EVALUATION OF THE HEALTH ASPECTS OF HESPERIDIN,
NARINGIN, AND CITRUS BIOFLAVONOIDS EXTRACTS
AS FOOD INGREDIENTS

1982

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

Contract No. FDA 223-78-2100
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Life Sciences Research Office
Federation of American Societies for Experimental Biology
9650 Rockville Pike
Bethesda, Maryland 20814
NOTICE

This report, one of a series concerning the health aspects of using the Generally Recognized as Safe (GRAS) or prior-sanctioned food substances as food ingredients, is being made by the Federation of American Societies for Experimental Biology (FASEB) under contract no. 223-78-2100 with the Food and Drug Administration (FDA), U.S. Department of Health and Human Services. The Federation recognizes that the safety of GRAS substances is of national significance, and that its resources are particularly suited to marshaling 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 (SCOGS), 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 Dockets Management Branch, 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.

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

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I. INTRODUCTION

This report concerns the health aspects of using hesperidin, naringin, and citrus bioflavonoid extracts as food ingredients. It has been based partly on the information contained in a scientific literature review (monograph) furnished by FDA (Bauer, 1978), which summarizes the world's scientific literature from 1920 through 1978. To ensure 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, announcement was made in the Federal Register on January 13, 1981 (46 FR 3064-3068) that opportunity would be provided for any interested persons 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 hesperidin, naringin, and citrus bioflavonoid complexes as food ingredients. The Select Committee held a hearing on June 22, 1981. Those who requested opportunity to present data, information, and views are identified at the end of this report. The material presented at the hearing has been considered by the Select Committee in reaching its final conclusions.

As indicated in the Food, Drug, and Cosmetic Act [21 USC 321(s)], GRAS substances are exempt from the prem-market clearance that is required for food additives. It is stated in the Act and in the Code of Federal Regulations (Office of the Federal Register, 1981) [21 CFR 170.3 and 170.30] 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. These sections of the Code also indicate 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 experimental data. FDA recognizes further [21 CFR 170.30] that it is impossible to provide assurance that any substance is absolutely safe for human consumption.

The Select Committee on GRAS Substances of LSRO reviewed and evaluated the available information on hesperidin, naringin, and citrus bioflavonoid extracts in full recognition of the foregoing provisions. In reaching its conclusions on safety, the
Committee, in accordance with FDA's guidelines, relied primarily on the absence of substantive evidence of, or reasonable grounds to suspect, a significant risk to the public health. This report is intended for the use of FDA in determining the future status of these substances under the Federal Food, Drug, and Cosmetic Act. The Committee anticipates that its conclusions will be reviewed as new information becomes available.
II. BACKGROUND INFORMATION

Flavonoids comprise a group of naturally occurring compounds which are among the most ubiquitous in the plant kingdom. They are found in every family and in nearly every species of the higher plants. Kühnau (1976) reported that about 800 different flavonoids were known and that new members of the group were being discovered "nearly every month." Although the term implies a yellowish coloration, flavonoids may vary in appearance from colorless to red or blue.

The basic flavone structure consists of 1,4-benzopyrone with a phenyl substitution in the 2-position (Fig. 1). Flavonoids differ in the number and position of substitutions on the aromatic rings and in the extent and character of oxidation in the pyrone portion of the molecule. Hydroxyl groups enable flavonoids to combine with sugars to form glycosides, and it is in this form that the flavonoids are usually found in nature. Glucose is the most common prosthetic group, although other sugars, as well as glucuronic and galacturonic acids, have been identified (Herrmann, 1976).

![Flavonoid structure](image)

Figure 1. Typical flavonoid structure

Table 1 summarizes the structure of some typical flavonoids found in various foodstuffs.

In 1936, Szent-Györgyi and coworkers (Bentsáth et al., 1936; Rusznyák and Szent-Györgyi, 1936) reported that crude extracts of lemon juice or red peppers were more effective than purified ascorbic acid in alleviating capillary lesions and sustaining the lives of scorbutic guinea pigs. The active principle was tentatively termed vitamin P (for "permeability vitamin"). This was originally thought to be identical with "citrin," a crystalline product isolated from lemon juice (Bentsáth et al., 1936). "Citrin" was later shown to be a mixture of the flavonoids hesperidin, eriodictin (Bruckner and Szent-Györgyi, 1936) and a quercetin-like compound (Robeznieks, 1938). Although these and a
Table 1. Structure of Some Typical Flavonoids*

<table>
<thead>
<tr>
<th>Flavonoid</th>
<th>R₁</th>
<th>R₂</th>
<th>R₃</th>
<th>R₄</th>
<th>Δ2:3†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diosmetin</td>
<td>-OH</td>
<td>-OCH₃</td>
<td>- OH</td>
<td>-</td>
<td>Yes</td>
</tr>
<tr>
<td>Diosmin</td>
<td>-OH</td>
<td>-OCH₃</td>
<td>- ORG$</td>
<td>-</td>
<td>Yes</td>
</tr>
<tr>
<td>Eriodictin</td>
<td>-OH</td>
<td>- OH</td>
<td>- ORG$</td>
<td>- H</td>
<td>No</td>
</tr>
<tr>
<td>Eriodictyol</td>
<td>-OH</td>
<td>- OH</td>
<td>- OH</td>
<td>- H</td>
<td>No</td>
</tr>
<tr>
<td>Hesperidin</td>
<td>-OH</td>
<td>-OCH₃</td>
<td>- ORG$</td>
<td>- H</td>
<td>No</td>
</tr>
<tr>
<td>Hesperetin</td>
<td>-OH</td>
<td>-OCH₃</td>
<td>- OH</td>
<td>- H</td>
<td>No</td>
</tr>
<tr>
<td>Kaempferol</td>
<td>- H</td>
<td>- OH</td>
<td>- OH</td>
<td>- OH</td>
<td>Yes</td>
</tr>
<tr>
<td>Naringenin</td>
<td>- H</td>
<td>- OH</td>
<td>- OH</td>
<td>- H</td>
<td>No</td>
</tr>
<tr>
<td>Naringin</td>
<td>- H</td>
<td>- OH</td>
<td>- ORG$</td>
<td>- H</td>
<td>No</td>
</tr>
<tr>
<td>Quercetin</td>
<td>-OH</td>
<td>- OH</td>
<td>- OH</td>
<td>-OH</td>
<td>Yes</td>
</tr>
<tr>
<td>Rutin</td>
<td>-OH</td>
<td>- OH</td>
<td>- ORG$</td>
<td>-OH</td>
<td>Yes</td>
</tr>
</tbody>
</table>

