EVALUATION OF THE HEALTH ASPECTS OF SORBIC ACID
AND ITS SALTS AS FOOD INGREDIENTS

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Prepared for
Bureau of Foods
Food and Drug Administration
Department of Health, Education, and Welfare
Washington, D. C.

Contract No. FDA 223-75-2004
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Life Sciences Research Office
Federation of American Societies
for Experimental Biology
9650 Rockville Pike
Bethesda, Maryland 20014
NOTICE

This report is one of a series concerning the health aspects of using the Generally Recognized as Safe (GRAS) or prior sanctioned food substances as food ingredients, being made by the Federation of American Societies for Experimental Biology (FASEB) under contract no. 223-75-2004 with the Food and Drug Administration (FDA), U.S. Department of Health, Education, and Welfare. The Federation recognizes that the safety of GRAS substances is of national significance, and that its resources are particularly suited to marshalling the opinions of knowledgeable scientists to assist in these evaluations. The Life Sciences Research Office (LSRO), established by FASEB in 1962 to make scientific assessments in the biomedical sciences, is conducting these studies.

Qualified scientists were selected as consultants to review and evaluate the available information on each of the GRAS substances. These scientists, designated the Select Committee on GRAS Substances, were chosen for their experience and judgment with due consideration for balance and breadth in the appropriate professional disciplines. The Select Committee's evaluations are being made independently of FDA or any other group, governmental or nongovernmental. The Select Committee accepts responsibility for the content of each report. Members of the Select Committee who have contributed to this report are named in Section VII.

Tentative reports are made available to the public for review in the Office of the Hearing Clerk, Food and Drug Administration, after announcement in the Federal Register, and opportunity is provided for any interested person to appear before the Select Committee at a public hearing to make oral presentation of data, information, and views on the substances covered by the report. The data, information, and views presented at the hearing are considered by the Select Committee in reaching its final conclusions. Reports are approved by the Select Committee 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 reports are approved and transmitted to FDA by the Executive Director of FASEB.

While this is a report of the Federation of American Societies for Experimental Biology, it does not necessarily reflect the opinion of all of the individual members of its constituent societies.

C. Jeff D. Carr, Ph.D., Director
Life Sciences Research Office
FASEB
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I. INTRODUCTION

This report concerns the health aspects of using sorbic acid and its salts as food ingredients. It has been based partly on the information contained in a scientific literature review (monograph) furnished by FDA (1), which summarizes the world's scientific literature from 1920 through 1973.* To assure completeness and currency as of the date of this report this information has been supplemented by searches of over 30 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; and by the combined knowledge and experience of members of the Select Committee and the LSRO staff. In addition, an announcement was made in the Federal Register of February 10, 1976 (41 FR 5862 and 5863) that opportunity would be provided for any interested person to appear before the Select Committee at a public hearing to make oral presentation of data, information and views on the health aspects of using sorbic acid and its salts as food ingredients. The Select Committee received no requests for such a hearing on sorbic acid and its salts.

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. It is stated in the Code of Federal Regulations 21 CFR 121.1, revised April 1, 1975 that GRAS means general recognition of safety by experts qualified by scientific training and experience to evaluate the safety of substances on the basis of scientific data derived from published literature. This section of the Code also indicates that expert judgment is to be based on the evaluation of results of credible toxicological testing or, for those substances used in food prior to January 1, 1958, on a reasoned judgment founded in experience with common food use, and is to take into account reasonably anticipated patterns of consumption, cumulative effects in the diet, and safety factors appropriate for the utilization of animal experimentation data. FDA recognizes further (21 CFR 121.3) that it is impossible to provide assurance that any substance is absolutely safe for human consumption.

The Select Committee on GRAS Substances of LSRO is making its evaluations of these substances in full recognition of the foregoing provisions. In reaching its conclusions on safety the Select Committee, in accordance with FDA's guidelines, is relying primarily on the absence of substantive evidence of, or reasonable grounds to suspect, a significant risk to the public health. While the Select Committee realizes that a conclusion based

*The document (PB-223 864/0) is available from the National Technical Information Service, U.S. Department of Commerce, P.O. Box 1553, Springfield, Virginia 22161.
on such reasoned judgment is expected even in instances where the available information is qualitatively or quantitatively limited, it recognizes that there can be instances where, in the judgment of the Select Committee, there are insufficient data upon which to base a conclusion. The Select Committee, aware that biological testing is dynamic, bases its conclusions on information now available; it cannot anticipate the results of experiments not yet conducted or those of tests that may be reconducted, using new technologies. These conclusions will need to be reviewed as new or better information becomes available.

