aspects of using sulfiting agents as GRAS food ingredients available for public inspection on October 15, 1984 and an opportunity to appear before the ad hoc Panel at an open meeting to make oral presentation of data, information, and views on this tentative report was published in the Federal Register of October 25, 1984 (FDA, 1984b). The open meeting was held on November 29, 1984. Individuals and organizations who made or submitted comments on the tentative report are listed in Section IX of this report.

* See Appendix
As indicated in the Food, Drug, and Cosmetic Act [21 USC 321(s)], GRAS substances are exempt from the premarketing clearance that is required for food additives. The Code of Federal Regulations* (CFR) [21 CFR 170.30], as revised April 11, 1984, states that general recognition of safety may be based only on the views of experts qualified by scientific training and experience to evaluate the safety of substances directly or indirectly added to food. This section of the Code also indicates that expert judgment may be based on published studies which may be corroborated by unpublished studies and other data and information or, in the case of a substance used in food prior to January 1, 1958, through experience based on common use in food. FDA recognizes further [21 CFR 170.3] that it is impossible in the present state of scientific knowledge to establish with complete certainty the absolute harmlessness of the use of any substance.

LSRO's ad hoc Review Panel on Reexamination of the GRAS Status of Sulfiting Agents made its evaluations of these substances in full recognition of the foregoing provisions. In reaching its conclusions, the ad hoc Panel, in accordance with FDA's guidelines, has relied primarily on the absence of substantive evidence of, or reasonable grounds to suspect, a significant risk to the public health. These conclusions will need to be reviewed as new or better information becomes available.

In this context, the LSRO ad hoc Review Panel has reviewed the available information on sulfiting agents and submits its interpretation and assessment in this report, which is intended for the use of FDA in determining the future status of these substances under the Federal Food, Drug, and Cosmetic Act, as amended.

II. BACKGROUND INFORMATION

"Sulfiting agents" is a term used to designate sulfur dioxide and any one of the five sulfite salts that may be used in some foods. Since the sulfite salts release sulfur dioxide, the effective agent under conditions of food processing, levels of sulfiting agents are usually expressed as sulfur dioxide equivalents (SDE). Sulfiting agents effectively serve a number of purposes in food processing including the inhibition of nonenzymatic browning; the inhibition and control of microorganisms; the inhibition of various enzymatic reactions such as enzymatic browning; as antioxidants and reducing agents, including dough conditioners; as bleaching agents; as processing aids; and, secondarily as pH control and stabilizing agents (Taylor and Bush, 1983).

To accomplish these purposes, sulfiting agents are added under controlled conditions during the processing of some foods. Because good manufacturing practice limits the amount added, the concentration of sulfite at maximum treatment levels is usually a small fraction of 1%. The amount of residual sulfite in processed foods as consumed will vary depending on the length and nature of subsequent storage and on the manner of preparation of the food for consumption.

In recent years, with the increased popularity of salad bars in restaurants and other food service establishments, sulfiting agents have come to be used by the restaurateur to retain the "freshness" of some salad items. They are also used by some suppliers of produce intended for salad bar use or of vegetables, particularly potatoes, intended for cooking. A large number of commercial products, consisting principally of sulfite salts, are available for these purposes. Labels direct users to dissolve the product (usually one tablespoon in a gallon of water), to dip the fresh produce in the solution for a stated period of minutes, and to drain the produce before making it available to consumers. The degree of care exercised in the control of such procedures would be expected to vary, leading to variation in the sulfite content of the treated products. However, current information indicates that use in food service establishments of sulfiting agents on salad bar items and the use of these agents by suppliers of fresh and ready-to-cook produce to such establishments have declined sharply in the last 2 years. For example, the National Restaurant Association, which advised its members in February 1983 to cease applying sulfites at retail levels, found in a subsequent survey that less than 4% of its members were using sulfiting agents (Neville, 1983). The Produce Marketing Association reported in November 1984 that a recent survey showed that 5% of its members were using sulfiting agents and only 2% on a regular basis
(Ahlberg, 1984). The Produce Marketing Association concluded that, for all intents and purposes, their industry no longer uses sulfiting agents on items to be consumed in the fresh state. They also concluded that sulfites are still being used only in isolated instances on items that are subsequently washed and cooked.

The CFR permits use of potassium bisulfite (KHSO₃), potassium metabisulfite (K₂S₂O₅), sodium bisulfite (NaHSO₃), sodium metabisulfite (Na₂S₂O₅), sodium sulfite (Na₂SO₃), and sulfur dioxide (SO₂) as GRAS ingredients provided that they are not used in meats or foods recognized as a source of thiamin (vitamin B₁). Specific GRAS listings of sulfiting agents for use as chemical preservatives are to be found in the following sections of the CFR*: potassium bisulfite [21 CFR 182.3616]; potassium metabisulfite [21 CFR 182.3637]; sodium bisulfite [21 CFR 182.3739]; sodium metabisulfite [21 CFR 182.3766]; sodium sulfite [21 CFR 182.3798]; and, sulfur dioxide [21 CFR 182.3862]. Other sections of the CFR pertaining to the use of sulfiting agents are: caramel [21 CFR 73.85(2)]; dextrose monohydrate [21 CFR 168.111]; glucose syrup [21 CFR 168.120]; bleached starch [21 CFR 172.892(b)]; boiler water additives [21 CFR 173.310(c)]; cellophane [21 CFR 177.1200(c)]; water-soluble hydroxyethylcellulose film [21 CFR 177.1400]; and wine [27 CFR 240.1051]. The CFR listings for dextrose monohydrate, glucose syrup, and bleached starch limit residual sulfur dioxide concentrations in these products to not more than 20, 40, and 500 ppm, respectively. Food Chemicals Codex specifications place an upper limit of 80 ppm residual sulfur dioxide in modified food starches (NRC, 1981). In addition to the GRAS and regulated food additive uses of the sulfiting agents listed above, prior sanctions and advisory opinion letters for these substances have been issued by FDA. Prior sanctions allow use of sodium sulfite and sulfur dioxide in molasses, dried fruits, and foods that are not good sources of vitamin B₁ (thiamin) and use of sodium sulfite as dips to prevent darkening of fresh-peeled uncooked potatoes and to control the incidence of black spot in shrimp (FDA, 1982). Advisory opinions have addressed the following uses of specific sulfiting agents: potassium metabisulfite is permitted at levels up to 1% by weight as a stabilizer for preparation of dry vitamin A palmitate; sodium bisulfite is

permitted in wash water for mushrooms; sodium bisulfite is permitted as a preservative in citron brining; sulfur dioxide is permitted at levels up to 400 ppm in corn syrups that are subsequently applied to meats; and, sodium sulfite is permitted at levels up to 1% in the wash water of sweet potatoes (FDA, 1982). Letters to the Food and Drug Administration subsequent to publication of the proposed rule in 1982 identify additional uses. The maximum sulfur dioxide level permitted in raw shrimp is 100 ppm (FDA, 1985).

The Food Chemicals Codex (NRC, 1981) provides specifications for food grades of potassium metabisulfite, sodium bisulfite, sodium metabisulfite, sodium sulfite, and sulfur dioxide. No specifications for food grade potassium bisulfite have been established.

With the exceptions noted above, specific limits are not currently set for levels of use of sulfiting agents in most foods. However, sulfiting agents are required to be used in accordance with good manufacturing practice which restricts the quantity added to food to levels not to exceed those reasonably required to accomplish their technical effects in food [21 CFR 182.1]. The residual amount of SDE's in foods as consumed is generally less than the amount added during processing because sulfites can combine with other food components, are liberated as sulfur dioxide, or are oxidized to sulfate.
III. CONSUMER EXPOSURE DATA

Three basic pieces of information are needed for estimating intake of food ingredients: a) the amount of the ingredient present in the various components of a diet at the time of consumption; b) the kinds of foods in the daily diet and the frequency with which each is consumed; and, c) average portion size for the various foods consumed. From this information it is possible to compute the weight of the ingredient consumed from each food in the diet by multiplying the weight percent of the ingredient in the food by the portion size and the frequency with which it is consumed.

Information on the kinds of foods consumed, the frequency of consumption, and the usual portion size can usually be obtained with reasonable accuracy. However, obtaining reasonably accurate information on the amount of an added ingredient present in the food at the time of consumption is much more difficult. This is especially true with substances like the sulfiting agents which can be lost from foods during processing, storage, distribution, and home preparation. True loss can occur through leaching or through volatilization of sulfur dioxide at pH below 4; loss of sulfite, per se, i.e., loss of "free sulfite" can occur through reversible reactions with other food constituents, particularly those containing aldehyde or ketone groups. Residual free sulfite (gaseous or hydrated sulfur dioxide, bisulfite and sulfite ions) is usually determined by iodometric titration following acidification to reduce the rate of dissociation of reversibly bound sulfites. Total sulfite, which consists of free sulfite and reversibly reacted sulfite, is defined as that measured, for example, by the Monier-Williams analytical method (AOAC, 1984). Sulfite contents of foods and beverages are usually reported as total sulfite.

Reversibly bound sulfite may account for most of the sulfite present in wines (Burroughs and Sparks, 1973a) and perhaps in other beverages. The combined forms of sulfite may be stable to digestive processes. Sulfite in wine reacts with acetaldehyde, pyruvic acid, 2-ketoglutaric acid, galacturonic acid, and other carbonyl compounds that may be present (Burroughs and Sparks, 1973b). Acetaldehyde binds bisulfite strongly; the dissociation constant of its bisulfite compound is 1.4 to $2.4 \times 10^{-6}$ over the pH range 2.0 to 6.0 (Burroughs and Sparks, 1973b). The acetaldehyde present in some wines may bind 100 ppm SDE (20 mg/200 g serving) and little of this would be expected to be released in the stomach on ingestion. Although the bisulfite compounds of the other carbonyl compounds in wine have larger dissociation constants than that of acetaldehyde and would release a greater
percentage of their bound sulfite on dilution, some would be expected to be retained in the bound form at pH levels in the stomach.

In laboratory analyses, under the strongly acidic, elevated temperature conditions of the Monier-Williams method, carbonyl bisulfite compounds are dissociated and both free and bound sulfite are converted to sulfur dioxide. However, all reaction products are not converted to sulfur dioxide under the conditions of the Monier-Williams analysis. Some sulfite is oxidized to sulfate in certain foods during processing (Thewlis and Wade, 1974). Furthermore, in some cases sulfite reacts with food components to produce organic sulfur compounds that are stable under the conditions of the Monier-Williams analytical method. Several examples can be cited. In the laboratory, dehydration of potatoes, cabbage, and carrots using $^{35}$S-sulfur dioxide, about 55-65% of residual $^{35}$S was present in stable organic compounds and not released as $SO_2$ in a modified Monier-Williams procedure (Gilbert and McWeeny, 1976). After 6 months storage of strawberries in $^{35}$S-sulfite solution, 62% of the total $^{35}$S present in the berries was recovered as sulfur dioxide by the Monier-Williams method, but 32% was present as irreversible reaction products. Only about 3% of residual $^{35}$S in jam prepared from the strawberries was recoverable as sulfur dioxide (McWeeny et al., 1980). Some of the stable reaction products present in dehydrated cabbage have been identified as 3-deoxy-4-sulfoosuloses, derived from the reaction of sulfite with reducing sugars and ascorbic acid (Wedzicha and McWeeny, 1975).

The foregoing discussion indicates that sulfites are present in foods and beverages in one or more of three forms: free sulfite, reversibly bound sulfite, and as stable reaction products. The role of these forms as they occur in foods in eliciting adverse reactions, i.e., their biological activity, has not been defined. Taylor and Bush (1983) have suggested that free sulfite in food is primarily responsible for adverse reactions in sulfite-sensitive individuals. However, exposure studies to reversibly bound sulfite compounds such as acetaldehyde hydroxy-sulfonate have not been reported nor have tests been reported with irreversibly bound sulfite compounds.

Similarly, in most animal studies of chronic toxicity, sulfite salts are fed as dry mixtures with other components of the diet or as a component of the drinking water. Much less interaction with dietary components to produce irreversibly bound sulfur compounds would be expected in such animal diets than would likely occur in processed foods containing added sulfites, particularly those subjected to high temperatures in the processing operation and/or long storage times. Thus, animal studies are most
likely to reflect the effect of free sulfite, or that which is reversibly bound and released in vivo, and are less likely to reflect the physiological and toxicological properties of the stable organic sulfur compounds that may be present in many sulfited foods. Studies with the isolated sulfur compounds would be necessary to elucidate their biological properties.

After considering all available information, the following data sources were used in estimating food intake of sulfites in the U.S.: a) the 1977 Survey of Industry on the Use of Food Additives by the National Research Council (NRC, 1979); b) responses of the food industry to FDA's proposed order on the GRAS status of sulfites in 1982 (FDA, 1982); c) the 1977-1978 National Food Consumption Survey (NFCS) of the U.S. Department of Agriculture (Pao et al., 1982; USDA, 1983a,b); d) Agricultural Statistics (USDA, 1983c) and other USDA statistical publications (USDA, 1984a,b); and, e) U.S. Imports for Consumption and General Imports (USDC, 1984). Using information obtained from these sources supplemented by contacts with manufacturers and users in certain instances, Table 1 was prepared to assemble the following information: added and residual levels of sulfiting agents in processed foods, estimated level of sulfites in the food as prepared for consumption, human intake of specific foods and/or food categories, and estimated per capita daily intake of sulfites. All sulfite levels given are total sulfites expressed as sulfur dioxide equivalents (SDE), i.e., the proportion of the weight of the various sulfiting agents that can dissociate into sulfur dioxide. The added and residual SDE levels in Table 1 are the levels reported in the NRC 1977 survey, those reported in comments to FDA after July 1982 and/or to LSRO after July 1984, and those reported to LSRO in written statements commenting on the Panel's tentative report (Matthys, 1984; Mosebar, 1984a; Taylor, 1984b). Levels for a given food reported in the 1977 NRC Survey are generally weighted mean values obtained by weighting the added or residual level of each company reporting the use of sulfite in the food by its fraction of the total poundage of sulfites for all uses reported by these companies. Information on the analytical methods used and the standard deviations of the values listed in Table 1 were not reported for most food items. For some products, levels were stated to be calculated values based on reported sulfite concentrations in the ingredients, e.g., the sucrose, high fructose corn syrup, and caramel ingredients in soft drinks.