* Adapted from Booth et al. (1958a). Substituent nomenclature refers to Fig. 1

† Double bond

$ RG$ is rhamnoglucoside

$ R$ is rhamnoside
number of other flavonoids have been shown to modify membrane permeability, or to display other biological effects, all have failed to meet the criteria of true vitamins, namely, that they are essential and indispensable food constituents, and that deficiency syndromes are known which can be cured specifically by their administration. Consequently, the Joint Committee on Biochemical Nomenclature of the American Society of Biological Chemists and the American Institute of Nutrition (1950) recommended that the term vitamin P be discontinued. In its place, the less restrictive term "bioflavonoids" has been adopted to encompass the many flavonoids with some form of biological activity. Because bioflavonoids are nonessential food substances with biologic effects, the Committee on Dietary Allowances of the Food and Nutrition Board, (National Research Council, 1980) categorized them as pharmacologic rather than nutritional agents.

A vast, confusing literature has accumulated on the purported pharmacologic or therapeutic effects of one or another bioflavonoid. Willaman (1955), in reviewing the various reports, listed 33 separate types of biologic effects which had been attributed to bioflavonoids, including estrogentic, bactericidal, diuretic, antihistaminic, cathartic, hypotensive, hypertensive, and many others. In the intervening 25 years, claims have been made for still other activities by this group of compounds. Although the early claims of antiscorbutic action have proved unfounded, many of the bioflavonoids are effective antioxidants which protect sensitive, biologically important compounds. Kühnau (1976) stated that flavonoids are the most common and active antioxidants in our food supply, with the possible exception of tocopherols. Unlike the tocopherols, the flavonoids are active in hydrophilic as well as in lipophilic systems. Another general property of flavonoids is their ability to chelate metals, especially copper, to form metal complexes (Kühnau, 1976). Since the oxidation of vitamin C is catalyzed by the presence of copper, the antioxidant and chelating properties of flavonoids may be responsible for their oft-cited "sparing action" of vitamin C.

Three bioflavonoid preparations were given prior-sanctioned status by FDA: naringin, hesperidin, and lemon bioflavonoid complex (lemon peel infusion) (Wulfsberg, 1961a). Use of these substances in amounts up to 1 g daily was authorized in special dietary foods. A subsequent decision by FDA (Wulfsberg, 1961b) accorded prior-sanctioned status to a broader range of citrus preparations; namely, "dried concentrates of water-soluble flavonoids from washed, deoiled, ground peel and pulp of oranges, grapefruit and tangerines." These were authorized in special dietary foods in amounts up to 600 mg daily. Hesperidin complex was stated to be GRAS by FDA when distributed over-the-counter with recommended dosages of no more than 1 g daily (Smith, 1956).

Naringin has been accorded GRAS status as a flavoring agent in food [21 CFR 182.20] (Office of the Federal Register, 1981) and hesperidin has been given similar status for enhancing
rutin. The rutin content of this preparation ranges from 240-640 μg/g with an average of 440 μg/g. No free quercetin was detected. A lemon bioflavonoid complex marketed by another firm was reported to contain an estimated 50% carbohydrate and 10-15% flavonoids (Brewster, 1980). The flavonoids were not identified.

**Lemon bioflavonoid complex concentrates (LBC concentrates):** Although the Select Committee has no information that such products are marketed, animal feeding studies have been conducted with two products designated LBC concentrate (2x) and LBC concentrate (6x) (Beisel, 1981d). LBC concentrate (2x) was prepared by multiple extractions of LBC with isopropanol to preferentially extract flavonoids followed by distillation of the solvent and vacuum drying the residual syrup. LBC concentrate (6x) was prepared by extraction of flavonoids from LBC with methyl ethyl ketone followed by removal of solvent. No information was available on the composition of the products. The concentration factor (2x or 6x) refers to the measured increase in citrate concentration in the extract which presumably was related to an increase in concentration of flavonoids.

**Orange, grapefruit, and tangerine bioflavonoid complexes:** The Select Committee has no information on the flavonoid composition of the concentrates of water soluble flavonoids derived from oranges, grapefruit, and tangerines, or whether such preparations are currently being marketed. A feeding study has been reported with orange bioflavonoid complex concentrate but the company reporting this study has stated that they have discontinued production of this item (Beisel, 1981d). The orange bioflavonoid complex concentrate was prepared by the same techniques used in the preparation of LBC concentrates.

Citrus peel contains a mixture of flavonoids and related compounds, not all of which may be extracted in the commercial process using water. Analyses of organic solvent extracts have detected the flavonoids listed in Table 2 (Harborne, 1967; Hendrickson and Kesterson, 1965; Horowitz and Gentili, 1960; Maier and Metzler, 1967). The flavonoids generally occur in the peel in their glycosidic forms (Horowitz and Gentili, 1960), and many of the aglycones listed in the table were obtained from enzymatically hydrolyzed extracts. In addition to these flavonoids, numerous chemically related compounds, especially derivatives of phenol, coumarin, and cinnamic acid, have also been identified in citrus peel (Horowitz and Gentili, 1960; Maier and Metzler, 1967).

Beisel (1981a) reported that orange juice reconstituted from the frozen concentrate contains about 3.2 μg rutin/g, reconstituted grapefruit juice less than 1 μg rutin/g, and lemonade about 2.9 μg rutin/g.