In this context, the LSRO Select Committee on GRAS Substances has reviewed the available information on sorbic acid and its salts 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.

II. BACKGROUND INFORMATION

Sorbic acid, trans,trans-2,4-hexadienoic acid, was isolated in 1859 from the berries of the mountain ash, Sorbus aucuparia L., where it occurs as the lactone, parasorbic acid (2). Commercially, sorbic acid and its salts are now manufactured by organic synthesis and used as antimicrobial preservatives.

Sorbic acid and its sodium, potassium and calcium salts are GRAS substances under provisions of the Code of Federal Regulations (3) for use as chemical preservatives [21 CFR 121.101(d)(2)]. Potassium and sodium sorbate are also GRAS substances as they might migrate to food from paper and paperboard products used in food packaging [21 CFR 121.101(h)]. Federal standards of identity limit the addition of sorbates to many foods. For example, many cheese products may contain sorbic acid, potassium sorbate or sodium sorbate as an optional mold inhibiting ingredient in an amount not to exceed 0.3 percent by weight calculated as sorbic acid [21 CFR 19.500 to 19.787]. However, only sorbic acid and potassium sorbate are used widely as chemical preservatives; specifications for these compounds appear in Food Chemicals Codex (4) and the National Formulary XIV (5). The Joint FAO/WHO Committee on Food Additives considers sodium sorbate too unstable for satisfactory use as a food additive (6). The results of a comprehensive survey by a National Research Council subcommittee indicate that neither calcium sorbate nor sodium sorbate is used in food (7).

The antimicrobial activity of sorbates is demonstrated below pH 6.5 and increases with the concentration of the undissociated acid as the pH of the medium is lowered (8). Broad-spectrum fungistatic activity is exhibited against yeasts and molds and bacteriostatic activity is exhibited against catalase-positive organisms (9). Sorbic acid at a concentration of $10^{-4}$ molar inhibits in vitro some sulfhydryl dependent enzymes, such as
alcohol dehydrogenase and flicin, but not aldolase and urease (10). As
chemical preservatives, sorbates can be used as sprays, dips, or coatings
on wrapping material, or can be incorporated directly into food. The
particular sorbate used is determined to a large extent by its solubility
in water. Potassium sorbate (58.2 g per 100 ml at 20°C) is more soluble
than sorbic acid (0.15 g per 100 ml at 20°C) (11).

Sorbic acid and its salts are somewhat unstable. By virtue of their
double bond system, they polymerize readily when catalyzed by free radicals.
Autoxidation results in the formation of peroxides, followed by degradation
and polymerization (11).

III. CONSUMER EXPOSURE DATA

A subcommittee of the National Research Council (NRC) surveyed
manufacturers by questionnaire in 1970 concerning their use of the GRAS
sorbates in foods (7). No manufacturers reported using calcium or sodium
sorbates but the addition of sorbic acid and potassium sorbate to at least
one food in several food categories was reported. Weighted means of the
usual levels of addition are shown in Table I.

The values in Table I represent survey responses and, as is the
case for the addition level for soft candy which is based on fewer than
three survey responses, the values may not indicate a general practice
for the addition of sorbic acid to foods in the category. Because these
values are weighted means, some foods may contain sorbates at higher
concentrations. An independent estimate of the range for sorbate addition
of 0.05 to 0.3 percent was made by the Grocery Manufacturers of America
(GMA) (12). The Select Committee has no information concerning changes
in the level of addition of sorbates to foods in recent years.

The NRC subcommittee estimated the possible average daily intake
(Table II) of sorbic acid and potassium sorbate from Market Research
Corporation of America data on the mean frequency of eating foods by food
category, U.S. Department of Agriculture data on mean portion size of
foods, and the assumption that all food products within a category contained
these sorbates at the levels shown in Table I. Such an assumption is
likely to lead to overestimates of intake because many foods within a
category may not contain added sorbates. The NRC subcommittee has
recognized that in most cases its calculations of possible intakes are
overstated, often by considerable margins.* Because of factors detailed
in Section XI of the NRC report, the estimated intakes (Table II) are likely

