EVALUATION OF THE HEALTH ASPECTS OF GUM GUAIAOC

AS A FOOD INGREDIENT

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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
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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. Jelleff Carr, Ph.D., Director
Life Sciences Research Office
FASEB

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I. INTRODUCTION

This report concerns the health aspects of using gum guaiac as a food ingredient. 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 April 22, 1976 (41 FR 16848 and 16849) 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 gum guaiac as a food ingredient. The Select Committee received no requests for such a hearing on gum guaiac.

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 document (PB-228 547/6) is available from the National Technical Information Service, U.S. Department of Commerce, P.O. Box 1553, Springfield, Virginia 22161.
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 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 gum guaiac and submits its interpretation and assessment in this report, which is intended for the use of FDA in determining the future status of this substance under the Federal Food, Drug, and Cosmetic Act.

II. BACKGROUND INFORMATION

Gum guaiac, also called resin guaiac, guaiac resin, guaiacum, and gum guaiacum, is a resin with a slight balsamic odor, obtained from Guaiacum officinale L. (lignum vitae) and G. sanctum L. (bastard lignum vitae or holywood) --trees that are native to tropical America, especially the West Indies and northern South America. The gum is an exudate on the trunks, occurring "as irregular masses enclosing fragments of vegetable tissues, or in large, nearly homogeneous masses, and occasionally in more or less rounded or ovoid tears" (2-5).

Gum guaiac has a melting range of 85 to 90°C, is insoluble in water, freely soluble in alcohol, ether, chloroform, and alkaline solutions, and sparingly soluble in fat (2, 3). The Food Chemicals Codex (2) sets a maximum of 15 percent alcohol-insoluble residue, and the following upper limits of impurities: arsenic, 3 ppm; total ash, 5 percent; acid-insoluble ash, 2 percent; heavy metals (as lead), 40 ppm; lead, 10 ppm. Tentative specifications for guaiac resin that are essentially the same as those of the Food Chemicals Codex, have been prepared by the Joint FAO/WHO Expert Committee on Food Additives (6, 7).
According to the Joint FAC/WHO Expert Committee on Food Additives (3,7), gum guaiac has the following components: about 70 percent α- and β-guaiaconic acids; about 10 percent guaiaretic acid; and 15 percent guaiac yellow, vanillin, and other compounds. The Merck Index (8) mentions also the components guaiacol, guaiacic acid, and guaiac saponin (guaiacin). Additional details concerning the composition of gum guaiac are to be found in a number of reports (9-16).

The structures of some of these substances are given below.

\[
\text{α - Guaiaconic acid} \\
2,5-di(4-hydroxy-3-methoxyphenyl)-3,4-dimethyl furan
\]

\[
\text{Guaiaretic acid} \\
1,4-bis(4-hydroxy-3-methoxyphenyl)-2,3-dimethyl-1-butene
\]
Gum guaiac was used in medicine for centuries for treatment of various ailments, however, it is not listed in the current Official Drug Standards.

Because tincture of gum guaiac turns a blue color when oxidized, it has been used as a reagent to detect various organic and inorganic oxidizing agents, including oxidative enzymes and in tests for hemoglobin (17). The active principle is stated by Kratochvil (18) to be $\alpha$-guaiaconic acid, which on oxidation is converted to the highly conjugated substance, guaiacum blue.
Guaiacum blue
bis-methylenequinone

The merits of gum guaiac as an antioxidant in fats and oils were first pointed out by Newton and Grettie (19) in a patent granted in 1933, and by Grettie (20) in a paper published the same year. The antioxidant properties of the substance and its food applications were further discussed in a number of papers and patents issued between 1938 and 1952 (21-39).

The 1945 edition of Bailey's Industrial Oil and Fat Products (40) stated that gum guaiac was "the one antioxidant which has been satisfactory enough on all counts to receive extensive commercial use." The 1951 edition of Bailey's book (41) noted that "gum guaiac...was used to the extent of about 0.05 percent in a popular bland-type lard product for a number of years," but did not indicate why its use had been discontinued. Gum guaiac was being marketed in 1953 and 1968 (4, 42). However, a recent survey by a National Research Council subcommittee (43) indicates that "guaiac, extract" was not used in the food industry in 1970. Inquiries by the Select Committee indicate that gum guaiac may be commercially obtainable and that perhaps a hundred pounds of the substance are used in the United States each year, chiefly as a chemical reagent. These inquiries also indicate that if gum guaiac has little if any present use in the food industry, it is because other more potent, purer, and less expensive antioxidants have been developed.