The most thorough analyses of flavonoid content in various edible plants appear to be those of kaempferol and quercetin glycosides. The concentrations of these flavonoids have been
Table 2. Flavonoids in Citrus Peel Extracts*

<table>
<thead>
<tr>
<th></th>
<th>Grapefruit†</th>
<th>Lemon</th>
<th>Orange</th>
<th>Tangerine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apigenin§</td>
<td>Apigenin</td>
<td>Auranetin</td>
<td></td>
<td>Hesperidin§</td>
</tr>
<tr>
<td>Dihydrokaempferol</td>
<td>Apigenin 7-rutinoside</td>
<td>Hesperidin§</td>
<td>Nobiletin</td>
<td></td>
</tr>
<tr>
<td>Eriodictyol</td>
<td>Chrysoeriol</td>
<td>Isosakuranetin 7-rutinoside</td>
<td>Tangeretin</td>
<td></td>
</tr>
<tr>
<td>Hesperetin</td>
<td>Diosmin§</td>
<td>Naringin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hesperidin</td>
<td>Eriocitrin§</td>
<td>Neohesperidin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isorhamnetin</td>
<td>Hesperidin§</td>
<td>Nobiletin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isosakuranetin§</td>
<td>Isorhamnetin</td>
<td>Rutin§</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kaempferol</td>
<td>Limocitrin</td>
<td>Sinensetin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naringenin</td>
<td>Limocitrol</td>
<td>Tangeretin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naringin§</td>
<td>Luteolin 7-rutinoside</td>
<td>Vitexin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neohesperidin</td>
<td>Naringin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poncirin</td>
<td>Neohesperidin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quercetin</td>
<td>Poncirin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rutin§</td>
<td>Quercetin</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Flavonoids occur naturally in glycosidic form (Horowitz and Gentili, 1960). The aglycones listed in this table were identified after enzymatic hydrolysis.

† All aglycones were detected in grapefruit endocarp as well as peel after enzymatic hydrolysis (Maier and Metzler, 1967).

§ Flavonoids present in greatest concentrations.

§ Found in Satsumelo, a hybrid of grapefruit and Satsuma orange (Krewson and Couch, 1948).
determined in numerous fruits and vegetables (Table 3). The flavonoid concentrations are consistently and considerably greater in the leaves, skin, and peel of the various plants than in their deeper tissues (Herrmann, 1976).

The bitter taste of naringin has been used to enhance the piquant flavor of certain beverages and to replace "bitter tonic" preparations. Naringin has also been used as an intermediate in the preparation of certain water-soluble, yellow-red dyes for wool and silk (Kesterson and Hendrickson, 1953). In sharp contrast to naringin, hesperidin is practically tasteless (Wilson and DeEds, 1940). Presumably through its action as an antioxidant, hesperidin has been reported to delay flavor deterioration of milk-based beverages, thereby extending shelf life by 6-12 mo (Nelson, 1980a). Hesperidin also is used as a reagent in the refining and reclaiming of lead and zinc, and as a raw material in the production of the dihydrochalcone of neohesperidin, a nonnutritive sweetener (Nelson, 1980a).
Table 3. Content of Quercetin and Kaempferol Glycosides in Some Vegetables and Fruits Estimated as mg Aglycone/kg Fresh Weight*

<table>
<thead>
<tr>
<th>Vegetable or Fruit</th>
<th>Quercetin</th>
<th>Kaempferol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asparagus spears</td>
<td>6.7</td>
<td>0.7</td>
</tr>
<tr>
<td>Broccoli</td>
<td>30</td>
<td>6</td>
</tr>
<tr>
<td>Tomato</td>
<td>7</td>
<td>0.2</td>
</tr>
<tr>
<td>Chives</td>
<td>300</td>
<td>10</td>
</tr>
<tr>
<td>Lettuce (Blanco)</td>
<td>31</td>
<td>†</td>
</tr>
<tr>
<td>Lettuce (Valentine)</td>
<td>276</td>
<td>†</td>
</tr>
<tr>
<td>Bell Pepper</td>
<td>63</td>
<td>0</td>
</tr>
<tr>
<td>Brussels sprouts</td>
<td>25</td>
<td>40</td>
</tr>
<tr>
<td>Cauliflower</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Radish</td>
<td>0</td>
<td>1-8</td>
</tr>
<tr>
<td>Leek (9 varieties)</td>
<td>10-25</td>
<td>90-200</td>
</tr>
<tr>
<td>Endive (outer leaves)</td>
<td>†</td>
<td>150</td>
</tr>
<tr>
<td>Kohlrabi</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Potato</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Apple</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peel</td>
<td>58-263</td>
<td>&lt;1-7</td>
</tr>
<tr>
<td>Remaining tissue</td>
<td>&lt;1-2</td>
<td>0-0.1</td>
</tr>
<tr>
<td>Pear</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peel</td>
<td>28</td>
<td>12</td>
</tr>
<tr>
<td>Remaining tissue</td>
<td>&lt;0.1</td>
<td>0</td>
</tr>
</tbody>
</table>

* Adapted from Herrmann (1976)

† Not reported
III. CONSUMER EXPOSURE DATA

Data are sparse on the use of bioflavonoids as food additives. In its 1977 survey, the Committee on GRAS List Survey (1979) queried industry on the use of hesperidin and of lemon bioflavonoid complex. No report on the use of the lemon complex was received. Reports on hesperidin indicated that it had been used as a flavor enhancer in flavored milk products at levels of 30 mg/l and at a level of 1.5% in dietary supplements. The total reported use by industry in 1976 was 420 pounds (190 kg), which corresponds to a per capita daily consumption of 2.5 μg.

Naringin was not included in the 1977 survey. However, an earlier (1970) survey indicated that a total of 3527 pounds (1600 kg) had been used in processed foods (Subcommittee on Review of GRAS List, 1972). This usage corresponds to a per capita daily consumption of 21 μg. Its reported use is shown in Table 4.