*An explanation for such overstatements is detailed in Section XI,
"Significance and Use of Data in Safety Evaluations," of the NRC subcom-
mittee report (7).
<table>
<thead>
<tr>
<th>Food category</th>
<th>Sorbic acid Weighted mean percent</th>
<th>Potassium sorbate Weighted mean percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baked goods, baking mixes</td>
<td>0.03</td>
<td>0.06</td>
</tr>
<tr>
<td>Fats and oils</td>
<td>0.06</td>
<td>0.14</td>
</tr>
<tr>
<td>Milk, milk products</td>
<td>&lt;0.01</td>
<td>0.02</td>
</tr>
<tr>
<td>Cheese</td>
<td>0.15</td>
<td>0.15</td>
</tr>
<tr>
<td>Frozen dairy desserts, mixes</td>
<td>0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Processed fruits, juices and drinks</td>
<td></td>
<td>0.06</td>
</tr>
<tr>
<td>Fruit ices, water ices</td>
<td></td>
<td>0.06</td>
</tr>
<tr>
<td>Meat products</td>
<td>&lt;0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>Fish products</td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td>Processed vegetables, juices</td>
<td>0.03</td>
<td>0.05</td>
</tr>
<tr>
<td>Condiments, relishes, salt substitutes</td>
<td>0.01</td>
<td>0.03</td>
</tr>
<tr>
<td>Soft candy</td>
<td>1.40</td>
<td>0.05</td>
</tr>
<tr>
<td>Sugar, confections</td>
<td>&lt;0.01</td>
<td>0.08</td>
</tr>
<tr>
<td>Jams, Jellies, sweet spreads</td>
<td>0.05</td>
<td>0.06</td>
</tr>
<tr>
<td>Sweet sauces, toppings, syrups</td>
<td>0.05</td>
<td>0.06</td>
</tr>
<tr>
<td>Gelatinas, puddings, fillings</td>
<td>&lt;0.01</td>
<td>0.58</td>
</tr>
<tr>
<td>Snack foods</td>
<td></td>
<td>0.03</td>
</tr>
<tr>
<td>Beverages, nonalcoholic</td>
<td>&lt;0.01</td>
<td>0.02</td>
</tr>
<tr>
<td>Beverages, alcoholic</td>
<td></td>
<td>0.02</td>
</tr>
<tr>
<td>Gravies, sauces</td>
<td>0.09</td>
<td>0.05</td>
</tr>
<tr>
<td>Dairy product analogs</td>
<td>0.05</td>
<td>0.06</td>
</tr>
<tr>
<td>Seasonings and flavors</td>
<td></td>
<td>0.01</td>
</tr>
</tbody>
</table>

Blanks in the table mean that sorbic acid is not added to foods in the categories indicated. Level of addition is the weighted mean of the levels reported by manufacturers as their usual level of addition to one or more products in a food category. For discussion of weighted mean see Section X and Exhibit 50 of reference 7.
TABLE II

Possible Average Daily Intake of Sorbic Acid and Potassium Sorbate by Age Group (7)

<table>
<thead>
<tr>
<th>Substance</th>
<th>0-5 months</th>
<th>6-11 months</th>
<th>12-23 months</th>
<th>2-65+ years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mg</td>
<td>mg/kg</td>
<td>mg</td>
<td>mg/kg</td>
</tr>
<tr>
<td>Sorbic acid</td>
<td>5</td>
<td>1</td>
<td>60</td>
<td>8</td>
</tr>
<tr>
<td>Potassium sorbate</td>
<td>20</td>
<td>4</td>
<td>166</td>
<td>21</td>
</tr>
</tbody>
</table>

Possible average daily intakes were estimated as explained in the text and reference 7 from the data in Table I. The intakes per kg body weight were based on an average weight of 60 kg for an adult (13) and the following weights for infants by age groups: 0-5 mo, 5 kg; 6-11 mo, 8 kg; and 12-23 mo, 11 kg (14).
to be much higher than would be the intakes achieved through consumption of a diet consisting totally of processed foods to which the substances had been added at the maximum levels. The GMA believes that these estimates of possible average intakes are too high and the use of sorbates in baked goods (Table I) would be limited because propionates are the preservatives normally used in this category (12).