Several characteristics of the 1977 NRC Survey (source a) should be noted because they have a bearing on the reliability of the SDE intake data reported by NRC. There are factors favoring overestimation of intake values. When a processor reported the addition of a sulfite to a single food, the NRC calculation procedure caused all foods in the pertinent NRC food subcategory
Table 1. Levels of Sulfiting Agents (Sulfur Dioxide Equivalents, SDE) in Foods and Estimated Per Capita Daily Intake

<table>
<thead>
<tr>
<th>Food Category and Subcategory</th>
<th>Level in Product as Processed ppm</th>
<th>Level in Product as Consumed ppm</th>
<th>Food Intake g/capita/d</th>
<th>SDE Intake mg/capita/d</th>
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<th>Food Category and Subcategory</th>
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<th>Level in Product as Consumed ppm</th>
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<th>SDE Intake mg/capita/d</th>
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<td>(domestic and imported)</td>
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Table 1. Levels of Sulfiting Agents (Sulfur Dioxide Equivalents, SDE) in Foods and Estimated Per Capita Daily Intake (continued)

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<th>Food Category and Subcategory</th>
<th>Level in Product as Processed ppm</th>
<th>Level in Product as Consumed ppm</th>
<th>Food Intake(^4) g/capita/d</th>
<th>SDE Intake(^5) mg/capita/d</th>
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See footnotes at end of table.
Table 1. Levels of Sulfiting Agents (Sulfur Dioxide Equivalents, SDE) in Foods and Estimated Per Capita Daily Intake (continued)

<table>
<thead>
<tr>
<th>Food Category and Subcategory</th>
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<th>Level in Product as Consumed ppm</th>
<th>Food Intake g/capita/d</th>
<th>SDE Intake mg/capita/d</th>
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|                            | NRC 1977 Survey 
  Added Residual | Reported to FDA/LSRO 
  Added Residual | Reported 
  Added Residual | Estimated 
  Added Residual |                         |
| FROZEN FRUIT²¹ | | | | | |
| Unspecified | | | | | 0.025 |
| CANNED FRUIT²² | | | | | |
| Maraschino Cherry | | | | | |
| Applesauce | | | | | |
| Bartlett pear, heavy syrup | | | | | |
| Crushed pineapple, heavy syrup | | | | | |
| Fruits for salad | | | | | |
| FRESH VEGETABLES²³ | | | | | |
| Mushrooms | | | | | 0.63 |
| Salad Bar | | | | | 0.6 |
| Unspecified | | | | | 0.325 |
| CANNED VEGETABLES²⁴ | | | | | |
| Potatoes | | | | | 0.27 |
| Pickled cocktail onions | | | | | 0.12 |
| Pickled peppers | | | | | |
| Sauerkraut (in glass) | | | | | |
| Sauerkraut (in metal cans) | | | | | |
| Unspecified | | | | | |

See footnotes at end of table.
Table 1. Levels of Sulfiting Agents (Sulfur Dioxide Equivalents, SDE) in Foods and Estimated Per Capita Daily Intake (continued)

<table>
<thead>
<tr>
<th>Food Category and Subcategory</th>
<th>Level in Product as Processed ppm</th>
<th>Level in Product as Consumed ppm</th>
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### Table 1. Levels of Sulfitting Agents (Sulfur Dioxide Equivalents, SDE) in Foods and Estimated Per Capita Daily Intake (continued)

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<th>Food Category and Subcategory</th>
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<th>Level in Product as Consumed ppm</th>
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<th>Level in Product as Consumed ppm</th>
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<td>10</td>
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<tr>
<td>Beer</td>
<td>10, 15</td>
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<td>Wine</td>
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<td>180, 180</td>
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<td>59, 87</td>
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See footnotes at end of table.
Table 1. Levels of Sulfiting Agents (Sulfur Dioxide Equivalents, SDE) in Foods and Estimated Per Capita Daily Intake (continued)

<table>
<thead>
<tr>
<th>Food Category and Subcategory</th>
<th>Level in Product as Processed ppm</th>
<th>Level in Product as Consumed ppm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NRC 1977 Survey&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Reported to FDA/LSRO&lt;sup&gt;2&lt;/sup&gt;</td>
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<tr>
<td></td>
<td>Added   Residual</td>
<td>Added   Residual</td>
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<tr>
<td>SOUPS&lt;sup&gt;31&lt;/sup&gt;</td>
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<td></td>
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<tr>
<td>Dry mix</td>
<td>&lt;10, 20</td>
<td>0, 0.5 mean 25 max</td>
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<tr>
<td>Canned</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vegetable beef</td>
<td>(&lt;10)</td>
<td>0</td>
</tr>
<tr>
<td>Chicken with noodles</td>
<td>(&lt;10)</td>
<td>0</td>
</tr>
<tr>
<td>GELATIN&lt;sup&gt;32&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flavored mix</td>
<td>5, &lt;10-36</td>
<td>5</td>
</tr>
<tr>
<td>Unflavored mix</td>
<td>&lt;11, 14, 40</td>
<td>4</td>
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<tr>
<td>SNACK FOODS</td>
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<tr>
<td>Apple bits&lt;sup&gt;33&lt;/sup&gt;</td>
<td>275</td>
<td>0.5</td>
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<tr>
<td>Crackers, filled&lt;sup&gt;34&lt;/sup&gt;</td>
<td>75</td>
<td>0.5</td>
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<tr>
<td>Corn based snacks&lt;sup&gt;35&lt;/sup&gt;</td>
<td>&lt;1</td>
<td>0.5</td>
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<tr>
<td>Pretzels&lt;sup&gt;35&lt;/sup&gt;</td>
<td>&lt;1</td>
<td>0.5</td>
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<tr>
<td>PROTEIN ISOLATES, SOY&lt;sup&gt;36&lt;/sup&gt;</td>
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<td>2-5</td>
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<td>NUT PRODUCTS</td>
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<td>Coconut&lt;sup&gt;37&lt;/sup&gt;</td>
<td>5</td>
<td>5</td>
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<tr>
<td>Unspecified</td>
<td>25</td>
<td>5</td>
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See footnotes at end of table.
Table 1. Levels of Sulfitting Agents (Sulfur Dioxide Equivalents, SDE) in Foods and Estimated Per Capita Daily Intake (continued)

<table>
<thead>
<tr>
<th>Food Category and Subcategory</th>
<th>Level in Product as Processed ppm</th>
<th>Level in Product as Consumed ppm</th>
<th>Food Intake(^4) g/capita/d</th>
<th>SDE Intake(^5) mg/capita/d</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NRC 1977 Survey(^1)</td>
<td>Reported to FDA/LSRO(^2)</td>
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<tr>
<td></td>
<td>Added</td>
<td>Residual</td>
<td>Added</td>
<td>Residual</td>
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<tr>
<td>BEVERAGES, ALCOHOLIC(^4) (cont.)</td>
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<tr>
<td>Wine (cont.)</td>
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<tr>
<td>fortified</td>
<td>120</td>
<td>120</td>
<td>133</td>
<td>133</td>
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<tr>
<td>sparkling</td>
<td>140</td>
<td>175</td>
<td>200</td>
<td>100</td>
</tr>
</tbody>
</table>


2. Values reported to FDA subsequent to the proposed order on the GRAS status of sulfitting agents published in the Federal Register, July 9, 1982 and/or to LSRO after July 9, 1984. Underlined figures are analytical values obtained by the Monier-Williams method and submitted by S.L. Taylor, University of Wisconsin. Figures in parentheses are analytical values obtained by the Monier-Williams method or ion chromatography by the National Food Processors Association (NFPA). Figures in brackets were submitted by the Dried Fruit Association of California (DFA). Taylor's data and that from NFPA and DFA were submitted to LSRO in written statements commenting on the Panel's Tentative Report.

3. Estimates made by LSRO staff.

4. Estimates of average values of daily food intake per capita are based on data from the National Food Consumption Survey (Pao et al., 1982; USDA, 1983a,b); USDA statistical sources (USDA, 1983c; 1984a,b); U.S. Imports (USDC, 1984), and information provided by industry associations and companies. Estimates based on food purchased and used in households have been increased by 11% to allow for food eaten in food service establishments (USDA, 1979).
5. Product of reported or estimated SDE level in food as consumed × intake of food.

6. Although all reported levels of sulfite in baked products as consumed were <6 ppm, a value of 5 ppm was selected because of the uncertainty in analytical results at low SDE levels. An exception is cake with dried carrots with a reported residual SDE level of 0-20 ppm.

7. Analyses of commercial products reported to the Life Sciences Research Office, FASEB, by S.L. Taylor, Food Research Institute, University of Wisconsin, Madison, WI.

8. Estimates based on reported intakes of pies and pizzas (Pao et al., 1982) and percent of crust in pies (USDA, 1966).

9. Residual SDE levels as processed and intake data for corn starch and modified corn starch were reported by the Corn Refiners Association, Inc., Washington, DC. Intake level of spinach pasta is based on industry estimates; intake of hominy estimated by LSRO.


11. Proposed maximum level of use.

12. Canned and bottled olives were reported by the California Industry not to contain added sulfites. The unspecified olive product(s) could not be identified; to provide for sulfite in such products, an average SDE level of 2 ppm was assigned to olives.

13. Some relishes, but not pickles (i.e., pickled cucumbers), are reported to contain added sulfite. Intake is based on industry estimate relative to that of cucumber pickles.

14. An average dilution factor of 5 was used in calculating SDE level as consumed. Salad dressings from dry mixes were estimated to constitute 5% of the intake of all salad dressings reported by Pao et al. (1982).

15. Intakes of malt and wine vinegars are based on industry estimates of sales.

16. Intake is based on 1982 sales of filled milk (USDA, 1984b). According to USDA, filled milk sales largely account for the difference between total sales of fluid milk products and the sum of sales of products listed, or 28 million lb. in 1982.

17. Residual levels in shrimp meat as processed and as consumed after cooking were taken from paper by Wood et al. (1976). Intake data for frozen fabricated products were not available; 10 ppm was selected as the average SDE level for all fish and seafood products.

18. Intake of sulfited fruit salad and the identity of unspecified fresh fruits were not determined. To account for these possible sources of sulfite and also include the contribution of table grapes, 5 ppm was selected as the average SDE level in all fresh fruits consumed. Levels in table grapes were reported by the California Grape and Tree Fruit League, Fresno, CA.
19. The dried fruit category is discussed in the text. Intake is for dried fruits that have been treated with sulfur dioxide, not all dried fruits.

20. Intake of imported apple and grape juice concentrates are based on 1983 import figures (USDA, 1984). SDE level in imported apple juice concentrate is based on information from industry. SDE level in imported grape juice concentrate is the level reported in one shipment; intake in Table 1 is for the concentrate, and the calculated SDE intake assumes no loss of sulfite in further processing. Intake of white and sparkling grape juices was estimated to be 10% of total grape juice intake reported by Pao et al. (1982). Intake of nonfrozen lemon and lime juices is based on 1983 consumption of canned and chilled lemon and lime juices (USDA, 1984a). Identity and intake of dietetic fruit juices containing added sulfite were not established.

21. Some cherries and sliced apples are reported to be treated with sulfite prior to freezing but information on quantities and residual SDE levels was not obtained. An average SDE level of 5 ppm was assigned to the reported intake of frozen fruits.

22. SDE level in maraschino cherries as consumed is based on report of Nardlee et al. (1985). Intake is based on production data submitted by National Cherry Growers and Industries Foundation, Inc., Corvallis, OR.

23. The fresh vegetable category is discussed in the text. SDE level in sulfite-treated mushrooms is that reported by ESS Laboratory Services (1983).

24. Information from industry indicates that sulfite is added only to sauerkraut packed in glass to prevent browning. The "added" level in Table 1 was taken from the NRC 1970 survey (NRC, 1972). No information was available on added levels in pickled cocktail onions and peppers. Residual levels were assumed to be the same as that reported for relishes (condiment category). Information on the intake of these three products was not available, and an average SDE level of 5 ppm was assigned to the intake reported for all canned vegetables to account for the SDE intake of the foods listed and the unspecified canned foods which may not have been identified.

25. Estimated intake of dried potatoes represents quantity of hydrated product as consumed.

26. Information from major processors of frozen potatoes indicates that less than 25% of commercially processed frozen products contain added sulfite. Intake represents estimate of product containing sulfite.

27. Sauerkraut juice is the only vegetable juice identified as containing added levels of sulfite. Identity of unspecified juices containing <800 ppm SDE (Table 1) was not established. An average SDE level of 5 ppm was selected for the intake of all vegetable juices.

28. Residual SDE levels in cane and beet sugar were reported by the Cane Sugar Refiners Association, Inc., Washington, DC; the level for dextrose was reported by the Corn Refiners Association, Inc., Washington, DC. Intake of sugar is based on per capita domestic disappearance of cane and beet sugar (USDA, 1983c) and annual consumption of dextrose reported by the Corn Refiners Association, Inc. Other data sources are identified in footnote 2.

29. Residual SDE levels and intake figures are based on data reported by the Corn Refiners Association, Inc., Washington, DC.
30. SDE level in domestic jams and jellies is based on analytical data reported by the International Jams and Jellies Association, Atlanta, GA, by S.L. Taylor, University of Wisconsin, and by the National Food Processors Association. The NFCS intake value includes jams, jellies, fruit butters, fruit topping, pastry filling, pectin, and jelling agents. SDE level in imported jams and jellies is based on the report of Howlett (1980) which states that maximum SDE level permitted in English jams is 200 ppm and the average is 13.6 ppm. Intake of imported jams and jellies is taken as 1% of the jam and jelly intake reported by NFCS. This is based on data on imports and domestic production provided by the U.S. Department of Commerce which shows that poundage imported is about 1% of domestic production.

31. Residual values in dry mixes were not reported by all manufacturers. Dilution ratios reported for dry soup mixes ranged from 1:6 to 1:18. The value, 25 ppm max., is a calculated value based on dilution of the dry mix and does not include any reduction resulting from cooking in preparation for serving.

32. Residual levels reported in product as processed (column 5) are for dry gelatin mixes. A dilution ratio of 1:5 was assumed in estimating levels in product as served.

33. Included in dried fruits category.

34. Included under crackers in baked goods category.

35. SDE levels are based on information reported by the Potato Chip/Snack Food Association, Laguna Beach, CA.

36. About one-half of estimated production of soy protein isolate is estimated to contain added sulfite. Soy isolate is used as an ingredient in other foods at levels generally less than 5% (SCOGS, 1976) and SDE levels in these foods contributed by soy isolate is 2-5 ppm. Food intake in Table 1 is for soy isolate per se and SDE intake is total for soy isolate not adjusted for processing losses in food formulation.

37. Intake is based on 1983 imports of shredded and desiccated coconut (USDC, 1984).

38. NFCS reports do not separate soups, sauces, and gravies (USDA, 1983a). It is estimated that purchased sauces and gravies are about 5% of total soups, sauces, and gravies.

39. SDE levels in soft drinks (calculated from residual SDE in their ingredients) were reported by the National Soft Drink Association (NSDA), Washington, DC. Other data sources are identified in footnote 2. Market share of each type beverage was also reported by the NSDA. Average level (3.3 ppm) in all soft drinks was calculated from these data. Other data sources are identified in footnote 2.