Table 4. Levels of Addition of Naringin Extract to Foods by Food Categories (Subcommittee on Review of GRAS List, 1972)

<table>
<thead>
<tr>
<th>Food Category</th>
<th>Level of Addition mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beverages, alcoholic</td>
<td>37.5</td>
</tr>
<tr>
<td>Baked goods</td>
<td>61.6</td>
</tr>
<tr>
<td>Soft candy</td>
<td>59.4</td>
</tr>
<tr>
<td>Gelatin puddings</td>
<td>52.9</td>
</tr>
<tr>
<td>Beverages, nonalcoholic</td>
<td>38.4</td>
</tr>
<tr>
<td>Frozen dairy products</td>
<td>28.5</td>
</tr>
</tbody>
</table>

Sunkist Growers, Inc., a major producer of citrus bioflavonoids reported their 1980/1981 sales of purified hesperidin to be about 100 kg, and hesperidin complex sales to be about 16,000 kg (Beisel, 1981b). Their estimated annual sales of naringin were about 20,000 kg and of lemon bioflavonoid complex about 15,000 kg (Nelson, 1980a). There are also several other domestic producers of bioflavonoids and sizeable quantities are imported from abroad. Principal use of hesperidin complex and lemon bioflavonoid complex appears to be as special dietary foods. Major use of naringin is for the preparation of chemical derivatives (Beisel, 1981c). A
number of bioflavonoid products are sold over-the-counter as "nutritional supplements," but no data are available on the extent of such usage. Nutrilite Products, a manufacturer of lemon bio-
fluavonoid complex, reported that 31 products containing bioflavon-
oids were purchased in Southern California from grocery, drug, and health food stores and from direct sales and mail order houses (Cupello, 1981). Health food stores were the most common marketing source, representing the source of supply for more than half the products obtained. Mail order and direct sales organizations pro-
vided most of the remaining products. Fourteen of the 31 prepara-
tions contained no rutin fortification and 30 to 1000 mg lemon bio-
fluavonoid complex (commercial source not stated). Rutin content of the tablets ranged from 0-42 µg, and averaged 12 µg/tablet.
Recommended daily dose was 1 tablet for 74% of the 31 preparations, 1-2 tablets for 10%; 3, 4, or 6 tablets were recommended for 3% each of the preparations.

Rough calculations suggest that the per capita intakes of these bioflavonoids in natural sources are many times the amounts added to food or employed as "nutritional supplements." Kühnau (1976) has estimated that the average total flavonoid intake from a normal mixed diet in the United States is approximately 1 g/d. Accurate data on the intake of individual flavonoids are not avail-
able because of the complex mixture of these compounds in the fruits and vegetables normally consumed. Kühnau (1976) has calcu-
lated that approximately 160-175 mg of 4-oxoflavonoids would be consumed daily with a normal diet, and that approximately one-
third of this amount would be obtained from fruit juice. This chemical group includes the most common bioflavonoids (hesperidin, naringin, diosmin, etc.) found in citrus fruits. Brown (1980) has estimated that perhaps 50 mg (quercetin equivalents) of promuta-
genic glycosides are included in the daily diet.

Orange juice represents the single most important source of hesperidin in the average American diet. About 10.5 million tons (9.8x10^3 kg) of oranges were produced in the United States in 1978/1979 (U.S. Department of Agriculture, 1980). About 330 thou-
sand tons were exported, leaving 10.2 million tons (9.3x10^3 kg) for domestic consumption. Assuming half this amount consists of orange juice containing 375 mg hesperidin/kg (range 150-600 mg/kg) (Hendrickson and Kesterson, 1965), the daily per capita amount of hesperidin available for consumption would be about 44 mg from this source alone. This is probably an underestimate since the rag and pulp components eaten with the fresh fruit contain con-
siderably higher concentrations of hesperidin than does the juice.

The juice of Florida grapefruit has been reported to contain 0.02-0.03% naringin (Kesterson and Hendrickson, 1953) and that of California grapefruit, about 0.06% (Poore, 1934). Assum-
ing half the grapefruit is juice, the juice equivalent of grape-
fruit produced in the United States in 1978/1979 (U.S. Department of Agriculture, 1980) was about 1.1x10^3 kg. With an average naringin content of 0.04%, the daily per capita amount of naringin available for consumption from grapefruit was about 5.6 mg.
Reconstituted orange juice from the frozen concentrate contains about 3 μg rutin/g or about 550 μg in a 6 oz serving (Beisel, 1981a). This amount of lemonade would contain about 500 μg rutin. Reconstituted grapefruit juice contains <1 μg/g juice. Vegetables appear to be a more important food source of rutin than citrus fruits. Based on the composition data given in Table 3 and average serving size data (Pao, 1981), and assuming quercetin is present as rutin and no rutin is lost in table preparation, an average serving of tomatoes (raw) would provide about 1.1 mg rutin; potatoes (baked), 0.4 mg; lettuce, up to 20 mg depending on variety; Brussels sprouts, 5.3 mg; bell peppers (raw), 5.1 mg; and asparagus spears, 1.5 mg. Herrmann (1976) reported that the outer dry skins of colored onions (Allium cepa L.) contained 2.5–6.5% quercetin mainly in the free form. The outer and inner epidermis of the first three non-dried scales (Stuttgart Riesen variety) contained 24,000 and 540 mg total quercetin per kg, respectively, in the form of glucosides; concentrations in the fourth to eighth scales were 10,600 and 400 mg/kg, respectively.
IV. BIOLOGICAL STUDIES

Absorption and metabolism

Most flavonoids are present in food as β-glycosides, and must be hydrolyzed before they can be absorbed (Kühnau, 1976). Enzymes splitting these glycosidic bonds are not normally present in digestive secretions or in the intestinal wall (Griffiths and Barrow, 1972). However, these flavonoid glycosides are extensively hydrolyzed by intestinal flora. Scheline (1968) reported that hesperidin incubated with rat cecal contents was rapidly converted to its aglycone (hesperetin) and was further metabolized to m-hydroxyphenylpropionic acid (m-HPPA). These products do not occur in germ-free animals and their formation is completely inhibited by antibiotic sterilization of the intestine (Griffiths and Barrow, 1972). Both the bacterially-generated aglycone and its catabolic products may be absorbed. The relative percentage of the glycoside which escapes bacterial destruction depends on the activity of the bacterial flora and on the degree of hydroxylation of the flavonoid molecule. Increased hydroxylation appears to increase the compound's susceptibility to bacterial degradation, e.g., luteolin, quercitrin, and rutin are preferentially subject to destruction by intestinal microorganisms (Brown and Dietrich, 1979). Kühnau (1976) estimated that approximately half of the daily flavonoid intake is absorbed from the gut as the aglycone.