Average daily intakes of sorbates (calculated as sorbic acid), by the 2-65+ yr age group are likely to be closer to the per capita daily intake (17 mg) calculated from the total amount of sorbates used in foods in 1970 (Table III). The use of sorbic acid and potassium sorbate by manufacturers that reported use to NRC in both 1960 and 1970 increased 13.4 and 4.5 fold, respectively. In 1974, the GMA estimated that 2.18 million kg of sorbates were used annually in foods intended for human consumption (15). Assuming that half of this amount is potassium sorbate, per capita daily consumption of sorbates calculated as sorbic acid was about 25 mg.

At present, the Select Committee believes that the best estimate of average adult daily consumption of sorbic acid and potassium sorbate in foods is 25 mg (as sorbic acid) calculated from total usage data provided by GMA and that the intake estimates for younger age groups (Table II) are greatly exaggerated by the food categories of baked goods and soft candy. The use of sorbates in infant formulas was not reported in the NRC survey. Satisfactory data are not currently available for estimating maximal intakes that may be achieved by a few individuals.

The Joint FAO/WHO Expert Committee on food additives has estimated the acceptable daily intake of sorbic acid and its salts (expressed as sorbic acid) to be 25 mg per kg body weight (16).

IV. BIOLOGICAL STUDIES

Sorbic acid is a carboxylic acid and readily forms salts in biological systems. Thus the physiological effects of the acid and its salts may be expected to be similar with respect to the sorbate ion.

Metabolism

The metabolism of \([1^{-14}C]\)sorbic acid (NaOH neutralized) administered by stomach tube to female Sprague-Dawley rats (about 920 mg sorbic acid per kg body weight) was reported as follows: 85 percent of the radioactivity was found in the expired carbon dioxide within 4 to 10 hours, 0.4 percent in the feces, 2 percent in the urine, 3 percent in internal organs and blood, 3 percent in skeletal muscles, and 6.6 percent elsewhere in the carcass (17). There was no labeling of the liver or muscle glycogen, and some radioactivity was associated with the lipid fraction of the carcass, internal organs and skin. The percentage of the radioactivity found in expired carbon dioxide
TABLE III

Consumption of Sorbic Acid and Potassium Sorbate Based on Total Quantity Used Annually in Foods (7)

<table>
<thead>
<tr>
<th>Substance</th>
<th>Relative amounts used&lt;sup&gt;a&lt;/sup&gt; 1970/1960</th>
<th>Total used&lt;sup&gt;b&lt;/sup&gt; (1970) kg</th>
<th>Per capita daily intake&lt;sup&gt;c&lt;/sup&gt; mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorbic acid</td>
<td>13.4</td>
<td>680,000</td>
<td>9</td>
</tr>
<tr>
<td>Potassium sorbate</td>
<td>4.5</td>
<td>820,000</td>
<td>8</td>
</tr>
</tbody>
</table>

<sup>a</sup>Based only on the reports from those respondents to the NRC survey who submitted information for both 1960 and 1970.

<sup>b</sup>Based on the sum of the usage reported to NRC and FEMA (Flavoring Extract Manufacturers' Association) recalculated to 100 percent from survey data that the NRC subcommittee estimated to represent about 60 percent of the actual usage.

<sup>c</sup>Based on total used in 1970 calculated as sorbic acid and a U.S. population of 205 million.
was independent of dosage between 61 to 1213 mg sorbic acid per kg body weight. Caproic acid in similar tests was oxidized at the same rate and to the same extent.

Fasting female rats received sodium sorbate or sodium caproate by stomach tube at levels of 75 or 150 mg (calculated as acetone) per 100 sq cm of body surface per day in two divided doses (about 6 g sorbic acid per kg body weight); the proportion excreted as ketone bodies was approximately the same (18). The authors concluded that sorbic acid and caproic acid were metabolized via acetone bodies, and that under normal conditions sorbic acid is completely oxidized to carbon dioxide and water.

The urine of rabbits fed sorbic acid (3 g per kg body weight) contained muconic acid (19). Small amounts of sorbic acid and muconic acid also have been reported in the urine of mice given water solutions of the sodium salt of sorbic acid by gastric intubation (40 and 3,000 mg per kg of body weight) (20). The mice were given food and water ad libitum and, in 4 days, 81 ± 10 percent of the sorbic acid was oxidized to carbon dioxide and water; about 4 percent was in the urine, part of it as muconic acid. Chicks utilize sorbic acid as a source of energy (21).