40. Two estimates are included for per capita daily wine intake: 5.4 g from the NFCS and 24.5 g based on the quantity of wine distributed in the U.S. in 1983 (USDA, 1984a). Corresponding values for SDE intake are 0.81 mg and 3.68 mg.
to be assigned the reported kind and level of added or residual sulfite. Thus, the NRC procedure typically resulted in an over-estimation of intake of the substance, sometimes by a rather substantial margin. Furthermore, food processors often reported the amount of sulfite added to the food rather than the amount remaining at the time of consumption. As explained earlier, sulfites can be lost during processing, storage, distribution, and home preparation, and in many processed foods much of the added sulfite may be converted to reacted forms. Finally, no correction was made for plate waste.

There are also factors favoring underestimation of intake values. Consumption of alchoholic beverages away from home was probably under-reported in the data on frequency of consumption gathered by the Market Research Corporation of America (Chicago, IL) and used by the NRC. Alcoholic beverages, especially wine, can contribute substantially to intake of sulfites. Food service establishments were not included in the 1977 NRC survey and use of proprietary sulfite solutions on salad bar vegetables was not considered. Salad bars can be a substantial source of sulfite intake.

NRC found no way to correct accurately for the factors that contribute to errors in estimation of intakes. Using the NRC data, the Panel has estimated per capita daily sulfite intake (as SDE) including consumption of wine and/or beer to be 19 mg, the 90th percentile intake to be 43 mg, and the 99th percentile 163 mg. These estimates were made in the following manner. The NRC data revealed the mean per capita daily consumption in SDE to be 4.8 mg of potassium metabisulfite, 17 mg of sodium bisulfite, 0.27 mg of sodium metabisulfite, 7.0 mg of sulfur dioxide, and 1.3 mg of sodium sulfite. By assuming that use of one of these sulfiting agents in a food subcategory precludes use of others and using only the contribution of the sulfiting agent that accounts for the largest consumption, the figures above can be corrected and become respectively: 0, 12, 0, 6.7, and 0.4 for a total of 19 mg. The 90th percentile daily consumption figures, similarly corrected, are respectively: 0, 25, 0, 16, and 1.6 for a total of 43 mg; the 99th percentile daily consumption figures, similarly corrected, are respectively: 0, 33, 0, 129, and 1.1 for a total of 163 mg.

Several characteristics and problems in interpreting data in Table 1 should be recognized because they too have bearing on the reliability of the data:

1) In Table 1, there is no relation, necessarily, between the values reported in the "Added" and "Residual" columns for a given food since companies frequently reported values for only one, not both. Exceptions are the values given for the first two items, pie doughs and the tortilla shells in the Baked Goods and
Baking Mixes Category. Added and residual levels as processed, and level in the product as consumed (after baking the dough) were reported for the same product. For tortilla shells the levels were 25, 25, and 0.3 ppm, respectively. Levels listed for the "Unspecified" subcategory are those designated by reporting companies as used in a general category, e.g., baked goods and baking mixes and thus may apply to one of the subcategories listed in Table 1, or to unidentified subcategories not listed. For most food products, relatively few companies, as compared to the total number manufacturing the food product, reported added or residual levels of sulfites. Thus, the generality of the use of sulfites in various food products manufactured by different companies as well as the representativeness of reported levels of addition may be inaccurate. It is also possible that sulfites are used in foods not reported in Table 1. Answers to such questions were sought by contacts with experts in food science and technology in USDA, universities, industry and industry associations, and from reports in the literature; the estimated sulfite levels in foods as consumed (Table 1) reflect the information obtained.

2) Reports of the NFCS (USDA, 1983b) generally identify the quantity of foods eaten as such by individuals in a 3-day survey period or used by households in a week during the survey year, April 1977 through March 1978. Not included are the quantities of those foods which were consumed as ingredients in processed foods. Examples of such foods that are reported to contain sulfites are sugar, corn syrup, dried fruit, corn starch, modified corn starch, and dextrose. The latter three substances are consumed almost entirely as ingredients of processed foods. In order to include the total contribution of the residual sulfite in these substances, per capita daily intake values calculated from total annual consumption of these products are entered in Table 1. Total annual consumption of sucrose and dried fruits was obtained from USDA statistics, and was provided by Corn Refiners Association, Inc. (Liebenow, 1984) for the corn-derived products.

Daily intake of sugar calculated from total annual consumption in 1982 (sucrose plus dextrose) is 99 g/capita as compared with 4.35 g/capita reported for sugar consumption by individuals (Pao et al., 1982). The respective intakes for corn syrup are 26 and 0.30 g/capita/day. Using intakes based on total annual consumption of these foods results in some duplication in the calculation of SDE intake. Sugar is a major component of jams, jellies, and gelatin desserts that also are entries in Table 1, and both sugar and corn syrup (high fructose corn syrup) are used as sweeteners in soft drinks, also an entry in Table 1.
3) Several dried fruits to which sulfites were reported to be added appear in Table 1. Contact with the dried fruit industry revealed that prunes and dark raisins, which constitute about 70% of all dried fruit, are not treated with sulfiting agents. Dried apples, apricots, some figs, peaches, pears, and golden raisins are treated with sulfur dioxide (Mosebar, 1984b). Household consumption of dried fruits other than prunes and raisins was reported as 0.01 lb/household/week or 0.235 g/capita/day based on an average of 2.76 members per household (USDA, 1983a). However, in addition to that purchased as such, dried fruit is also purchased and eaten as an ingredient of breakfast cereals, baked goods and baking mixes, snacks such as apple bits, and in reconstituted form in some pie fillings. In order to include such uses, daily intake (0.49 g/capita/day) was based on per capita consumption of all dried fruits less that of dark raisins, prunes, and dates as reported by USDA (1984a). The SDE level in dried fruits as consumed was estimated to be 1200 ppm based on information submitted by the Dried Fruit Association of California (Mosebar, 1984a). In contrast, a study in England found the average SDE content of 164 samples of dried fruit, excluding prunes, to be 275 ppm at the point of sale (Howlett, 1980).

4) In estimating the average SDE concentrations in the total intake of fresh vegetables eaten raw, 39.1 g/capita/day (Pao et al., 1982), the contribution of fresh vegetables eaten in restaurants, cafeterias, and other food service establishments was estimated as follows. It was assumed that the percent of fresh vegetables eaten raw in food service establishments was the same as the percent of all vegetables obtained and eaten away from home (15.7%), as found in the NFCS (USDA, 1983b); or that 39.1 x 0.157 = 6.1 g/capita/day is eaten in food service establishments. From a poll of its membership in 1983, the National Restaurant Association found that 3.9% of 17,000 respondents reported the use of sulfites, a decrease from the 20% who reported use of sulfites in 1982 (Neville, 1983). The Panel increased this figure (3.9%) to 10% to allow for possible wider use among nonmembers of the NRA, higher sulfite concentration than that assumed, and a possible disproportionate share of the market held by establishments that use sulfites. An SDE concentration of 950 ppm in cut lettuce was found in experiments with commercial sulfite solutions used according to directions (Taylor, 1984a). This value is assumed to be the level in leafy vegetables and also in other fresh vegetables served in restaurants and other food service establishments among the 10% which may use sulfiting agents.

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Sulfite consumed in these vegetables is 6.1 g x 10% x 950 ppm = 0.58 mg/capita/day. The fraction of mushrooms marketed fresh and treated with sulfites (about 10%) contributes about 0.003 mg SDE/capita/day to the total SDE consumed in fresh vegetables. The average SDE level in all fresh vegetables eaten raw based on the contribution of mushrooms and sulfite-treated vegetables as discussed above is 14.3 ppm. In order to allow for possible unidentified (e.g., unspecified uses, Table 1), the average was increased by about 10% to 16 ppm.

The NFCS (USDA, 1983b) provides data on the percentage of the population that drank wine on only one day of the 3-day dietary survey, on only two days of the three, and on all three. For the respective groups, the daily intake of SDE from wine is calculated to be 11, 22, and 36 mg based on an average SDE level of 150 ppm. The average daily intake for all three groups, i.e., for those who drank wine on at least one of the 3 days, is 17 mg. Only 4.8% of the population surveyed reported use of wine and per capita daily intake for the total population is calculated to be 5.4 g of wine and 0.81 mg SDE. It appears, however, that consumption of wine was under-reported in the NFCS. Based on USDA reports, wine amounting to 21 g/capita/day entered U.S. distribution channels in 1977. In 1983, 24.5 g/capita/day were distributed (USDA, 1984a); this quantity would contain an estimated 3.68 mg SDE.

Information on other food categories is provided in the footnotes to Table 1.

Based on the estimates in Table 1, the total per capita daily intake of sulfites from food, expressed as SDE, is about 6 mg. Beer provides an additional 0.4 mg/capita/day; wine, based on NFCS intake (USDA, 1983b), provides 0.8 mg but 3.7 mg based on the total quantity distributed. Thus, it seems reasonable to conclude that the mean daily intake of SDE from food, wine, and beer does not exceed 10 mg (0.17 mg/kg body weight). For those individuals who consume wine and/or beer regularly, there would be an additional 30 mg for each 200 ml of wine and 10 mg for each liter of beer consumed. For comparison, the Codex Alimentarius Commission estimated in 1975 that heavy consumers of foods and beverages containing high levels of sulfites (99th percentile consumption) might have a daily intake of 177 mg SDE. For further comparison, the following is an example of a meal that may provide a maximal amount of SDE:
Tossed salad 100 g x 950 ppm = 95 mg
Instant potatoes 160 g x 70 ppm = 11.2 mg
Shrimp 63 g x 30 ppm = 1.9 mg
Wine 200 g x 150 ppm = 30 mg
Total 138.1 mg

With dried apricots added 33 g x 1200 ppm = 39.6 mg
Total 177.7 mg

Thus, it also seems reasonable to conclude that the 99th percentile intake, including regular consumption of wine and beer, probably does not exceed 180 mg of SDE per day (3 mg/kg body weight).

The Panel has been unsuccessful in its attempts to obtain sufficient reliable data on the poundage of sulfites currently being used in food per annum and trends in usage of the several sulfiting agents since 1976. This issue is related to the extensive nonfood uses of food-grade sulfiting agents in industry. However, the International Food Additives Council is now assessing the production volume of food-grade sulfiting agents directed to food use in the United States (Cristol, 1984).

While intakes of sulfites from nonfood sources are not to be considered in the present evaluation, approximate levels of intake from such sources should be mentioned for comparative purposes and consideration of cumulative effects. Nonfood sources of sulfite intake include the atmosphere as well as ingested, inhaled, and injected medicinals.

Sulfur dioxide intake by inhalation can be estimated from standards of air quality (U.S. Congress, 1970) which require that average sulfur dioxide concentrations in communities do not exceed 0.14 ppm in any one 24-hour period and do not exceed 0.03 ppm per 24 hours over one year. For industrial environments, a threshold limit value of 2 ppm has been established for an 8-hour day (American Conference of Governmental Industrial Hygienists, Inc., 1980). The 0.14 ppm level would result in inhalation of 3.8 mg sulfur dioxide in 24 hours, the 0.03 ppm level 0.85 mg per 24 hours, and the 2 ppm level 24 mg per 8 hours.

Many injectable and oral drug preparations, including epinephrine, and other drugs frequently used in the treatment of asthmatic patients and those with respiratory problems, as well as local anesthetics, contain sulfite ranging from 0.25 to 1.0% as SDE (Pulmonary-Allergy Drugs Advisory Committee, 1983). Sulfite intake from such solutions, which are administered in small volumes, is quite small compared to that derived from intravenous infusion used for total parenteral nutrition (Metcalf, 1984). Infusion of 500 ml of a solution containing 0.1% sodium bisulfite, for example, would result in administration of 308 mg SDE.
IV. BIOLOGICAL STUDIES

The report of the Select Committee on GRAS Substances reviewed biological data relevant to the health effects of sulfiting agents available at that time (SCOGS, 1976). Except for information considered necessary to provide perspective and context for recent studies, literature cited in this section of the report represents studies completed since the 1976 evaluation of the GRAS status of sulfiting agents.

Metabolism of Sulfites

The chief pathway for metabolism of sulfite consists of its oxidation to sulfate. At high concentrations of sulfite (1 M sulfite, pH 7) an autooxidation reaction, initiated by superoxide or HSO₃⁻ radicals and enhanced by Mn²⁺ and Fe³⁺, proceeds readily (McCord and Fridovich, 1969). However, at 20 mM sulfite this route of oxidation is relatively ineffective either in oxidizing sulfite to sulfate or in initiating other biologically significant reactions (Hayatsu, 1976; Johnson and Rajagopalan, 1980; McCord and Fridovich, 1969). In vivo sulfite oxidation is catalyzed by sulfite oxidase (also called sulfite dehydrogenase or sulfite: ferricytochrome c oxidoreductase, EC 1.8.2.1). The enzyme is located in the intermembranous space of the mitochondria, and it exists as a dimer (molecular weight 120,000 daltons in the human) with subunits containing a molybdenum atom (Mo⁶⁺), a cytochrome b₅-type heme component and a pterin cofactor (Cohen and Fridovich, 1971; Johnson et al., 1980). Sulfite oxidase functions by transferring a pair of electrons from sulfite to molybdenum, heme, and cytochrome c sequentially. Sulfate and other anions inhibit sulfite oxidase activity in vitro; tungstate inhibits the enzyme in vivo and in vitro.

Sulfite oxidase is distributed widely in mammalian tissues with the highest concentrations in liver, heart, and kidney. Activity of the enzyme has been measured in the livers of many species including rats, dogs, cattle, monkeys, and man (Johnson and Rajagopalan, 1976; MacLeod et al., 1961). Sulfite oxidase activity measurements reported in the literature are difficult to compare because of the localization of the enzyme in the mitochondria and variations in the methods used. However, in general, sulfite oxidase activity in the human is slightly less than that of the rhesus monkey and substantially less than any of the other mammals studied except the rabbit. Cohen et al. (1973) estimated that the total activity of sulfite oxidase of the rat is capable of oxidizing 750 mmoles/kg body weight/day of sulfite,
corresponding to 48 g SDE/kg body weight/day. Human liver has only 5 to 10% of the sulfite oxidase activity of rat liver (Johnson and Rajagopalan, 1976). In biopsy samples from three of four normal subjects, hepatic sulfite oxidase activity was 1.78 μmoles of cytochrome c reduced/min/g protein; in the fourth subject, enzyme activity was 3.62 μmoles of cytochrome c reduced/min/g protein (Johnson et al., 1980). Sulfite oxidase activity in cultured fibroblasts of normal human subjects was 1.07 μmoles cytochrome c reduced/min/mg protein (range, 0.75-1.76) (Shih et al., 1977) and 2.10 μmoles/min/mg protein (range, 0.75-3.03) (Johnson et al., 1980).