After absorption, flavonoids are quickly bound in the liver as glucuronides and/or sulfate conjugates which are excreted as such in urine, or more often, in the bile (Kühnau, 1976). Biliary excretion into the intestine again exposes the flavonoid conjugate to possible bacterial degradation.

The major metabolic product of hesperidin and related flavonoids in rats and rabbits is m-HPPA (DeEds, 1968). 3,4-Dihydroxyphenylpropionic acid is the first metabolic product but this is rapidly subjected to microbiological dehydroxylations and methylations to form various compounds in addition to m-HPPA. Booth et al. (1958a) detected the following compounds in the urine of a rabbit given 330 mg/kg hesperidin by stomach tube: hesperetin, hesperetin glucuronide, m-HPPA, 3,4-dihydroxyphenylpropionic acid, 3-methoxy-4-hydroxyphenylpropionic acid, m-hydroxycinnamic acid, m-hydroxyhippuric acid, m-hydroxybenzoic acid, and 3-methoxy-4-hydroxybenzoic acid.

Honohan et al. (1976) administered hesperetin-3-14C (1.7 mg/kg body wt) to rats and found rapid absorption and subsequent excretion of radioactivity. They estimated that the intestinal absorption was more than 90% of the administered dose. This estimate was based upon the radioactivity detected in the urine, tissues, and expired air of the animals. Nearly 40% of the administered radioactivity was expired as carbon dioxide. Primary metabolic products found in the urine were m-HPPA, 3,4-dihydroxyphenylpropionic acid, and 3-methoxy-4-hydroxyphenylpropionic acid. No intact flavonoid was detected.
In a single human volunteer, the major product found after hesperidin ingestion was 3-hydroxy-4-methoxyphenylhydra- 
crylic acid, suggesting a species difference between man and 
rodents (Booth et al., 1958a).

The major metabolic product of naringin given to rats by 
stomach tube or subcutaneously was p-HPPA, rather than the meta- 
form found after administration of hesperidin and other flavonoids. 
Small amounts of p-hydroxycinnamic acid and of p-hydroxybenzoic 
acid and its ethereal sulfate were also detected (Booth et al., 
1958b), suggesting that some of the 3-carbon side chain of p-HPPA 
had undergone β-oxidation. When naringin was fed to a human vol- 
unteer, only the aglycone, naringenin, and its glucuronide could 
be detected in the urine. The failure to find evidence for split- 
ting the naringin molecule in man was unexpected, since both 
quercetin and hesperetin undergo further breakdown.

Rutin undergoes extensive hydrolysis to its aglycone, 
quercetin, by intestinal microflora (Scheline, 1968). Quercetin 
in turn is subject to further bacterial degradation. Gugler et 
Al. (1975) fed 4 g quercetin to human volunteers but detected none 
in the blood or urine at any of the intervals studied (20 to 540 
min). They concluded that less than 1% of the dose had been 
absorbed. Only 53% of the ingested dose could be recovered in the 
feces, indicating extensive breakdown in the gut. Analysis for 
quercetin metabolites was not performed. Booth et al. (1956) had 
previously shown that at least four metabolites were excreted 
after oral ingestion of rutin or quercetin by man, rat, rabbit, 
and guinea pig. When rabbits were given 2 g quercetin, 195–285 mg 
of identifiable metabolites were found in the urine.

Acute toxicity

Singleton and Kratzer (1973) characterized the toxicities 
of the common plant flavonoids as "negligible." Hesperidin complex, 
and lemon bioflavonoid complex (Sunkist Growers, Inc.'s products) 
were administered by stomach tube to groups of 10 young, male 
Long-Evans rats (Primorganics, Inc., 1955). No deaths occurred 
with doses of 16.0 g/kg body wt. During a 72-h observation peri- 
od, the rats appeared well and ate and drank in normal fashion. 
A lemon bioflavonoid complex and a lemon–orange flavonate glyco- 
side were similarly administered to young rats at maximum levels 
of 24 g/kg body wt. The compositions of these preparations were 
not described. Again, no deaths occurred and no ill-effects were 
apparent (Primorganics, Inc., 1956). The Select Committee is not 
aware of other reports concerning the acute oral toxicity of cit- 
rus bioflavonoids. Singleton and Kratzer (1973) claimed that 
studies with various flavonoids, including naringin, showed no 
acute toxicity, and DeEds (1968) has stated that: "None of the 
flavonoids administered to experimental animals in single doses 
orally, intraperitoneally, or intravenously when possible, pro- 
duced signs of acute toxicity."
Short-term studies

Citrus bioflavonoids were fed for 4 or 8 wk to 6-8-wk-old chicks at dietary levels of 0.5-5.0% (approximately 0.5-5.0 g/kg body wt) (Deyoe et al., 1962). The bioflavonoid composition was not stated, but hesperidin would presumably be the major member present. Normal growth, efficiency of feed conversion, and mortality occurred with dietary levels of 2.5% bioflavonoids; a marked reduction in growth and feed utilization was noted at the 5% level.

Guinea pigs were fed 10-20 mg rutin daily (about 15-30 mg/kg) for 8 wk at which time they were sacrificed (Griffith, 1955). The animals gained weight normally, showed no abnormal signs, and revealed no pathological changes at necropsy.

Wilson and DeEds (1940) fed rats up to 1.0% hesperidin or naringin in a standard diet (about 1 g/kg body wt) for 200 d. Although this level of naringin should have imparted a bitter taste to the diet, the food was not rejected by the rats. There was no significant difference between control and experimental rats in food intakes, growth curves, blood sugar levels, or visceral weights. No significant morphological changes were detected in the livers, hearts, spleens, adrenals, and testes of rats receiving hesperidin. Tissues of animals receiving naringin were not examined histologically.