Toxicity

The oral LD₅₀ for sorbic acid in fed Sherman rats has been reported to be from 7.36 g to 10.50 g per kg body weight (22, 23). In rats fasted for 18 hours prior to testing, the LD₅₀ for sodium sorbate (calculated as sorbic acid) was 3.6 g per kg for females (163 to 267 g body weight) and 4.3 g per kg for males (212 to 430 g body weight) (23). In fed rats a higher LD₅₀ for sodium sorbate (calculated as sorbic acid) was found: 5.9 g per kg (male and female rats, 90 to 120 g). The higher LD₅₀ value for sorbic acid as compared to sodium sorbate was attributed by the authors to its less rapid absorption from the gut. The oral LD₅₀ of potassium sorbate in the rat has been reported as 4.9 and 6.2 g per kg body weight for the "solid" and "mixed isomers", respectively (24).

Short-term feeding

Sorbic acid (KOH neutralized) fed as 2 percent of the diet (about 2 g per kg body weight) to 8-week-old Wistar rats for 10 weeks had no effect on growth (25). Slight enlargement but no histological abnormalities of the livers were noted. Sorbic acid fed for 22 weeks to rats at 1.5 percent of the diet (1.2 g per kg body weight) had no adverse effect on hepatic and pancreatic functions or on body and organ weights (26, 27). In these and other reports (28) changes were noted in concentrations of bilirubin and cholesterol in the bile and in secretion of pancreatic juice.
However, from the data given in the reports it is not possible to assess the significance of these findings or the causative factors.

Rats were fed an 8 percent sorbic acid diet (5.1 g per kg body weight) for 90 days (22). The only effect noted was slight enlargement of the livers that were otherwise normal. A 4 percent diet did not cause liver enlargement. Another report indicates that rats can tolerate 10 percent sorbic acid in the diet for 4 months (29). The test animals tended to have a higher ratio of liver weight to body weight than did the controls. Liver homogenates of first generation animals fed sorbic acid had lower oxygen consumption than controls. Reproductive performance of females fed at the 10 percent level was found to be similar to that of the controls.

Groups of 50 male and 50 female mice intubated daily with sorbic acid (80 mg per kg body weight) for 3 months gained less weight than did controls (30). Reduced weight gains were not attributed by the authors to reduced feed intake.

Potassium sorbate ("solid or mixed isomers") was fed to groups of 10 rats (5 male and 5 female) at levels of 0, 1, 2, 5 and 10 percent of the diet for 3 months (24). Relative liver weights were the same in all groups. Kidney weights were increased at 10 percent and to a lesser degree at the 5 percent level (2.5 g per kg for a 400 g rat consuming 20 g of feed per day). No controls for high potassium intake were described. Weight gains of female animals were depressed initially when fed at the 10 percent level and to a lesser degree at the 5 percent level. In the same report eight dogs received 1 percent and eight dogs 2 percent potassium sorbate in the diet for 3 months and gained the same weight as four control dogs. At autopsy, gross examination revealed no deleterious effects attributable to potassium sorbate. Other researchers reported that three dogs fed 4 percent sorbic acid in the diet for 3 months grew normally and showed no deleterious effects attributable to the sorbate on histopathological examination (23).

**Long-term feeding and special studies**

In a 17-month study, 25 male and 25 female mice were fed sorbic acid (40 mg per kg body weight) daily as a paste prior to the main feed (30). Compared to controls the weights of liver, kidney and testes relative to body weight were lower for the experimental animals sacrificed at the end of the test. These changes were not considered pathological by the investigators.

One hundred rats maintained on 0.1, 0.5 and 5.0 percent sorbic acid in the diet (50, 250 and 2500 mg per kg body weight per day) for a test period of 1000 days did not differ from controls in growth, reproduction,
health, life expectancy or cause of death (31). A group of rats maintained through the second generation on the 0.1 or 0.5 percent diets exhibited no differences from controls in growth or reproduction. Thirty rats of the second generation received 5 percent sorbic acid in the diet for 252 days with no demonstrable pathological findings. An unpublished report from the same laboratory concerned 100 rats (50 males, 50 females) fed a diet providing 5 percent sorbic acid during their life span (32). The average life span of males compared to controls was 811 vs. 709 days and for females 789 vs. 804 days. There were no differences in organ weights of individual groups. In each group (5 percent sorbic acid and controls) only two tumors were found. There were no abnormalities in liver, kidney, heart or testes.