At least seven cases of congenital deficiency of sulfite oxidase in humans have been reported (Gunnison and Jacobsen, 1983). No detectable activity of sulfite oxidase was found in liver or in skin fibroblasts of these patients (Johnson et al., 1980; Shih et al., 1977). Metabolically, the condition is characterized by greatly increased excretion of sulfite, thiosulfate and cysteine-S-sulfonate and by somewhat decreased excretion of sulfate. Clinically, the condition produces dislocated ocular lenses and severe neurological abnormalities resulting in mental and physical retardation.

In four sulfite oxidase-deficient patients, Shih et al. (1977) found that daily urinary sulfite excretion ranged from none to 4.28 mmole/g creatinine; thiosulfate excretion was increased from 0.79 to 1.97 mmole/g creatinine. Oral loading of one patient with 0.5 mmole each of methionine and cystine produced an increase in plasma sulfite from an initial level of 15 μM to 120 μM and 60 μM, respectively, after 4 hours. The loading tripled thiosulfate excretion.

Parents and siblings of sulfite oxidase-deficient patients frequently have lower levels of enzyme activity. Shih et al. (1977) and Johnson et al. (1980) reported that these relatives metabolized sulfite normally, confirming the occurrence of a large excess of sulfite oxidase activity in heterozygous as well as normal individuals.

A model system for study of sulfite oxidase deficiency can be produced in the rat by inclusion of 100-200 ppm of sodium tungstate in the drinking water (Johnson et al., 1974). In this early study, hepatic sulfite oxidase activity decreased from 40 to 0.05 Units/mg protein in 28 days. Tungsten competes with molybdenum for the metal binding site on the apoenzyme and sulfite oxidase activity can be diminished to any level by choosing an appropriate tungstate:molybdate ratio. Sulfite oxidase-deficient rats have markedly increased levels of urinary and tissue endogenous thiosulfate and S-sulfonates in proportion to the decrease in enzyme activity (Gunnison et al., 1981a,b,c). In sulfite
oxidase-deficient rats administration of 0.5 mmole/kg of sulfite produced amounts of plasma S-sulfonates equivalent to those produced in normal rats by administration of 10 mmole/kg sulfite. High levels of plasma sulfite also occurred. Intubation of 10 to 20 times as much sulfite into the normal rat was required to produce a systemic sulfite level equivalent to that of the sulfite oxidase-deficient rat even though the former had 100 times the activity of enzyme (Gunnison et al., 1981a). Probably the limiting factor for sulfite oxidation is the rate of diffusion into the mitochondria (Oshino and Chance, 1975).

Since the oxidation of sulfite by nonenzymatic reactions is minimal in the presence of the normal distribution of sulfite oxidase, sulfate excretion provides an estimate of the metabolism of sulfite. It has been estimated by Gunnison (1981) that endogenous sulfite generation in humans is about 0.3 to 0.4 mmoles/kg/day (19.2 to 25.6 mg SDE/kg/day). In the U.S. the mean dietary intake based on information on consumer exposure is calculated to be between 0.17 and 3.0 mg SDE/kg/day for a 60 kg individual. The endogenous sulfite arises in the mitochondria and only needs to diffuse across the inner membrane to contact sulfite oxidase. Such sulfite arises from cystine and methionine in the diet in excess of bodily requirements. Sulfite has not been detected in the plasma or urine of normal humans, nor that of other mammals, unless large quantities of sulfite had been administered (Gibson and Strong, 1973).

Exogenous sulfite enters the body by inhalation of SO₂ and by ingestion via the blood stream. Some sulfite is oxidized in the lung and intestine before it enters the circulation. Pfleiderer et al. (1968) reported that the empty intestine of rats oxidized about 50% of radiolabeled sulfite while filled intestines oxidized even more. This may be due to sulfite oxidase activity in the intestinal wall or to gut microflora. No reports of gastric absorption or metabolism have been noted.

Sulfite administered intravenously is cleared rapidly in the rhesus monkey. It has a biological half-life of 10 minutes for doses in the range of 0.3 to 0.6 mmole/kg (Gunnison and Jacobsen, 1983). Hepatic oxidation of infused sulfite in rats has been shown by Oshino and Chance (1975) to be diffusion limited. A constant proportion of the sulfite in the perfusate, up to 1 mM, is removed (mean, 33%, range 24–40%). Because all sulfite is not removed by the liver at first pass of the blood, all tissues will be exposed to a significant proportion of the administered dose. On the basis of data from rats and monkeys, Gunnison and Jacobsen (1983) speculated that the half-life of sulfite in man is 15 minutes. Thus, for example, approximately 0.25 mg of a 1 mg dose of potassium metabisulfite would remain in body fluids 30 minutes
after ingestion. An immediate second challenge of 5 mg of meta-
bisulfite would increase the total to 5.25 mg, declining to
1.31 mg in another 30 minutes. The immediate concentration after
injection of 1 mg of potassium metabisulfite would be 2.57 μM for
a 70 kg man assuming all the sulfite was confined to the plasma
and 0.21 μM if the compound were evenly distributed in total body
water.

Because of rapid clearance of sulfite by action of sulfite
oxidase, chronically ingested sulfite does not accumulate in the
tissues but is rapidly eliminated, primarily as sulfate. In all
species tested, Gunnison et al. (1977) found that no more then 10%
of the administered dose was excreted in the urine as sulfite.
Brief exposure of tissues to sulfites does not appear sufficient
to maintain sulfite adducts that are unstable. A sufficiently
large physiologic equilibrium constant has not been demonstrated
for the minor adducts to make them a factor in metabolism. Irre-
versible reactions, although quantitatively minor, could exert
more significant biological effects.

Sulfite persisting in body fluids undergoes a number of
reactions with tissue components. Thiosulfate is a product of
three enzymatic reactions: 1) the reaction of sulfite with mer-
captopyruvate (Sörbo, 1957); 2) metabolism of cysteine-S-sulfonate
(Sörbo, 1958); and, 3) the reaction of sulfite and thiocystine
(Szczepkowski and Wood, 1967). Sörbo and Öhman (1978) determined
the daily excretion of thiosulfate in the urine of normal human
subjects to be 31.7 mmole/day ± 12.8 (range 12.4-67.5). These
values probably do not represent actual formation of thiosulfate
in the body since thiosulfate is metabolized to sulfate and is
excreted in the urine (Gunnison et al., 1981c; Skarzynski et al.,
1959).

Several nonenzymatic reactions also occur between sulfite
and tissue components. Few of the products form in vivo at the
levels of sulfite arising from endogenous formation; however,
under conditions of sulfite loading appreciable amounts of sulfite-
derived compounds are produced.

Sulfite lyases disulfide bonds with formation of S-sulfo-
nates and thiols (Cecil, 1963):

\[
RSSR + SO_3^- \leftrightarrow RSSO_3^- + RS^- 
\]

The reaction is reversible, but the equilibrium lies well to the
right for small molecules such as cysteine-S-sulfonate and gluta-
thione-S-sulfonate (Cecil, 1963); the former is found in the urine
after sulfite loading (Gunnison and Palmes, 1974). Glutathione-S-
sulfonate was also found in bovine lenses (Waley, 1959). Evidently
only interchain disulfides of native proteins undergo sulfitolysis (Cecil and Wake, 1962). Protein S-sulfonates slowly release sulfite ions in the presence of sulfhydryl compounds (Swan, 1959).

Little information is available regarding other essential biological disulfide systems. No reports have been noted on modification of the dithiolane ring of lipoil-containing transacetylase cores (e.g., transacetylase of pyruvate dehydrogenase multienzyme complex, transsucclinylase of α-ketoglutaric dehydrogenase multienzyme complex or transacetylase of branched chain α-keto acid dehydrogenase) by sulfiting agents. The same considerations may apply to other essential disulfide systems, e.g., thio-redoxin.

The formation of protein S-sulfonates is concentration-dependent both in vitro and in vivo. At 2 mmole/kg/day intake of sulfite, plasma of rabbits and rhesus monkeys contained measurable levels of S-sulfonates while plasma of rats did not. However, parenteral administration of 3.2 mmoles of sulfite/kg/day for 5 consecutive days produced significant increases in plasma S-sulfonate levels in the rat from 5-10 nmole/ml plasma to 19-30 nmole. Plasma S-sulfonate fractions in the rat and rhesus monkey had half-lives of approximately 4 and 8 days, respectively (Gunnison and Palmes, 1978).

Gunnison and Palmes (1974) determined that the level of plasma S-sulfonates was related to exposure in human subjects inhaling sulfur dioxide at 0.3, 1.0, 3.0, 4.2, and 6.0 ppm for 120 hours. For each increment in exposure of 1 ppm, 1.1 ± 0.16 nmole of additional S-sulfonate per ml of plasma were found.

Portions of lungs and aortas of rabbits exposed to constant arterial sulfite concentrations of 545-560 μM for 0.6 to 6 hours were analyzed for S-sulfonates (Gunnison and Farruggella, 1979). The kinetics of formation was first order with asymptotic concentrations of S-sulfonates of approximately 900 and 9000 nmole/g of dry weight of lung and aorta, respectively. Clearance of S-sulfonates from both tissues was apparently first order with a half-life of 2 to 3 days. No appreciable amounts of S-sulfonates were found in liver, kidney, testes, heart, brain, skeletal muscle, stomach, ovaries, duodenum, spleen, or eye.

Levels of S-sulfonates in tracheas of rabbits exposed to 3 ppm sulfur dioxide for 3 and 24 hours were constant at approximately 53 nmole/g dry weight (Gunnison et al., 1981c). Preliminary results of subsequent experiments in which rabbits were exposed to 10 ppm sulfur dioxide for 1, 3, 10, 24, 48, and 72 hours showed formation of S sulfonate in 9 nmole/ml plasma in 3 hours and 30 nmole after 24 hours. No exogenous S-sulfonates were detected in aortas and scarcely any in the distal portions of posterior
lung lobes. Thus, the sulfur dioxide absorbed was partially metabolized in passing through pulmonary tissues. S-Sulfonate concentrations of 107 nmole/g dry weight of trachea were reported in animals exposed for 3 hours with a gradual increase to 163 nmole in animals exposed for 72 hours; however, increase was attributed to increased mucus production. During the exposure, S-sulfonates in plasma increased from 40 to 70 nmole/ml; sulfite was not detected in the plasma. It was concluded that with possible exception of heart and lungs, there was no transport of inhaled sulfur dioxide to organs some distance away from the site of absorption (Gunnison et al., 1981c).

Nasal mucus of four rats exposed to an initial concentration of 5 ppm of $^{35}$SO$_2$ for periods of 0.5, 1, 2, and 4 hours contained 90% of the inhaled $^{35}$S after 30 minutes (Cause and Barker, 1978). Later, the ratio of sulfur in mucus to serum leveled off at 3:1. After rats were exposed to 5 ppm or 20 ppm sulfur dioxide continuously for 7 days, electrophoresis of the glycoproteins from nasal mucus showed the appearance of three to five new bands from the acidic fraction, a finding interpreted to indicate an increase in crosslinking in the protein. The effect first appeared 2 hours after sulfur dioxide exposure. The polymerization of glycoprotein molecules could account for the decrease in flow rate of nasal mucus commonly seen with inhalation of sulfur dioxide. Habeeb (1971) found that sulfitolysis of seven disulfide bonds of bovine serum albumin, with concomitant reorganization of the topography of the molecule, caused an 80% reduction in ability to react with antiserum. However, Gunnison et al. (1981c) considered that localized tracheal concentrations of sulfur dioxide at or near 10 ppm would not be sufficient to produce protein crosslinking.

Metabolism of two relatively stable addition products of sulfite with food components (proteins or osuloses) has been investigated in rodents. Gibson and Strong (1974) administered a sulfonated protein (rat serum protein labeled with $^{35}$SO$_3^{2-}$) by stomach tube to 12 male albino rats. About 45 to 70% of the radioactivity was found in the carcass and urine. Highest concentrations of radioactivity were found in stomach, intestine, skin, and hair and 42 to 62% of radioactivity was excreted in the urine as inorganic sulfate after 24 to 48 hours. These investigators also fed a diet containing casein autoclaved with 0.6% sodium metabisulfite labeled with $^{35}$S to rats for seven weeks. Growth of the animals fed the sulfited casein was comparable to that of controls although some diarrhea occurred throughout the experiment. No evidence suggestive of toxic effects was observed. Metabolism of 3-deoxy-4-sulfohexulose, a sulfonate formed by the reaction between sulfite and deoxysuloses, was studied in rats and mice utilizing $^{14}$C- and $^{35}$SO$_3^{2-}$ labeled sulphonates (Walker et al., 1983). The compound appeared to be metabolically inert because
$^{14}\text{CO}_2$ was not expired, the patterns of excretion of radioactivity following administration of both labels were similar, and chromatographic evidence indicated that compounds excreted in the urine were associated with unchanged 3-deoxy-4-sulfohexulose. At 72 hours after administration, 90.9 to 99.6% of the radioactivity was accounted for in urine, feces and cage washings; at that time no residual radioactivity could be measured in plasma or carcass. Tissue distribution studies suggested that most of the radioactivity was associated with the gastrointestinal tract; however, considerable activity was found in the pancreas soon after administration (Walker et al., 1983). Whether a transient increase in concentration of 3-deoxy-4-sulfohexulose has an effect on pancreatic function remains to be determined.

**Metabolic Effects of Sulfites**

The cleavage of thiamin by sulfite was reviewed by Dwivedi and Arnold (1973). The reaction involves a nucleophilic attack by sulfite on the quaternary nitrogen of the thiazole ring to yield pyrimidine sulfonic acid and 4-methylhydroxyethyl thiazole. At pH 5 and 25°C, the half-life of 10 μM thiamin in the presence of 1.0 mM sulfite is approximately 13 hours (Dwivedi and Arnold, 1973).

It has not been demonstrated that destruction of thiamin by sulfite in vivo is sufficiently rapid and specific to deplete reserves of thiamin or that the symptoms of bisulfite toxicity coincide with thiamin avitaminosis (Gunnison et al., 1981a). In three rats fed a diet containing 6% sodium metabisulfite and supplemented with 50 ppm thiamin for 21 days, the hepatic thiamin values were $8.8 \pm 1.2 \mu g/g$ wet weight while the control values were $10.1 \pm 0.7 \mu g/g$. Although the test animals were severely anemic (hemoglobin, $9.5 \pm 2.6$ g/100 ml blood), Gunnison et al. (1981a) concluded that the systemic effect of sulfite was not due to destruction of thiamin. Activity of heme synthetase in brain and liver of male rats 3 months of age was also reduced after consumption of drinking water containing 900 ppm sodium sulfite for 7 weeks (Savelainen and Tenhunen, 1982).