Long-term studies

In a 400-d flavonoid feeding study, groups of 16 female weanling Sprague-Dawley rats were fed diets containing 2.5% (about 2-5 g/kg body wt/d) lemon bioflavonoid complex (LBC); LBC concentrate (2x), LBC concentrate (6x), hesperidin, naringin, or orange bioflavonoid complex concentrate (Patterson, 1960). At 70-75 d, half of the rats in each group were necropsied and groups of 8 animals were continued on each of the diets until 400 d had elapsed. Mean body weight of the group fed LBC was slightly (3%) but significantly less (P<0.05) than that of the control group at 75 d. Mean kidney:body wt ratios for all treated groups were less than the ratio for the control group but were significantly less (P<0.05) only for the animals fed naringin (9.8%), hesperidin (8.6%), and orange bioflavonoid complex concentrate (6.3%). Liver:body wt ratios were significantly greater for the groups fed LBC concentrate (2x) (9.7%), or LBC concentrate (6x) (17.1%), than the corresponding ratio for the control group. Histopathological examinations of organs at 75 d were made only for animals fed LBC concentrates. The pathologist reported that examination of kidney slices indicated a mild form of hydronephrosis. No significant histological changes were reported in the liver tissues.

Patterson (1961) reported the results of the examination of the rats (8 per group) that continued to be fed LBC, hesperidin, or bioflavonoid complex until killed at 400 d. No significant differences were found in body weights among treated or control
groups. Hematocrit, hemoglobin level, white cell count, percent polymorphonuclears and lymphocytes in the experimental and control animals did not differ significantly. There were no significant differences between treated and control groups in mean organ:body wt ratios for the thymus, heart, lungs, spleen, kidney, liver, or uterus, except for a 13.7% increase in liver:body wt ratio for the group fed orange bioflavonoid complex. Histopathological examination of the heart, spleen, kidney, liver, and lower left jaw revealed no abnormal changes.

Patterson (1962) reported the results of examination of the rats (8 per group) that were fed naringin, LBC concentrate (2x), or LBC concentrate (6x) until killed at 400 d. Mean body weight of the group receiving naringin was significantly (P<0.05) lower (10.8%) than that of the controls at necropsy. Consumption of the naringin diet was also lower, possibly attributable to its bitter flavor. No significant changes were found in hematological parameters in any of the treated groups. Differences found in lung:body wt ratios were associated with respiratory infections which occurred to various extents in all groups. Histological examination revealed a slight fatty metamorphosis (of an unnamed organ, presumably the liver) in four of the eight rats in the LBC concentrate (6x) group.

Quercetin and its derivatives (quercitrin, dihydroquercetin, and rutin) and neohesperidin dihydrochalcone, a citrus derived bioflavonoid, have been subjected to long-term animal feeding tests. Wilson et al. (1947) maintained six male and six female albino rats (strain not stated) on a diet containing 1% rutin (about 1 g/kg/d) for 400 d. Growth records were discontinued after 150 d, at which time weight records were normal. Necropsy examination at 400 d revealed no striking changes in any of the experimental rats compared with controls. A slight irregularity was noted in the vacuolation of adrenal cortical cells but was deemed to be of doubtful significance.

Ambrose et al. (1952) fed groups of 10 weanling rats, five of each sex, (strain not stated) diets containing 0.25, 0.5, or 1% quercetin or quercitrin (approximately 250, 500, and 1000 mg/kg/d) for 410 d. No abnormalities could be detected as judged by growth, food consumption, red and white blood cell counts, hemoglobin estimation, organ weights, or histopathological examination of adrenals, kidneys, spleen, liver, heart, thyroid, lungs, pancreas, stomach, small intestine, and bladder.

Booth and DeEds (1958) fed albino rats (strain not stated) dietary levels of dihydroquercetin as high as 1% (about 1 g/kg/d) for 450 d. Growth, food intake, organ weights, and gross and microscopic appearance of tissues did not differ significantly from controls. A high incidence of respiratory infections was noted in both control and experimental groups.
Gumbmann et al. (1978) fed neohesperidin dihydrochalcone to rats and dogs for more than 2 yr with no apparent carcinogenic or teratogenic effects.

A number of clinical studies have been reported in which bioflavonoid preparations have been given daily for periods up to 5 yr with no reported side-effects or toxic reactions. The preparations have been employed in a wide variety of conditions, generally those characterized by increased capillary fragility (Fostvedt, 1956). The usual maintenance dose of hesperidin has been 150–600 mg daily (about 2.5–10 mg/kg), together with equal amounts of vitamin C, and often in combination with lemon bioflavonoids, hesperidin methylchalcone, or other compounds. The diversity of therapeutic mixtures and dosages as well as the anecdotal and uncontrolled nature of the clinical reports complicate any evaluation of the therapeutic efficacy of these bioflavonoids. However, it is impressive that toxic effects have not been reported even when large doses were administered for many months. Van Buskirk (1946) reported no adverse effect on one individual susceptible to prolonged, severe bleeding, who had received from 1–4 g hesperidin daily for 2 yr and from 10–16 g daily for an additional 2 yr.

Mutagenicity

Recent reports have demonstrated the mutagenicity of several flavonoids which have been detected in certain citrus fruits (Bjeldanes and Chang, 1977; Brown et al., 1977; Sugimura et al., 1977; MacGregor and Jurd, 1978; Hardigree and Epler, 1978). All investigators utilized Salmonella typhimurium strains TA-98 and -100 as the test organisms. Bjeldanes and Chang (1977) found quercetin to be mutagenic without activation to both strains, as well as to TA-1538. Microsomal activation significantly increased its mutagenicity. The authors stated that the mutagenic activity of quercetin was 1–3 orders of magnitude less than the highly potent mutagens aflatoxin B₁ and 2-aminofluorene. Sugimura et al. (1977) confirmed the mutagenicity of quercetin and found that kaempferol was also a strong mutagen. The activities of both flavonoids were comparable with those of the known mutagens, o-aminoazotoluene and 4-aminobiphenyl with the TA-98 strain of S. typhimurium and with 3'-methyl-4-dimethylaminoazobenzene with the strain TA-100. MacGregor and Jurd (1978) and Hardigree and Epler (1978) also reported that quercetin and kaempferol were mutagenic without metabolic activation and that activation markedly enhanced their mutagenicity. Hardigree and Epler (1978) found quercetin to be mutagenic in strain D4 of Saccharomyces and in Escherichia coli as well as in S. typhimurium. Hardigree and Epler (1978) and Mortelmans and Griffin (1981) found rutin to be weakly mutagenic to S. typhimurium strains TA-98 and -100 with metabolic activation, but MacGregor and Jurd (1978), Brown and Dietrich (1979), and Tamura et al. (1980) reported no mutagenic activity. Hardigree and Epler (1978) noted that quercetin was detected after metabolic activation in their rutin
samples; the latter three groups of investigators found that treatment of rutin with mixed glycosidases was required for development of mutagenic activity.