Dickens et al. (33) attempted to study the carcinogenicity of sorbic acid; however, the results were inconclusive. In a repetition of these tests using sorbic acid from another source, no tumors were obtained in Wistar rats when sorbic acid (2 mg in 0.5 ml in peanut oil) was injected subcutaneously twice weekly for 56 to 60 weeks (34). Also potassium sorbate did not induce tumors when fed for 60 weeks to rats at 0.1 percent of the diet or when dissolved in their drinking water at 0.3 percent.

In another carcinogenicity study, mice that had been fed a control diet or a diet supplying up to 300 mg sorbic acid per kg body weight for 3 months received ascitic Ehrlich cancer intraperitoneally by transplant (35). Within a 66-day observation period, the percentage of animals that developed tumors in control and experimental groups did not differ.

No carcinogenic effect was demonstrated by sorbic acid in rats given dietary levels up to 10 percent (about 5 g per kg body weight daily) for 2 years (36). Groups of 48 male (90 to 145 g) and 48 female rats (80 to 130 g) were fed diets containing 0, 1.5 or 10 percent sorbic acid. At the 10 percent level the thyroid weight in males, the relative liver weights in both sexes, and the relative kidney, small intestine, and ovary weights in females were increased slightly. No significant differences were found between the control and treated groups by hematological examinations, analyses of serum, studies of renal function by histopathological examination, or in mortality rate.

Tests of potassium sorbate for teratogenicity by the chick embryo test (37) and for mutagenicity in Salmonella typhimurium and Saccharomyces cerevisiae (38) were negative. Daily administration of up to 460 mg per kg body weight to pregnant mice (albino CD-1) or up to 340 mg per kg body weight to pregnant rats (Wistar derived stock) for 10 consecutive days (day 6 to 15 of gestation) had no clearly discernible effect on nidation or on maternal or fetal survival (39). The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the
number occurring spontaneously in sham-treated controls. The Select Committee is unaware of similar tests on sorbic acid.

V. OPINION

Sorbic acid and its salts demonstrate very low acute or chronic toxicity for experimental animals. In animals sorbate is metabolized by the normal fatty acid pathway. Although no metabolic or toxicological studies have been conducted in man, the similarity of the pathways of fatty acid metabolism in man and animals suggests that no deleterious effects are to be expected from sorbic acid in the diet even in amounts many times greater than those at which it appears to be used.

Based on these considerations the Select Committee concludes that:

There is no evidence in the available information on sorbic acid and its sodium, potassium and calcium salts that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when they are used at levels that are now current or that might reasonably be expected in the future.
VI. REFERENCES CITED


VII. SCIENTISTS CONTRIBUTING TO THIS REPORT

1. Members of the Select Committee on GRAS Substances:

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

Harry G. Day, Sc.D., Professor of Chemistry and Special Assistant to the Vice Chancellor for Research and Development, Indiana University, Bloomington, Ind.

Samuel J. Fomon, M.D., Professor of Pediatrics, College of Medicine, University of Iowa, Iowa City, Iowa.

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

John R. McCoy, V.M.D., Professor of Comparative Pathology, New Jersey College of Medicine and Dentistry, Rutgers Medical School, New Brunswick, N.J.

Sanford A. Miller, Ph.D., Professor Nutritional Biochemistry, Massachusetts Institute of Technology, Cambridge, Mass.

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

Michael B. Shimkin, M.D., Professor of Community Medicine and Oncology, School of Medicine, University of California, San Diego, La Jolla, Calif.

Ralph G. H. Siu, Ph.D., Consultant, Washington, D.C.

John L. Wood, Ph.D., Distinguished Service Professor, Department of Biochemistry, University of Tennessee Medical Units, Memphis, Tenn.

George W. Irving, Jr., Ph.D. (Chairman), Research Associate Life Sciences Research Office, Federation of American Societies for Experimental Biology, Bethesda, Md.
2. LSRO staff:

C. Jelleff Carr, Ph.D., Director
Kenneth D. Fisher, Ph.D., Associate Director
Richard G. Allison, Ph.D., Research Associate
Samuel B. Detwiler, Jr., Research Associate
Andrew F. Freeman, Research Associate
Frederic R. Senti, Ph.D., Research Associate
John M. Talbot, M.D., Research Associate

Report submitted by:

April 30, 1976

Date

George W. Irving, Jr., Chairman
Select Committee on GRAS Substances