Destruction of cyanocobalamin by high concentrations of sulfite in the diet or in the gut was considered a possible mechanism in the production of anemia (Gunnison et al., 1981a). The cobalamins form photolabile complexes with sulfites (Gunnison and Jacobsen, 1983). During photolysis, sulfite is oxidized aerobically to sulfate. Cyanocobalamin is reported to be an effective blocking agent for sulfite-induced asthma (Jacobsen et al., 1984). The relation of complex formation to the blocking of sulfite-induced asthma by cyanocobalamin has not been explained.
Menadione (vitamin K₃) adds sulfite to the 2,3-double bond of the naphthoquinone ring. The reaction is reversible and the sulfite adduct can be used by chicks as a source of vitamin K (Nir et al., 1978).

Sodium sulfite added to the diet of rats and fed for periods up to 1.5 years produced evidence of vitamin E deficiency as measured by effects on the enamel of the teeth (Irving et al., 1952). Such evidence appeared only at levels of 500 mg of sodium sulfite per kg body weight and higher.

Amino acids are oxidized in the presence of sulfites. Methionine is oxidized aerobically to its sulfoxide by free radicals in the presence of sulfite and Mn²⁺ (Inoue and Hayatsu, 1971; Yang, 1970); similarly, tryptophan is destroyed by sulfite and Mn²⁺-induced free radicals (Yang, 1973).

Sulfite combines reversibly with aldehydes such as glucose and ketones such as fructose to form hydroxysulfonate derivatives (Petering and Shih, 1975). Compounds such as pyruvate and α-ketoglutarate form hydroxysulfonates which are somewhat more stable than the hydroxysulfonate of glucose, but would not be expected to persist under physiological conditions. A potential carbonyl addition is the sulfite adduct of pyridoxal phosphate, an important cofactor of many enzyme systems.

Sulfite adds to the 3,4-double bond of the pyridine ring of NAD. Riboflavin, as it occurs in coenzymes (e.g., FAD, FMN), forms chemical adducts with sulfites. The N⁵ atom of flavin is thereby substituted with a sulfonate group at the active site that accepts hydrogen. The free adducts dissociate readily at low sulfite concentrations, but may show a somewhat enhanced stability in protein combinations. This is the probable mechanism of inhibition of dehydrogenases by sulfite (Müller and Massey 1971). A number of flavoprotein oxidase enzymes (e.g., D- and L- amino oxidases, oxynitrilase, lactate oxidase, and glycolate oxidase) form stable sulfite adducts with dissociation constants from 10⁻⁴ to 10⁻⁷ M. The flavoprotein dehydrogenases did not form adducts at 20 mM sulfite (Müller and Massey, 1971).

The catalytic action of several oxidative enzymes such as xanthine oxidase, liver aldehyde oxidase, cytochrome oxidase, lipoxidase, and peroxidase can initiate aerobic oxidation of sulfite by intermediate formation of superoxide and other free radicals (Fridovich and Handler, 1961). Cytochrome oxidase was inhibited 37% by 0.5 mM sulfite at pH 7 (Cooperstein, 1963). α-Glucan phosphorylase was inhibited by 10 to 30 mM sulfite concentrations (Kamogawa and Fukui, 1973). Sulfite was a competitive inhibitor for phosphate in glycogen synthesis and in glycogen degradation. Alkaline phosphatase was inhibited in vivo.
Activity of 2,3-diphosphoglyceric acid phosphatase was enhanced 15-fold by 2.5 mM sulfite (Harkness and Roth, 1969). Sulfite was found to be a potent inhibitor of many sulfatases, e.g., sulfatase A, $K_I$, 0.2 μM (Roy, 1976).

Sulfite adds reversibly to the 5,6-double bonds of cytosine and uracil and their nucleosides and nucleotides (Gunnison, 1981; Shapiro, 1983). The additions are pH- and concentration-dependent and the adduct has a half-life of several hours. At 100 mM sulfite, only 12% of the uridine reacted in 0.5 hours. Uridine is regenerated from its sulfite adduct by removal of sulfite. The sulfonate adducts of cytosine and its derivatives are less stable and a high concentration of sulfite is necessary to maintain them at physiological pH.

The deamination of cytosine to uracil nucleotides in single stranded DNA occurs in bisulfite solutions of 1 M or higher at pH 5 to 6 (Hayatsu, 1976; Shapiro, 1983). Purine bases do not react under these conditions. This reaction has been used in a number of studies with microbial systems to demonstrate the mutagenic property of bisulfite. The concentrations of bisulfite used in chemical studies and microbial mutagenicity tests were about two or three orders of magnitude higher than is observed in biological systems.

The cytosine sulfonate adduct can also be transaminated with primary and secondary amines, including lysine, to produce N4-substituted cytosines and polycytidines (Shapiro and Gazit, 1977). Crosslinking was observed also with heat-denatured calf thymus DNA to the extent of 0.5% of the strands after 6 days in 0.15 M sodium bisulfite. Double-stranded DNA did not crosslink. However, Lukášová and Paleček (1976) found that treatment of native calf thymus DNA with 2.61 M bisulfite at pH 6.5 for 24 hours caused modification of the polarographic behavior which was explained on the basis of modification of less than 1% of the cytosine, presumably by conversion to uracil. The investigators suggested that cytosine residues on "open" loops in the native DNA were the reactive sites. Such crosslinking has not been demonstrated in vivo in mammalian organisms. In cultures of mouse liver cells, Hela cells, and human embryonic lung cells, lymphocytes and oocytes, significant inhibition of DNA synthesis has been observed at bisulfite concentrations from 0.1 to 10 mM (Shapiro, 1983). From alkaline sucrose density gradient measurements, Hayatsu and Miller (1972) concluded intranucleotide bonds of DNA were cleaved by 1 to 10 mM sodium bisulfite. Since the cleavage at pH 7 was enhanced by Mn2+ and inhibited by hydroquinone, it was considered to result from free radical formation.
Kaplan et al. (1975) found that low concentrations of bisulfite (0.5 mM) induced oxidation of corn oil emulsified in 1.5% polysorbate solution. The effect was concentration-dependent to 10 mM. The initial oxidation products presumably were peroxides. Because it was inhibited by Mn$^{2+}$ and antioxidants, sulfite autooxidation was not considered a significant factor in the oxidation process. Inouye et al. (1978) reported similar results in liver homogenates.

Incubation of unsaturated membrane lipids with a large excess of bisulfite produced significant changes in the behavior of such lipids on silica gel, suggesting the addition of bisulfite to fatty acid double bonds (Akooryam and Southerland, 1980). Such addition, if occurring in vivo, would change the topography of the membrane and could account for the toxic and irritating effect of sulfur dioxide on tissues.

In brains of guinea pigs exposed to 10 ppm sulfur dioxide for 1 hour daily for 21 days, total lipids and free fatty acids were decreased in all regions, but changes in other fractions varied among regions of the brain (Haider et al., 1981). The rates of peroxidation and the activity of lipase were increased significantly in all regions of the brain.

In summary, from the information on the metabolism of sulfiting agents in the current literature, the ad hoc Panel finds no reason to presume that individuals with the usual levels of sulfite oxidase activity and adequate nutritional status should develop adverse health effects from consumption of sulfite in foods at the levels currently used. However, there is sufficient information in the current literature to conclude that some individuals, or a select subpopulation with a congenital deficiency of sulfite oxidase activity, would metabolize sulfite more slowly and may be subject to adverse effects from sulfite at the current level of intake.

**Acute Oral Toxicity**

No animal feeding studies of acute oral toxicity of sulfiting agents published after 1976 were located for consideration by the ad hoc Review Panel. Acute exposure seems to be a factor in sensitivity reactions associated with ingestion of foods or beverages containing sulfiting agents (see section V), but this reaction appears to be separate and distinct from other manifestations of acute oral toxicity.
Short- and Long-Term Toxicity Studies

Early investigation of the chronic toxicity of sulfite was complicated by development of thiamin deficiency, resulting from the destruction of dietary thiamin by sulfite (Fitzhugh et al., 1946). In studies such as those of Cluzan et al. (1965) and Lockett and Natlof (1960), long-term administration of sulfites in drinking water (dosage ranges of 29-40 to 190 mg SO2/kg body weight/day) was not associated with effects on feed consumption, growth rate, reproduction, hematology, organ weight and histology, or mortality.

In the 1976 evaluation of the health aspects of sulfiting agents as food ingredients, the Select Committee considered the thorough investigation on ingestion of sulfites in thiamin-supplemented diets (Til et al., 1972a,b) as substantive evidence for levels of sulfiting agents required to produce chronic toxic effects in rats and pigs. In pigs fed diets containing sodium metabisulfite for 48 weeks, the no observed adverse effect level (NOAEL) was 3500 ppm, corresponding to dosage ranges of 42 to 179 mg SDE/kg body weight/day. In rats, the NOAEL for sodium metabisulfite was 2150 ppm, equivalent to an intake of 72 mg SO2/kg body weight/day. Based upon the data reported by Til et al. (1972a), the Joint FAO/WHO Expert Committee on Food Additives (1974) established an acceptable daily intake (ADI) of 0.7 mg SDE/kg body weight.

Few reports were found of short- or long-term studies of sulfiting agents published after 1976. Gastric lesions had been reported in several earlier chronic feeding studies (Feron and Wensvoort, 1972; Til et al., 1972a,b). In one study the types of gastric lesions induced in Cpb:Wu (Wistar Random) rats by feeding of sodium metabisulfite were examined by enzyme histochemistry and light and electron microscopy (Beems et al., 1982). Animals were fed thiamin-supplemented diets containing 0, 4, and 6% sodium metabisulfite for 8 or 12 weeks in a subchronic study or 0 and 6% sodium metabisulfite for 4, 7, 14, 21, or 28 days in a time-sequence study. Fundic mucosa of the rats fed sodium metabisulfite contained scattered hyperplastic glands lined with enlarged hyperactive gastric chief cells containing large numbers of pepsinogen granules, but no fat, glycogen, or mucus. Findings from the time-sequence study suggested that preexisting chief cells were transformed to hyperactive chief cells having proliferative capabilities. While it is considered unusual that chief cells of this type should be so involved rather than mucus cells, the pathogenesis of the lesions remains to be resolved (Beems et al., 1982).
Subchronic toxicity of sulfite was examined in female rats with low levels of sulfite oxidase activity induced by feeding of low molybdenum diets containing tungstate for 9 weeks (Gunnison et al., 1981a). Beginning on day 21, drinking water for two groups of animals also included 25 or 50 mM $\text{SO}_3^{2-}$. This treatment resulted in levels of hepatic sulfite oxidase activity 1% of that of untreated rats and 10% of that of normal humans. The authors reported that the general health of the rats appeared normal and differences in weight gains and organ weights of pregnant and nonpregnant animals were not correlated with exogenous sulfite levels. Nonpregnant animals given sulfite did not develop anemia and hematologic measurements in pregnant animals showed changes normally associated with pregnancy. Erythrocyte glutathione concentrations and prothrombin times were not affected and hepatic thiamin concentrations were not significantly reduced by administration of sulfite to rats with low levels of sulfite oxidase activity. S-Sulfonate concentrations in aorta, pinna, and plasma were elevated in animals with low levels of sulfite oxidase activity. Administration of sulfite produced additional increments in S-sulfonate levels in aorta. Trends appeared similar, but data were incomplete for pinna and plasma concentrations of S-sulfonates.

The Select Committee (SCOGS, 1976) concluded that "the level of sulfite that produces no observed toxic effects varies from about 30 to 100 or more mg of $\text{SO}_2$ per kg body weight per day, depending on the species and experimental conditions." Upon review of the information available to the Select Committee and in the absence of additional data conflicting with the reports considered by the group, the ad hoc Review Panel concurs with the conclusion of the Select Committee regarding the no observed adverse effects level of sulfiting agents for chronic toxic effects. Moreover, it is evident from examination of experimental protocols that the no observed adverse chronic effect level is probably nearer the upper than the lower portion of the range.

**Teratogenicity**

Reproductive performance was studied in female Wister-derived rats with induced sulfite oxidase deficiency and exposed to 25 or 50 mM sulfite (160 or 280 mg/kg/day) as sodium metabisulfite in drinking water from 3 weeks prior to mating until day 20 of gestation (Dulak et al., 1984). No treatment related trends were reported in reproductive performance or malformations after exposure to sulfite of animals having deficient or normal levels of sulfite oxidase activity.
Inhalation of sulfur dioxide in filtered room air for 7 hours/day by CF-1 mice (25 ppm on days 6 through 15 of gesta-
tion) and New Zealand rabbits (70 ppm on days 6 through 18 of
 gestation) resulted in no evidence of maternal toxicity except
for decreased food consumption by both species during the first
few days of exposure (Murray et al., 1979). An increase in minor
skeletal variants in both species was associated with maternal
exposure to sulfur dioxide, but no teratogenic effects were
observed in either species (Murray et al., 1979).

It is the opinion of the ad hoc Review Panel that
these data, in addition to the studies considered by the Select
Committee, do not provide evidence of teratogenic effects of
sulfiting agents.

Mutagenicity and Carcinogenicity

It was reported that bisulfite (10 mM; pH not specified)
induced mutations in Staphylococcus aureus and that bisulfite (5 mM)
induced mutations at pH 3.6 but not 5.5 in Saccharomyces cerevisiae
(Shapiro, 1983). Bisulfite (0.1 M) did not cause mutations in
Escherichia coli (Mallon and Rossman, 1981). In a Bacillus
subtilis test system, concentrations of sulfur dioxide similar
to those found in wines (150 ppm, pH 3.0 to 6.5) did not elicit
any mutagenic activity (Khoudokormoff and Gist-Brocades, 1978).
Also in a B. subtilis system higher concentrations of a sodium
sulfite-bisulfite mixture (0.1 M to 0.5 M; pH 7) showed mutagenic
effects whereas a lower concentration of this mixture (0.05 M;
pH 7) caused no mutagenic activity. Cells treated with adducts
of sodium bisulfite and cytidine monophosphate or uridine mono-
phosphate demonstrated mutagenic effects at concentrations of
0.25 M and 0.5 M (Chang et al., 1977).