Luteolin, diosmetin, hesperetin, hesperidin, naringin, and eriodictyol were nonmutagenic with the S. typhimurium assay with and without activation (Brown et al., 1977; MacGregor and Jurd, 1978).

Reproduction

Hesperidin complex, lemon bioflavonoid complex, and naringin were fed to mice in a study of the effect of flavonoids on fertility (Palmer and Patterson, 1954). It was estimated that daily flavonoid consumption ranged from 1.3-3.6 g/kg body wt. In a control period prior to adding bioflavonoids to the diets, the number of litters born to the three groups of nine females selected for treatment with naringin, hesperidin complex, and lemon bioflavonoid complex were 6, 8, and 8, respectively. After receiving the bioflavonoid diets, the number of females giving birth to litters was 9, 8, and 6, in the respective groups. Some of the rats from each treatment group were returned to the control diet, caged with males, and the number producing litters noted. However, the results reported in different tables in the report appear conflicting, and the Select Committee attached no significance to this aspect of the study. No adverse effects were noted in animals continued on the diets for various periods and then killed at the following times: lemon bioflavonoid complex diet, 176 d; hesperidin complex diet, 158 d; naringin diet, 219 d.

In another reproduction study, diets containing 4% (up to 10 g/kg body wt) LBC concentrate (2x), 2% LBC concentrate (6x), or 2% orange bioflavonoid complex concentrate were fed to groups of one male and two female weanling Sprague-Dawley rats which were caged together (Call and Patterson, 1960). After reaching puberty, the males were rotated among the cages. Ratios of the number of females that bore litters to the number fed the respective diets were: controls, 6/6; LBC concentrate (2x), 4/4; LBC concentrate (6x), 4/6; and orange bioflavonoid complex concentrate, 5/5. Mean number of days from start of the experiment to birth of litters was: controls, 67.3; LBC concentrate (2x), 56.8; LBC concentrate (6x), 77.8; and orange bioflavonoid complex concentrate, 62.0.

Wilson et al. (1947) maintained 15 female, 3-mo-old, albino rats (strain not specified) for 1 mo with a diet containing 1% rutin (about 1 g/kg/d). During this period they, together with control female rats from the same litter, were mated with the same males. Four litters were born to the females eating the rutin diet and two litters to the control females. Several of these litters were allowed to grow until weaning. No difference could be detected in the size or activity of the young from the two groups. The investigators also reported that the length of the estrus cycle in rats receiving the 1% rutin diet did not differ from that of control rats.
Carcinogenicity

No carcinogenic effects were reported from feeding rats with 1% rutin for 400 d (Wilson et al., 1947), 1% quercetin or quercitrin for 410 d (Ambrose et al., 1952), or 1% dihydroquercetin for 450 d (Booth and DeEds, 1958). However, Pamukcu and coworkers (1980) reported that quercetin is an intestinal and bladder carcinogen. They fed male and female weanling albino rats (Norwegian strain) a grain diet containing 1,000 ppm quercetin (about 100 mg/kg/d) for 14 mo. Weight gains and survival times were slightly less than those of the controls. Twenty of 25 rats fed quercetin developed multiple intestinal tumors of the ileal segment, seven fibro-adenomas, four adenomas, and nine adenocarcinomas. Three adenocarcinomas displayed mesenteric metastases. Five of the 25 rats developed bladder transitional cell carcinomas. No similar tumors were detected in control rats fed the grain diet.

Saito et al. (1980) found no significant difference in the incidence of tumors between control and quercetin-fed mice. Six-wk-old mice (ddY strain) of both sexes were fed pelleted diets containing 2% quercetin throughout their lifespan. Animals in both test and control groups developed leukemia and tumors of the lung, forestomach, mammary gland, adrenal, and soft tissues. However, four liver tumors were found only in quercetin-treated males and three uterine and two salivary tumors only in quercetin-treated females. The authors also called attention to a heart spindle cell sarcoma, an unusual tumor in mice, which developed in one quercetin-fed male and had metastasized to the liver, kidney, pancreas, forestomach, and diaphragm.

More recently, the carcinogenicity of quercetin and rutin was examined in an inbred ACI strain of rats (Hirono et al., 1981). Rats were fed diets containing 1% or 5% quercetin or 5% rutin for 540 d, or 10% quercetin or 10% rutin for 850 d. There was no significant difference in the incidence of tumors between the experimental groups and the control groups fed a normal basal diet.

In another study, Hosaka and Hirono (1981) utilized pulmonary bioassay to investigate the lung tumor response to quercetin in strain A mice. No significant differences in the incidence and multiplicity of lung adenomas were observed between mice fed diets containing 5% quercetin for 23 wk and those fed the basal diet. No metastases were observed.

Teratogenicity

No teratogenic effects were reported in reproductive studies with rutin by Wilson et al. (1947). Similarly, Gumbmann et al. (1978) could find no teratogenic effects in rats fed the synthetic bioflavonoid neohesperidin dihydrochalcone in a three-generation reproduction and teratology study.
Other studies