Transformation of Syrian hamster embryo cells treated
with 1, 5, or 10 mM bisulfite for 24 hours at neutral pH was
increased in a dose-dependent fashion (DiPaolo et al., 1981);
however, the authors suggested this transformation might not
occur by a mutagenic mechanism because bisulfite in combination
with UV irradiation did not synergistically increase transforma-
tion. Further work in this system indicated that bisulfite caused
no detectable DNA damage and may have decreased the rate of DNA
replication per cell by blocking operation of part of the function-
ing replicons (Doniger et al., 1982). In Chinese hamster ovary
cells, dose- and time-dependent inductions of sister chromatid
exchange were shown following exposure to 0.03 mM to 7.3 mM
concentrations of bisulfite for 2 or 24 hours (MacRae and Stich,
1979).
In contrast, Chinese hamster cells (V79) exposed for 15 minutes to 10 and 20 mM bisulfite, exhibited no mutations to ouabain resistance (Mallon and Rossman, 1981). Likewise, exposure for 15 minutes to 10 mM bisulfite produced no mutations to 6-thioguanine resistance. Long-term exposure of Chinese hamster V79 cells (exposed continually and recultured for 8 weeks in a complete growth medium containing 5 mM bisulfite) also failed to induce ouabain resistant mutations (Mallon and Rossman, 1981). Cultures of lymphocytes from human peripheral blood exhibited chromosomal abnormalities (clumping) and decreases in DNA synthesis, cell growth and mitotic indices after a single exposure to 100 ml of 5.7 ppm sulfur dioxide in air on days 0 or 1 of incubation but not on days 2 or 3 (Schneider and Calkins, 1970).

While chromosomal aberrations have been observed in response to sulfites in in vitro systems, mutagenic effects have not been reported in intact animals exposed to sulfur dioxide or sulfites. Dominant-lethal mutations were not increased in 10- to 12-week-old (C3H x 101) F₁ female mice given one intraperitoneal injection of 550 mg/kg sodium bisulfite and mated with untreated (101 x C3H) F₁ males within 4.5 days of treatment (Generoso et al., 1978). In the same study neither heritable translocations nor dominant-lethal mutations were detected when (101 x C3H) F₁ male mice were mated with (C3H x C57BL) F₁ females after intraperitoneal injections of 400 mg/kg sodium bisulfite 20 times during a 26-day period or with 300 mg/kg 38 times during a 54-day period. Chromosomal aberrations were not found in oocytes of female Camm mice given one intravenous injection of 1.0, 2.5, or 5.0 mg sodium sulfite although structural damage was reported during meiosis when cultures of Camm mouse oocytes were treated with sodium sulfite (Jagiello et al., 1975). The influence of low levels of hepatic sulfite oxidase activity on induction of cytogenetic effects was recently studied in Chinese hamsters and NMRI mice made sulfite oxidase-deficient by feeding of a low molybdenum diet plus administration of sodium tungstate in drinking water (Renner and Wever, 1983). No cytogenetic effects (measured by sister chromatid exchange, chromosomal aberration, and micronucleus tests) were induced in bone marrow cells of either species in response to subcutaneous or intraperitoneal injection or oral administration of sodium metabisulfite solution, although the authors noted that control animals tolerated higher doses of sulfite than those made sulfite oxidase-deficient (Renner and Wever, 1983).

Carcinogenic potentials of potassium metabisulfite and sulfur dioxide have also been examined. Male and female ICR/JCL mice administered 1 and 2% potassium metabisulfite in drinking water for 24 months had no increased incidence of tumors over
control animals, suggesting that potassium metabisulfite is not carcinogenic in mice (Tanaka et al., 1979). Exposure to sulfur dioxide by inhalation was associated with an approximate doubling of lung tumors, but no increases in hepatomas or lymphoid tumors (Peacock and Spence, 1967). The increased frequency of lung tumors was not statistically significant. Inhalation of sulfur dioxide in combination with benz(a)pyrene resulted in an increased incidence of tumors in rats over exposure to either substance alone; rats exposed only to sulfur dioxide had no tumors at the end of the experimental period (Laskin et al., 1976).

An unexpected finding of mammary adenocarcinomas after 9 weeks of treatment was reported by Gunnison et al. (1981a) in 4 of 149 female rats (two pregnant, two nonpregnant) with low activity of sulfite oxidase induced by feeding of a low molybdenum diet containing tungstate; no tumors were found in rats with normal levels of sulfite oxidase activity. The difference was not statistically significant.

Effects on peripheral blood cells of workers exposed to sulfur dioxide were examined in two Swedish studies. Nordenson et al. (1980) observed an increase in chromosomal aberrations (mostly gaps and chromatid-type breaks) in 7 of 19 workers who were exposed to other inhalants as well in a sulfite pulp factory. However, peripheral blood lymphocytes of eight workers whose individual mean daily exposure to sulfur dioxide in an aluminum foundry was estimated to be 1.0 ± 0.85 ppm had no greater incidence of chromosomal aberrations or sister chromatid exchange than eight age-control subjects (Sorsa et al., 1982). Average daily sulfur dioxide exposures in the aluminum foundry were estimated to range from 0.2 to 3.0 ppm and mean employment time for the exposed workers was 19.5 years (Sorsa et al., 1982).

Possible synergistic effects of sulfur dioxide and sulfites with other compounds have been examined in an effort to determine whether sulfiting agents might act as comutagens or cocarcinogens. Mutation frequency was approximately doubled in UV-irradiated Chinese hamster V79 cells exposed to 10 mM bisulfite either during or after irradiation exposure and tryptophan revertants were increased by more than eight-fold in UV-treated E. coli cells exposed to 75 mM bisulfite (Mallon and Rossman, 1981). Treatment of bacteriophage-λ with bisulfite-amine mixtures (1 mM bisulfite plus 1 M semicarbazide, hydrazine, methoxyamine, or hydroxylamine) produced increases in clear mutation (plaque-forming activity) over treatment with bisulfite alone (Hayatsu and Kitajo, 1977). Combination of bisulfite (150 ppm) with nitrite (100, 200, or 400 ppm) was reported to produce a weak mutagenic effect after 2 weeks in B. subtilis (Khoudokormoff and Gist-Brocaes, 1978). Mutagenic effects of coffee on Salmonella typhimurium strains TA 100 and TA 98 without S9 mix were completely inhibited by addition of 300 ppm sulfiting agents (sulfite, bisulfite, or
metabisulfite) and phage-inducing activity of coffee (prophage-λ induction test) was suppressed by 300 ppm sulfite ion (Suwa et al., 1982). Sodium sulfite was also a weak inhibitor of mutagenic effects induced by benz(a)pyrene in S. typhimurium strain TA 98 (Calle and Sullivan, 1982). Bisulfite concentrations relevant to use in foods (0.5, 2.5, and 5.0 μg/ml) as well as a higher concentration of 100 mg/ml inhibited transformation of C3H 10T 1/2 cells by x-rays and benz(a)pyrene; pretreatment of hamster embryo cells with 100 ppm bisulfite inhibited transformation by x-rays (Borek, 1984a,b).

Upon consideration of these studies as well as the data available to the Select Committee in 1976, the ad hoc Review Panel concludes that sulfites are mutagenic to several microorganisms and may produce chromosome damage to mammalian cells in vitro. However, sulfites also inhibit mutagenic effects of some known mutagens and carcinogens. Sulfites are not carcinogenic or mutagenic in vivo to rats and mice.
V. SULFITE SENSITIVITY REACTIONS

Ingestion of foods or beverages containing sulfites, inhalation of sulfur dioxide, and parenteral administration of medications containing sulfites have been reported to cause adverse reactions in some asthmatic individuals. The most often reported sign following exposure to sulfites or sulfur dioxide has been bronchial hyperreactivity (bronchoconstriction and bronchospasm) although reactions resembling anaphylaxis (shock, gastrointestinal disturbances, and urticaria/angioedema) as well as flushing, hypotension, and tingling sensations have also been reported (National Institute of Allergy and Infectious Diseases, 1984).

In 1973, Kochen reported that a mildly asthmatic child experienced acute, transient asthmatic reactions following ingestion of freshly opened sulfite-containing foods. However, challenge testing was not carried out to determine if sulfites were the causative agents in this case. Subsequently, Prenner and Stevens (1976) presented a case report of anaphylaxis occurring in a 50-year-old nonasthmatic male who consumed a restaurant meal that included a green salad sprayed with a product containing bisulfite. Oral challenge with sodium bisulfite (10 mg total dose) resulted in erythema, itching, nausea, warmness, coughing, and bronchoconstriction for about 1 hour. Lung function measurements were not made nor was a placebo administered as a part of the challenge.

Freedman (1977) interviewed 272 asthmatic patients and reported that 30 experienced exacerbations of asthma following ingestion of orange drinks made with sodium bisulfite and sold in England. Fourteen of the 30 patients allowed challenge tests with a single dose of a sodium metabisulfite solution containing 25 mg SDE in a weakly acidic solution (sulfur dioxide concentration 100 ppm). Within 2 to 25 minutes, eight of the 14 patients challenged gave a positive response, defined as a drop of at least 12% in FEV₁ (forced expiratory volume at 1 second). However, because of the experimental conditions, no placebo was given.

One case of bronchospasm in an asthmatic patient following ingestion of canned crabmeat salad with a vinegar dressing was reported by Baker et al. (1981). Oral challenge of this patient with sodium metabisulfite (dose not reported) resulted in severe bronchospasm within 30 minutes; no reaction was observed after ingestion of the canned crabmeat alone when given as a clinical challenge. In a second patient whose asthma was provoked by wine, a single-blind oral challenge with a capsule containing 500 mg sodium metabisulfite caused a drop in peak flow rate from about
440 l/min before challenge to 100 l/min 30 minutes after challenge. Challenge with a placebo capsule (lactose) did not produce a significant pulmonary change in the second patient.

Clinical presentation of vague, general symptoms were reported following oral challenge with metabisulfite in two patients who developed dizziness, weakness, nausea, chest tightness, tachycardia, and dyspnea associated with restaurant meals (Schwartz, 1983). Pulmonary function studies during an oral metabisulfite challenge showed no changes.

Clinical investigations on four patients with histories of severe bronchoconstriction and anaphylaxis associated with consumption of restaurant meals were reported by Stevenson and Simon (1981). Single-blind oral challenges were administered to these patients in the fasting state and while they were taking their usual medications. Placebo capsules containing lactose were administered orally every 30 minutes on the first morning of testing and capsules containing 1, 5, 10, 25, or 50 mg potassium bisulfite were given sequentially every 30 minutes on the second day. FEV$_1$ values were measured at 30-minute intervals on both days. All four patients reacted to bisulfite challenges, developing asthmatic symptoms 10 to 15 minutes after ingestion of a provocative dose (10, 25, or 50 mg). FEV$_1$ decreased maximally (34 to 49%) at 30 to 90 minutes after provocation. Systemic symptoms including flushing, tingling, and/or faintness occurred in all subjects (Stevenson and Simon, 1981). Subsequent oral challenge of six sulfite-sensitive asthmatic (SSA) patients with sulfite solutions produced reactions equal to the reactions observed after oral capsule challenge, but at levels approximately one-half of the provocative capsule dose (Goldfarb and Simon, 1984). Fifteen additional asthmatic patients with a history of increased asthmatic reactions associated with consumption of food and beverages were serially challenged with capsules containing 5, 10, 25, and 50 mg sodium metabisulfite (Koopke and Selner, 1982). Only one of these patients had a significant reaction to the challenge; administration of 5 mg sodium metabisulfite produced a fall of 28% in FEV$_1$ in 2 minutes.

Capsules containing 1.4, 14, 144, or 288 mg metabisulfite as the potassium salt were sequentially administered to 134 patients selected from a clinic population of 1073 patients having asthma and related allergic symptoms (Buckley et al., 1985). Decreases in FEV$_1$ values at least 15% were reported in 50 of the 134 patients challenged. Based upon these challenges, Buckley et al. (1985) estimated that 4.6% of asthmatic patients respond to sulfite challenge.
Twelve patients with idiopathic anaphylaxis, nine of whom had a history of reactions associated with restaurant meals, and ten control subjects were challenged with increasing oral doses (1, 5, 10, 25, 50, 100, and 200 mg) of sodium metabisulfite dissolved in lemonade (Sonin and Patterson, 1985). A similar extent of mild nonspecific irritant and subjective symptoms were reported in both groups of patients. No anaphylactic reactions occurred in the 12 patients with idiopathic anaphylaxis. No bronchospasm occurred, although pulmonary function was abnormal in three of these patients (Sonin and Patterson, 1985). Capsule challenge with 1, 5, 10, 25, 50, 100, and 200 mg sodium bisulfite of 32 patients (14 with recurrent idiopathic anaphylaxis, 8 with systemic mastocytosis, and 10 with instances of allergic reactions with meals) resulted in anaphylactic episodes in two of the patients with idiopathic anaphylaxis. However, these two patients also reacted in the same way to placebo challenge (Metcalf, 1984).

In a presentation made at the Open Meeting of the ad hoc Review Panel, Taylor (1984b) reported that oral capsule challenge of 100 non-steroid-dependent asthmatic patients with potassium metabisulfite resulted in no cases of sulfite sensitivity that could be confirmed by double-blind challenge. Single-blind challenges of 69 steroid-dependent asthmatic patients resulted in a decrease in FEV$_1$ of at least 20% in 14 cases. Double-blind challenges of five of these steroid-dependent patients resulted in significant decreases in FEV$_1$ in two cases, leading Taylor and coworkers to suggest that perhaps 5 to 10% of steroid-dependent asthmatic patients (who number about 2 million individuals) may be sulfite sensitive. Extrapolation of this estimate would suggest that 1 to 2% of all asthmatics might be sensitive to sulfites (Taylor, 1984b).

FEV$_1$ values did not decline and no manifestations of sulfite sensitivity were reported following administration of bisulfite to five steroid-dependent asthmatic patients without histories of reactions associated with restaurant meals (Stevenson and Simon, 1981). Of 61 additional asthmatic patients not having a history suggestive of sulfite sensitivity, five individuals (8.2%) had a fall in FEV$_1$ of at least 25% following single-blind oral challenge of metabisulfite (Simon et al., 1982). In this study, patients were challenged with capsules containing increasing concentrations (10, 25, 50, 100 mg) of bisulfite at 30-minute intervals. If no reaction occurred to these capsules, patients were further challenged by ingestion of acidic solutions containing 1 or 10 mg of metabisulfite. Those reacting positively to metabisulfite challenge were subsequently given a placebo challenge. Although the data were not presented, Simon et al. (1982) reported that the reactions of these five patients were milder and
required larger provocative challenges than the reactions in six SSA patients having histories of reactions associated with restaurant meals. Administration of atropine, cromolyn, doxepin, or vitamin B₁₂ prior to sulfite challenge of six SSA patients partially or fully blocked asthmatic reactions (Simon et al., 1984).

Mean activity of sulfite oxidase was 0.15 nmole/min/mg protein in skin fibroblasts of four SSA patients (Jacobsen et al., 1984). This level of enzyme activity is below that reported in skin fibroblasts of normal persons (Johnson et al., 1980; Shih et al., 1977); however, it remains to be shown whether the levels of sulfite oxidase activity in skin fibroblasts is representative of tissues containing the highest concentrations of the enzyme (liver, heart, and kidney).

Pulmonary function was evaluated in 25 asthmatic patients (history of food or beverage related reactions not specified) and 25 nonasthmatic individuals consuming 112 ml of commercial white wine containing 140 mg/l of sulfur dioxide (15.7 mg sulfur dioxide total dose) (Seyal et al., 1984). A decrease in FEV₁ greater than 12% was recorded in one nonasthmatic subject and in five asthmatic patients during or following ingestion of the wine. Two of the asthmatic responders were challenged with two model solutions: the first was reported to contain all ingredients found in wine except metabisulfite; the second was a metabisulfite solution. FEV₁ was decreased in both of these subjects following ingestion of the metabisulfite solution and in one subject ingesting the model wine solution without metabisulfite.

Lettuce treated with sodium bisulfite was employed as an oral challenge to evaluate pulmonary function of five stable, previously documented SSA patients after consumption of food containing sulfiting agents (Howland and Simon, 1985; Simon, 1984). Three ounce portions of lettuce were dipped according to package instructions in a commercial vegetable freshener containing sodium bisulfite or in a similar commercial product that did not contain a sulfite salt. Approximately 10 ml of solution (80 to 90 mg bisulfite) adhered to the lettuce after draining. All five patients showed a significant decrease in FEV₁ (mean decrease 44%, range 31 to 64%) after consuming the sulfite-treated lettuce. None reacted to the control lettuce. Four of the patients were described by Simon (1984) as having moderate asthmatic reactions while the fifth had a life-threatening reaction requiring extensive emergency treatment.

Bronchoconstriction and bronchospasm reactions have been reported more frequently to inhalation of sulfur dioxide than to ingestion of sulfiting agents. Both asthmatic and nonasthmatic
individuals react to inhalation of sulfur dioxide (Koenig et al., 1982; Nadel et al., 1965; Schachter et al., 1984; Sheppard et al., 1980). Mildly asthmatic individuals inhaling sulfur dioxide through a mouthpiece developed bronchoconstriction at a lower concentration of sulfur dioxide (1 to 3 ppm) than healthy nonasthmatic control subjects, and their bronchoconstriction was more severe (Sheppard et al., 1980). However, exposure to a maximum concentration of 1 ppm sulfur dioxide in an environmental chamber (oronasal breathing) did not result in respiratory effects in either asthmatic or nonasthmatic individuals (Schachter et al., 1984). Inhalation of bronchodilators containing sulfites has also been associated with bronchospasm and anaphylactic reactions (Koepke et al., 1984; Twarog and Leung, 1982). Nadel et al. (1965) demonstrated in seven healthy subjects that injection of atropine prevented bronchoconstriction induced by breathing air containing 4 to 6 ppm sulfur dioxide; additional studies in cats indicated that parasympathetic motor pathways must be intact for sulfur dioxide to elicit bronchoconstriction.

Inhalation of sulfur dioxide induced falls in FEV₁ greater than 25% at concentrations 1/10 to 1/100 of the concentrations of ingested sulfites in six known SSA patients (Goldfarb and Simon, 1984). In a letter, Werth (1982) reported that one patient with a history of asthmatic reactions related to ingestion of certain foods and beverages began wheezing after breathing from a bag of dried apricots. However, subsequent oral challenges of this patient with capsules containing potassium metabisulfite up to a dose of 50 mg produced no change in peak flow rate.

Opinions differ on the influence of eructation of sulfur dioxide on the reaction of patients to oral challenge with capsules containing sulfite salts. Concentrations of 4 to 50 ppm of sulfur dioxide were reported in the stomachs of five patients following ingestion of capsules containing 25 or 50 mg metabisulfite under unspecified conditions (Allen and DeLohery, 1985). However, no noticeable eructation was reported by patients after oral challenge with capsules containing sulfites (Metcalf, 1984).

The contribution of inhaled sulfur dioxide to the food- and beverage-associated episodes of bronchoconstriction and bronchospasm in asthmatic patients is not certain. Freedman (1977) cited an estimate that the 3 cm air space above a water solution containing 70 ppm sulfur dioxide contained 1 ppm sulfur dioxide at room temperature, a concentration causing bronchoconstriction in some mildly asthmatic patients (Sheppard et al., 1980). Administration of mouthwash containing incremental doses of metabisulfite up to 100 mg in 30 ml of citric acid solution resulted in a fall of at least 20% in FEV₁ in nine of 15 asthmatic subjects (Allen and DeLohery, 1985). Rechallenge of these nine patients with the same concentrations of metabisulfite while the
subjects were holding their breath did not produce the 20% decrease in FEV₁ considered a positive response. Changes in pulmonary function observed in the studies of Allen and De lohery (1985) and Sonin and Patterson (1985) could have been caused by irritant reactions to inhalation of sulfur dioxide from the acidic solutions administered. Administration of citric acid or lemonade solutions without sulfites were not reported as placebo controls for these studies. Acid fumes are also airway irritants (Rom and Barkman, 1983) and the pulmonary effects reported could result from exposure to acid as well as to sulfur dioxide.

Intravenous infusion of a solution of glucose, theophylline, and dexamethasone which also contained bisulfite severely worsened an asthmatic episode in one patient who had previously shown a large decrease in peak flow rate following an oral capsule challenge of 500 mg sodium metabisulfite (Baker et al., 1981). Intravenous injection of metaclopramide which contained metabisulfite also resulted in bronchospasm in this patient. Injection of a dose of lidocaine hydrochloride containing 0.9 mg sodium metabisulfite was followed by development of plantar pruritis in an individual who had experienced similar symptoms after ingestion of such food items as chili soups, sandwiches, salads, jalapeños, pizza, Chinese pickled green turnips, and dried shrimp (Huang and Fraser, 1984).

Patients receiving total parenteral nutrition (TPN) solutions receive much greater quantities of sulfiting agents than the general population. Administration of TPN solutions containing bisulfites may result in infusion of about 950 mg/day (Metcalf, 1984). One report of excretion of abnormal sulfur metabolites in a patient receiving TPN for 18 months (Abumrad et al., 1981) led to speculation that tachypnea in this patient might be related to abnormal sulfite metabolism (Gunnison and Jacobsen, 1983). No reports of sulfite sensitivity reactions to administration of TPN solutions were found in the literature. Similarly, no sensitivity reactions attributed to sulfites in TPN solutions have been reported to the Pharmacy and Therapeutics Committee at the National Institutes of Health (Metcalf, 1984).

Experience with oral challenge testing of sulfites has led to differing opinions concerning the extent of sensitivity reactions to sulfiting agents. Based upon their clinical work with capsule and solution challenges of a group of asthmatic patients, Simon et al., (1982) and Simon (1984) estimate that 5 to 10% of the 10,000,000 asthmatic patients in the U.S. may be sensitive to orally ingested sulfiting agents. Buckley et al., (1985) suggest a prevalence of 4.6% for sulfite sensitivity based on capsule challenge of selected members of a clinic population.
having asthma and related unusual allergic symptoms. A lower prevalence of sulfite sensitivity (1 to 2% of the overall asthmatic population) is estimated by Taylor (1984b) whose clinical results with capsule challenge suggest that sulfite sensitivity is limited to steroid-dependent asthmatic patients. Patterson and colleagues have yet to identify sulfite sensitivity among idiopathic anaphylactic patients selected from an extensive asthmatic population and consider the sulfite sensitivity may be a minor problem (Patterson, 1984). Although a number of individuals have been clinically tested for sulfite sensitivity by oral challenge, there is no compilation of data available on the distribution of asthmatic and nonasthmatic patients sensitive to sulfiting agents according to age, sex, race, genetic traits, ethnicity, and other variables.

The ad hoc Review Panel is aware of, but has had no experience with, the use of commercially available kits for individuals to test for the presence of sulfites in foods and beverages.

The Food and Drug Administration has received more than 300 letters reporting various types of adverse reactions occurring after consumption of foods containing sulfiting agents. A review of these reports has established that many are accounts submitted by individual consumers (both asthmatic and nonasthmatic persons), some are thorough case reports submitted by physicians, and some include investigations by FDA field investigators. These reports indicate an association of adverse reactions with ingestion of meals including foods containing sulfiting agents. Indeed, life-threatening reactions and deaths of four persons diagnosed as asthmatic individuals have been reported to the FDA following ingestion of restaurant meals that included foods treated with sulfiting agents. Following two of the four deaths, samples of the foods ordered by the two individuals were analyzed for sulfite content. In one case, the report of an FDA investigator included an analysis of items from the meal by an independent laboratory which indicated that two samples of lettuce served with different components of the meal contained 78 and 409 ppm sulfite and guacamole contained 272 ppm sulfite (Riddle, 1983). In the second case, analysis by FDA laboratories of shredded potatoes (cottage fries) served by the restaurant indicated that the product [fresh, raw, refrigerated potatoes containing sodium acid pyrophosphate, sodium bisulfite, calcium and sodium benzoate (Williamson, 1984)] contained 96 ppm sulfite. Reanalysis of the same product before and after cooking gave values of 615 and 582 ppm, respectively (Spears, 1984). No explanation was given for the large difference between the two analyses.
In another instance, an individual diagnosed by oral challenge as a sulfite-sensitive asthmatic patient went into a coma for three weeks after consuming a meal that included cottage fried potatoes in a restaurant; six months after the incident the patient had severe motor and neurological deficits (Simon, 1984). Analyses of samples of the potatoes used for cottage fries were 2240 ppm for those stored in the restaurant cooler prior to cooking and 2210 ppm for those cooked with oil added (Whetstone, 1984). FDA inspection of the plant where the potatoes were processed indicated that raw potatoes were peeled by abrasion, steam-cooked with water containing sodium bisulfite (approximately 2000-2500 ppm bisulfite), sliced, and refrigerated prior to distribution to restaurants (Kam, 1984).

There are few data regarding sulfite sensitivity reactions, life-threatening events or other sequelae on the part of nonasthmatic individuals ingesting foods treated with sulfiting agents. Despite the availability of the clinical reports and limited data on asthmatic patients, the Panel has found little scientific evidence that sulfiting agents added to foods contribute to sulfite sensitivity reactions of nonasthmatic individuals. Therefore, the Panel is basing its consideration of these reactions primarily on the published clinical studies and case reports of sensitivity reactions to sulfites by asthmatic patients. The analysis of the available published case reports of sensitivity reactions to sulfiting agents indicates to the ad hoc Review Panel that six different patterns of response have been described. These include:

1. Asthmatics who experience acute exacerbations of severe asthma after eating in restaurants. They respond with bronchoconstriction on oral challenge with 5 to 100 mg of metabisulfite.

2. Asthmatics with no clear-cut history of bronchial reactions following ingestion of sulfiting agents who respond with bronchoconstriction on oral challenge to 10 to 500 mg of metabisulfite.

3. Asthmatics with other allergic-type symptoms who have systemic anaphylactic reactions historically associated with ingestion of sulfites. These individuals respond with systemic symptoms after oral challenge with 10 mg of metabisulfite.
4. Asthmatics who have acute asthmatic reactions after parenteral administration of pharmaceutical agents containing sulfiting agents. They may, in addition, also belong to classes 1 to 3 above. Acute bronchoconstriction has been reproduced in these individuals by oral challenge with 20 to 500 mg of metabisulfite.

5. Nonasthmatics who may not necessarily have a history of other allergic-type reactions, but who have a history of anaphylaxis following ingestion of sulfiting agents. These individuals develop anaphylaxis after purposeful oral challenge with 10 mg of metabisulfite.

6. Normal subjects given challenges of inhaled sulfur dioxide (9 to 21 ppm) who develop bronchoconstriction with subsequent tachyphylaxis on repeated challenge. This is in contrast to the general asthmatic population who develop bronchoconstriction following inhalation of 1 to 5 ppm of sulfur dioxide.

As a result of the examination of the available data, questions have arisen regarding the prevalence of reactions to sulfiting agents used as food ingredients and the proportion of the susceptible population at risk of life-threatening reactions. It is clear that challenge with sulfiting agents may elicit acute reactions of unpredictable severity in sensitive individuals. One controlled study demonstrates that these agents used on raw lettuce can elicit the same reactions in sulfite-sensitive asthmatic patients. There is also some evidence that associates consumption of some types of potatoes, processed for restaurant use and shown by laboratory analysis to contain sulfites, with life-threatening reactions in asthmatic patients. It remains to be shown whether sulfites used in the processing of other foods are capable of eliciting reactions in sensitive individuals.
VI. OPINION

The ad hoc Review Panel is aware that exposure to sulfiting agents involves more than their use as GRAS food ingredients. Sulfur dioxide can be an air pollutant in urban areas. Many medicinals contain sulfites as preservatives; wine and beer contain sulfites; and, residuals from sulfites used as pesticides may remain in foods as consumed. These sources are subject to regulatory provisions other than those that apply to sulfites as GRAS food ingredients. This report addresses only the GRAS uses of sulfiting agents; nevertheless, the Panel recognizes that all of these sources of sulfites need to be considered, if the issues of total sulfite exposures and body burden are to be addressed.

Although the Panel has been able to obtain considerable data on the use of sulfiting agents, an accurate measure of the poundage of sulfites currently being used by the food industry and the trend in the use of sulfiting agents in food since 1975 cannot be made from information now available. We understand that steps are being taken to obtain these data to serve as a benchmark for ascertaining future trends in the use of sulfiting agents in foods.

The Panel estimates that the mean per capita daily consumption of sulfur dioxide equivalents (SDE) from food, wine, and beer is about 10 mg/day (0.17 mg/kg/day). This mean value is about the same as the intake estimate in the 1976 report of the Select Committee on GRAS Substances. The 99th percentile consumption, reflecting that of the most frequent consumers of the more highly sulfited foods and beverages, is estimated to be approximately 180 mg SDE/day (3 mg/kg/day). These estimates are necessarily derived from various sources of information including values for the amounts of sulfite added to foods and beverages. However, the Panel believes that determination of the level of consumption of sulfiting agents should be based on direct analyses of foods and beverages as consumed. Analyses should include both free and total sulfite as presently defined as well as irreversibly bound sulfite compounds remaining in food. Firm data obtained in this way for sulfite-treated foods would obviate the need to make approximations of their sulfite content based on the amount of sulfite added to foods and presumptions concerning the amount lost or irreversibly reacted in processing, storage, and preparation for the table.

Virtually all consumed sulfite is metabolized by sulfite oxidase in the mitochondria of various organs and tissues at a rate which is probably diffusion limited. The amount of endogenous sulfite is several orders of magnitude greater than that normally
obtained from exogenous sources. Except for the few individuals identified as having congenital sulfite oxidase deficiency, it would appear that most individuals have sufficient enzyme to metabolize both endogenous and exogenous sulfite. Whether sulfite oxidase-deficient patients are sulfite sensitive as well remains to be established.