Flavonoids have been reported to have inhibitory effects on various enzyme systems, including hyaluronidase, histidine decarboxylase, xanthine oxidase, and succinoxidase (Griffith, 1955; Rodney et al., 1950). Of special interest is the finding that quercetin and other flavonoids hydroxylated in 5,3',4'- or 5,3',4',5'-positions inhibit o-methyltransferase which normally inactivates epinephrine and norepinephrine (Axelrod and Tomchick, 1959; DeEds, 1968). This enzymatic inhibition is demonstrable at flavonoid concentrations of \(10^{-5}\) M, levels which may be present in body fluids under normal nutritional conditions (Kühnau, 1976). Prolongation of catecholamine action by this mechanism might account for some of the vascular effects which have been attributed to bioflavonoids. Varma and Kinoshita (1976) reported that a large number of flavonoids were highly active inhibitors of aldose reductase, an enzyme implicated in cataract formation in diabetes. Quercetin and quercitrin 2-acetate are the most potent inhibitors of aldose reductase thus far reported, inhibiting enzyme activity by 50% at levels of \(10^{-7}\) and \(4\times 10^{-8}\) M, respectively. Preliminary studies by the investigators indicated that these flavonoids prevented or delayed formation of cataracts in diabetic animals. Wattenberg et al. (1968) investigated the capacity of several flavonoids to induce increased aryl hydrocarbon hydroxylase activity (AHH) in the liver and lung of the rat. Tangeretin and nobiletin were found to be active inducers. Rutin was reported to have very weak AHH-inducing capacity (Wattenberg, 1980).
V. OPINION

Hesperidin is found in all citrus fruits as well as in a number of the fruits and vegetables commonly consumed. Naringin is found in relatively large amounts in grapefruit and in other citrus fruits as well. The amount of each of these bioflavonoids normally consumed in citrus fruit and in other dietary items is several orders of magnitude greater than that added to foods as flavoring agents.

Acute toxicities of purified hesperidin, hesperidin complex, and naringin are extremely low. Short-term (200 d) and long-term rat feeding studies with purified hesperidin and naringin at levels up to 2.5 g/kg body wt/d have revealed no adverse effects. Both compounds have been shown to be nonmutagenic in microbial systems, and no mutagenic flavonoids have been identified as constituents of hesperidin complex. Reproduction studies conducted with a limited number of mice consuming about 2.5 g/kg body wt of hesperidin complex or naringin daily indicated no adverse effect on fertility. Hesperidin complex, and purified hesperidin to a much lesser extent, have been used prophylactically and therapeutically for a variety of disorders, and is freely available without prescription. Hesperidin preparations have not proved toxic even when doses of several grams have been used daily for months or years. The Select Committee recommends that food grade specifications for hesperidin and hesperidin complex be developed.

In view of the foregoing, the Select Committee concludes that:

There is no evidence in the available information on hesperidin (purified or hesperidin complex) or naringin 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.

The acute toxicity of lemon bioflavonoid complex is very low. No adverse effects were observed in a 400 d rat feeding study with lemon bioflavonoid complex fed at a level of 2.5 g/kg/d. Concentrates of lemon bioflavonoids included in the same study were associated with a mild form of hydronephrosis in animals necropsied at 75 d, but no significant histopathology was noted in animals necropsied at 400 d. Studies reporting a reduction in the number of rats bearing litters after being fed diets providing 2.5 g/kg body wt/d of lemon bioflavonoid complex or 5 g/kg/d of a lemon bioflavonoid complex concentrate were not considered to demonstrate a reduction in fertility in view of the very limited
number of animals involved. Lemon bioflavonoid complex contains rutin which can be hydrolyzed in vitro by intestinal bacteria to liberate quercetin. Whether such hydrolysis occurs in humans is not known. Quercetin has been shown to have mutagenic activity in microbial systems but investigators disagree on the mutagenicity of rutin. Conflicting reports have recently appeared concerning the carcinogenicity of quercetin. One group of investigators has reported a greater incidence of intestinal and bladder tumors in rats fed diets containing 0.1% quercetin than in rats fed a control diet. Another group of investigators has reported the occurrence of unusual tumors (but no overall increase in incidence of tumors) in mice fed 2% quercetin in their diet. Other investigators have failed to find increased incidence of tumors in rats fed diets providing 1, 5, or 10% quercetin. Although the weight of currently available data suggests noncarcinogenicity of quercetin, the definitive settlement of the issue merits further attention. Long-term feeding studies of rutin at levels of 1, 5, and 10% in the diet of rats have not demonstrated an increased incidence of tumors.

Information available to the Select Committee indicates the major use of the lemon bioflavonoid complex is as a component of special dietary foods. Food grade specifications for the complex should be developed. The amount of quercetin potentially derivable from the rutin present in the recommended daily intake of these foods is orders of magnitude lower than that present in glycosidic form in the vegetables, fruits, and fruit juices commonly consumed daily. Thus, hazard from consumption of quercetin glycosides can be little affected by the intake of lemon bioflavonoid complex. However, in the opinion of the Select Committee, questions exist about whether consumption of rutin from other food sources by humans results in exposure to quercetin.

Accordingly, the Select Committee concludes that:

There is no evidence in the available information on lemon bioflavonoid complex 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.

No information was available to the Select Committee on the commercial production, marketing, composition, or animal feeding studies with dried concentrates of water-soluble flavonoids from washed, deoiled, ground peel and pulp of grapefruit and tangerines. No significant changes were observed in rats receiving about 2.5 g/kg/d of orange bioflavonoid complex concentrate in 75 day- or 400 day-feeding studies nor were adverse effects reported in reproduction studies in which the rats consumed up to 5 g/kg/d. However, the Select Committee has no information on the composition, production, or consumption of orange bioflavonoid complex concentrate.
In view of the foregoing, the Select Committee concludes that:

In view of the deficiency of relevant data, the Select Committee has insufficient information upon which to base an evaluation of dried concentrates of water-soluble flavonoids from washed, deoiled, ground peel and pulp of oranges, grapefruit, and tangerines.
VI. REFERENCES CITED


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Report submitted by:

February 19, 1982

Date

George W. Irving, Jr., Chairman
Select Committee on GRAS Substances
PUBLIC HEARING ON HESPERIDIN, NARINGIN, AND CITRUS BIOFLAVONOID EXTRACTS
HELD JUNE 22, 1981*

The following individuals made presentations:

1. C. Gordon Beisel, Director of Research and Development, Products Group, Sunkist Growers, Inc., Ontario, CA.


3. James M. Cupello, Ph.D., Technical Director, Nutrilite Products, Inc., Buena Park, CA.


A written statement was also submitted after the meeting by Dr. Cupello.

* A transcript of the hearing is available from Ace Federal Reporters, Inc., 444 North Capitol Street, Washington, DC 20001.