The no observed adverse effect level (NOAEL) of sulfiting agents in humans, based on animal toxicity data, is estimated to range from 30 to 100 mg SDE/kg/day. The margin between the amount of SDE ingested by high intake consumers and the lowest estimated NOAEL is about 10-fold and between the mean per capita daily consumption and the lowest NOAEL, about 180-fold. The margin of only 10-fold between the sulfite ingestion by high intake consumers and the lowest NOAEL represents a relatively narrow factor of safety. However, consideration of the significance of this difference should recognize the difficulties in estimating with confidence the components which are the basis of the calculated margin.

The scientific literature indicates that sulfiting agents are not teratogenic, mutagenic, or carcinogenic in laboratory animals.

From information and data available in 1976, the Select Committee on GRAS Substances found little evidence of possible hazard to the public from use of sulfiting agents as food ingredients. However, the Select Committee cautioned that additional data would be needed to assess possible health effects if consumption increased. In 1982, FDA proposed to affirm certain sulfiting agents as GRAS and specified limitations on conditions of use.

The ad hoc Review Panel has found no new metabolic or toxicological data in this current re-review of sulfiting agents that suggest a need to change the NOAEL. Examination of exposure and consumption data indicates that the level of consumption of sulfites from foods and beverages is about the same as that estimated by the Select Committee in 1976. However, in recent years, two new aspects of the use of sulfiting agents as food ingredients have emerged. First, sulfiting agents have been widely used to preserve "freshness" in raw fruit and vegetable salad ingredients. Second, a segment of the population, predominantly asthmatic patients, has been shown to experience acute bronchial reactions following doses of sulfiting agents as low as 5 mg. The Panel recognizes that this segment of the population is not yet clearly identifiable but anticipates that it will be shown to be a small proportion of the population. In some cases, sensitive individuals have had life-threatening reactions following exposure to sulfiting agents. Indeed, there are reports during the past two
years of deaths of four asthmatic individuals associated with consumption of meals including foods purported to contain sulfiting agents. Although sulfite sensitivity has been demonstrated in some asthmatic patients by direct oral challenge, a cause and effect relationship between consumption of sulfite-containing foods and the onset of adverse reactions in sulfite-sensitive individuals has not been conclusively established. However, the reported associations are sufficiently numerous and the reactions sufficiently severe to deserve serious attention. Thus, practical means need to be found to protect sulfite-sensitive individuals from the potential hazard of sulfites.

The Panel concludes that additional labeling requirements alone would not assure protection. It concludes further that it would seem advisable to specify safe conditions of the use of sulfites in situations where levels shown to elicit adverse reactions in sulfite-sensitive individuals are likely to occur at the point of consumption. This is particularly likely when sulfite-treated fresh fruits and vegetables and precut potato products are dispensed in food service establishments or sold in grocery stores, and consumers, servers, and store personnel are not aware that sulfiting agents are present. Information provided to the Panel indicates that use of sulfites on fresh produce in food service establishments is being discouraged by the National Restaurant Association and the Produce Marketing Association, and that use has decreased over the past two years. Such voluntary curtailment of sulfite use on such products is an important step in reducing opportunities for unsuspecting sulfite-sensitive individuals to be exposed, and discontinuance of these uses should be encouraged by appropriate use of the regulatory process.

It would be desirable to learn whether sulfite-sensitive individuals react differently to sulfite-treated foods, in which the sulfite may be present in both the free and bound forms, than to clinical challenge with free sulfite. It might also be desirable for such individuals to learn whether they are affected adversely by other ingredients of their diet. The Panel recognizes that such clinical tests are difficult to perform and may be dangerous because of the potential hazards to sulfite-sensitive subjects.

In view of these considerations and others described in the body of the report, the Panel finds that none of the five conclusion statements considered by the Select Committee on GRAS Substances for its 1976 report is appropriate and concludes that:
A) For the majority of the population, there is no evidence in the available information on potassium bisulfite, potassium metabisulfite, sodium bisulfite, sodium metabisulfite, sodium sulfite, and sulfur dioxide that demonstrates or suggests reasonable grounds to suspect a hazard to the public when these substances are used at levels that are now current and in the manner now practiced. However, it is not possible to determine, without additional data, whether a significant increase in consumption would constitute a dietary hazard.

B) For the fraction of the public that is sulfite sensitive, there is evidence in the available information on potassium bisulfite, potassium metabisulfite, sodium bisulfite, sodium metabisulfite, sodium sulfite, and sulfur dioxide that demonstrates or suggests reasonable grounds to suspect a hazard of unpredictable severity to such individuals when they are exposed to sulfiting agents in some foods at levels that are now current and in the manner now practiced.
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VIII. SCIENTISTS CONTRIBUTING TO THIS REPORT

A. AD HOC REVIEW GROUP ON THE REEXAMINATION OF THE GRAS STATUS OF THE SULFITING AGENTS

Joseph F. Borzelleca, Ph.D.
Professor of Pharmacology
Medical College of Virginia
Health Sciences Division
Virginia Commonwealth University
Richmond, Virginia 23298

Jordan N. Fink, M.D.
Professor
Department of Medicine
Medical College of Wisconsin
8700 W. Wisconsin Avenue
Milwaukee, Wisconsin 53226

C. Wayne Callaway, M.D.
Director
Nutrition and Lipid Clinics
Mayo Clinic
200 First Street, SW
Rochester, Minnesota 55901

Samuel J. Pomson, M.D. *
Professor of Pediatrics
University of Iowa
College of Medicine
Iowa City, Iowa 52242

Harry G. Day, Sc.D.
Professor Emeritus of Chemistry
Indiana University
Bloomington, Indiana 47405

George W. Irving, Jr., Ph.D. (Chairman)
Senior Scientific Consultant
Life Sciences Research Office
Federation of American Societies for Experimental Biology
9650 Rockville Pike
Bethesda, Maryland 20814

Owen Fennema, Ph.D.
Professor
Department of Food Science
University of Wisconsin
1605 Linden Drive
Madison, Wisconsin 53706

Bert N. La Du, Jr., M.D., Ph.D.
Professor
Department of Pharmacology
University of Michigan Medical School
Ann Arbor, Michigan 48109

* Unable to serve
Donald B. McCormick, Ph.D.  
Professor and Chairman  
Department of Biochemistry  
Emory University  
School of Medicine  
Atlanta, Georgia 30322

Michael B. Shimkin, M.D.  
Emeritus Professor of Community Medicine and Oncology  
University of California  
School of Medicine  
La Jolla, California 92037

John R. McCoy, V.M.D.  
Emeritus Professor of Comparative Pathology  
New Jersey College of Medicine and Dentistry  
Rutgers Medical School  
P.O. Box 101  
Piscataway, New Jersey 08854

Ralph G.H. Siu, Ph.D.  
Consultant  
4428 Albermarle Street, NW  
Washington, D.C. 20816

Albert I. Mendeloff, M.D.  
Professor of Medicine  
Johns Hopkins University  
School of Medicine  
2109 Northcliff Drive  
Baltimore, Maryland 21209

Willard J. Visek, M.D., Ph.D.  
Professor, Clinical Sciences  
College of Medicine at Urbana-Champaign  
University of Illinois  
Urbana, Illinois 61801

Gabriel L. Plaa, Ph.D.  
Professor  
Department of Pharmacology  
University of Montreal  
Faculty of Medicine  
Montreal, Quebec  
Canada

John L. Wood, Ph.D.  
Emeritus Distinguished Service Professor  
Department of Biochemistry  
University of Tennessee Medical Units  
Memphis, Tennessee 38111
B. REVIEWING CONSULTANTS

Dean D. Metcalfe, M.D.
Senior Clinical Investigator
Laboratory for Clinical Investigation
National Institute of Allergy
and Infectious Diseases
National Institutes of Health
Bethesda, Maryland 20205

Roy Patterson, M.D.
Chairman
Department of Medicine
Northwestern University
Medical School
Chicago, Illinois 60611

Dorothy D. Sogn, M.D.
Special Assistant to the Director
Immunology, Allergic, and
Immunologic Diseases Program
National Institute of Allergy
and Infectious Diseases
National Institutes of Health
Bethesda, Maryland 20205

C. LIFE SCIENCES RESEARCH OFFICE STAFF

Sue Ann Anderson, Ph.D.
Staff Scientist

Sandra Schnell
Administrative Aide

Kenneth D. Fisher, Ph.D.
Director

Frederic R. Senti*, Ph.D.
Senior Scientific Consultant

Beverly R. Lea
Scientific Literature/
Technical Report Specialist

John M. Talbot, M.D.
Senior Medical Consultant

Susan M. Pilch, Ph.D.
Staff Scientist

Martha A. Watt
Secretary
IX. INDIVIDUALS AND ORGANIZATIONS RESPONDING TO THE TENTATIVE REPORT

A. OPEN MEETING PARTICIPANTS*

The Open Meeting of the ad hoc Review Panel on the Reexamination of the GRAS Status of Sulfiting Agents was held November 29, 1984. Requests were received from nine individuals and organizations for opportunity to make oral presentations. The following 12 individuals participated in the presentations:

Clifford I. Chappel, Ph.D., ILSI consultant, President, F.D.C. Consultants, Inc., Oakville, Ontario, Canada

Sherwin Gardner, Ph.D., Grocery Manufacturers Association, Washington, D.C.

Michael J. Goldblatt, Ph.D., Chairman, ILSI Committee on Food-Associated Reactions, General Foods Corporation, White Plains, New York

Michael F. Jacobson, Ph.D., Executive Director, Center for Science in the Public Interest, Washington, D.C.

Allen W. Matthys, Ph.D., Director, Labeling and Food Standards, Eastern Research Laboratory, National Food Processors Association, Washington, D.C.

James T. Rogers, Senior Director, Government Affairs, National Restaurant Association, Washington, D.C.

Ronald A. Sarasin, Director, Government Relations, National Restaurant Association, Washington, D.C.

Ronald A. Simon, M.D., Scripps Clinic and Research Foundation, La Jolla, California

* Copies of the Open Meeting transcript are available from:

Ace Federal Reporters
444 North Capitol
Washington, D.C. 20001

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Steve L. Taylor, Ph.D., Associate Professor, Food Research Institute, University of Wisconsin, Madison, Wisconsin

Boardman C. Wang, M.D., Clinical Professor of Anesthesiology, New York University Medical Center, New York, New York

John F. Wilk, Wine Consultant, Sterling Forest, New York

Mitchell Zeller, Staff Attorney, Center for Science in the Public Interest, Washington, D.C.

B. WRITTEN COMMENTS

The following organizations and individuals submitted written materials for consideration by the ad hoc Review Panel:

American Bakers Association, Washington, D.C.
Aristan Associates, Placentia, California
David Baltimore, Ph.D., Cambridge, Massachusetts
Mrs. Mary Bessent, Whittier, California
California Grape and Tree Fruit League, Fresno, California
Sherry N. Carr, San Jose, California
Choc Padrinos, Childrens Hospital Foundation of Orange County, Orange, California
Corn Refiners Association, Inc., Washington, D.C.
Ann Coutu, Gainsville, Florida
Leo H. Cummins, M.D., Orange, California
DFA of California, An Association of Dried Fruit and Tree Nut Processors, Santa Clara, California
Allie Dichl, Toledo, Ohio
Faye M. Dong, R.D., Ph.D., University of Washington, Seattle, Washington
Carol A. Foote, Santa Cruz, California
Cathy J. Frankel, New York, New York
Joan Friedland, Ph.D., Downstate Medical Center, Brooklyn, New York
Ralph Goldstein, NYS Assembly Committee on Consumer Affairs and Protection, New York
Margaret Granda, Kapaa, Hawaii
Lynn Hamel, Elk Grove, California
Harmax Laboratories, Inc., El Paso, Texas
The Hartwell Family, Los Angeles, California
Alice I. Henry, Hemet, California
International Food Additives Council, Atlanta, Georgia
International Foodservice Distributors Association, Falls Church, Virginia
International Technical Caramel Association, Washington, D.C.
Elizabeth Johnson, Seattle, Washington
Janet R. Jones, Medford, New York
Mrs. W. Ralph Kemp, Hollywood, California
Stanley R. Lane, M.D., Moorestown, New Jersey
Mrs. William K. Lawson, Hemet, California
Bruce M. Prenner, M.D., San Diego, California
Robert Reynolds, County of Lake, Air Pollution Control District, Lakeport, California
Dorothy L. Robinson, Lake Elsinore, California
Vi Sant, Diamond Bar, California
H. Sherman, San Jacinto, California
Stamp Out Sulfites, Santa Monica, California

Wilma Thomas, Placentia, California

United Fresh Fruit and Vegetable Association, Alexandria, Virginia

George Welch, Patents and Processes of California, Santa Clara, California

Wine Institute, San Francisco, California

W.T. Wood, San Bernardino, California
X. BIBLIOGRAPHY OF OTHER MATERIALS REVIEWED


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APPENDIX*

Evaluation Statements Used by the Select Committee on GRAS Substances

In reaching its conclusions, the Select Committee on GRAS Substances relied primarily on the absence of substantive evidence of, or reasonable grounds to suspect, a significant risk to the public health. A conclusion, based on reasoned judgment, was expected even in instances where the available information was qualitatively or quantitatively limited. It was recognized at the outset that there needed to be agreement on the language of the conclusions so that there would be minimal opportunity for misunderstanding the Committee's intent when translating evaluation statements into appropriate regulatory action.

Accordingly, four conclusion statements were agreed upon as likely to cover all cases. However, in utilizing the four conclusions, it was soon recognized that there were instances where there were insufficient data upon which to base a conclusion, making it necessary to add a fifth statement. With very few exceptions, the Committee found that its views could be expressed in one or another of the following five conclusion statements:

1. There is no evidence in the available information on ________ that demonstrates or suggests reasonable grounds to suspect a hazard to the public when it is used at levels that are now current or that might reasonably be expected in the future.

2. There is no evidence in the available information on ________ that demonstrates or suggests reasonable grounds to suspect a hazard to the public when it is used at levels that are now current and in the manner now practiced. However, it is not possible to determine without additional data, whether a significant increase in consumption would constitute a dietary hazard.

* From SCOGS (1982), with permission.
3. While no evidence in the available information on _______ demonstrates a hazard to the public when it is used at levels that are now current and in the manner now practiced, uncertainties exist requiring that additional studies should be conducted.

4. The evidence on _______ is insufficient to determine that the adverse effects reported are not deleterious to the public health when it is used at levels that are now current and in the manner now practiced.

5. In view of the deficiency of relevant biological (and/or other) studies, the Select Committee has insufficient data upon which to base an evaluation of _______ when it is used as a food ingredient.