Gum guaiac is listed [21 CFR 121.101 (d)(2)] in the Food and Drug Administration's GRAS list (44) for use in edible fats or oils, at a tolerance of 0.1 percent (equivalent antioxidant activity 0.01 percent). Gum guaiac is also listed in the Code of Federal Regulations (44) as an antioxidant employed in the manufacture of food-packaging materials under conditions that the addition to food will not exceed 0.0005 percent [21 CFR 121.2005]. The Department of Agriculture regulations (45) permit "resin guaiac" as an antioxidant in rendered animal fat or a combination of such fat and vegetable fat, at a limit of 0.02 percent "in combination."
According to an FAO report (46), Canadian food and drug regulations permit the use of gum guaiac in lard, shortening, and other fats and oils, and mono- and diglycerides in accordance with "good manufacturing practice." The Japanese Standards of Food Additives (47) permit "resin guaiac" in fats and oils, and in butter, to the extent of 1,000 ppm.

A related point concerning "guaiac" deserves mention. In addition to gum guaiac the antioxidant, the literature refers to one or more related substances used in connection with food flavors and/or perfumes. This report is concerned only with gum guaiac, the antioxidant, but the following information on the "guaiac" substances used in flavor and perfumes has been noted.

Guenther's Essential Oils (48) indicates that oil of guaiac wood is a substance obtainable by steam distillation of the heartwood of G. officinale and G. sanctum. Since yields from these trees are small, it is commercially produced from the heartwood of Bulnesia sarmienti, a related small tree that grows wild in Paraguay. The oil has a pleasant, mellow odor resembling that of tea roses and is a viscous liquid that coagulates at room temperature to a crystalline mass that can be reliquified in the range of 40-50°C. It has been characterized as containing two isomeric sesquiterpene alcohols, guaiicol and bulnesol.

\[
\text{Guaicol (C}_{15}\text{H}_{26}\text{O)} \\
3,8\text{-dimethyl-5-alpha-hydroxyisopropyl-delta}^9\text{-octahydroazulene}
\]

The NRC subcommittee survey (43) indicates that 30 pounds of guaiac wood, extract and 2,046 pounds of guaiac wood, oil were used as flavors by the food industry in 1970. These substances are listed among the "natural flavoring substances and natural substances used in conjunction with flavors" (21 CFR 121.1163) that may be safely used in food (49).
III. CONSUMER EXPOSURE DATA

The National Research Council subcommittee survey on the usage of chemicals in 1970 (43) provided no information to indicate that gum guaiac was commercially used as an antioxidant in food products in the United States in 1970.

A very rough indication of usage may be obtained from the previously mentioned estimate that perhaps a hundred pounds of gum guaiac are used in the United States each year. Assuming a population of 205 million, this would amount to a possible usage of 0.6 micrograms per capita per day.

The Joint FAO/WHO Expert Committee on Food Additives has set an acceptable daily intake of gum guaiac for man at a maximum of 2.5 mg per kg body weight (6); in a 60-kg adult this would amount to 150 mg per day. Under the FDA tolerance for gum guaiac in fats and oils (0.1 percent), as much as 150 mg of gum guaiac could be contained in 150 g of fat, an amount that is unlikely to be exceeded in average daily consumption.

IV. BIOLOGICAL STUDIES

Most of the pertinent biological data on gum guaiac was reported in 1938 by Johnson et al. (50) and in 1951 by Lehman et al. (51). This information was reviewed in 1962 by the Joint FAO/WHO Expert Committee on Food Additives (3).

According to Johnson et al. (50), little if any ingested gum guaiac is absorbed into the blood of rats, dogs, and man. Much is passed out in the feces, although an appreciable quantity may be destroyed in the colon. For example, in one experiment with 4 dogs fed 2, 20, or 40 g of gum guaiac mixed in the food, 67 to 99 percent was recovered in the feces over the ensuing 2 to 4 days. Other in vitro experiments showed that no destruction of gum guaiac occurred in gastric or pancreatic juice but most of the gum guaiac added to feces was not recoverable after 24 hours of incubation.

The LD₅₀ of gum guaiac in three species of animals has been reported as follows:
<table>
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<th>Animal</th>
<th>Route</th>
<th>LD&lt;sub&gt;50&lt;/sub&gt; (mg/kg body weight)</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>Rats</td>
<td>oral</td>
<td>&gt;5000</td>
<td>51, 52</td>
</tr>
<tr>
<td>Rats</td>
<td>oral</td>
<td>&gt;2000</td>
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<tr>
<td>Guinea pigs</td>
<td>oral</td>
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<td>51</td>
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Six human subjects were given a total of ten doses of 2 or 3 grams of gum guaiac at a time, over an unspecified period. In some instances, one or two loose stools were passed; otherwise, there were no untoward effects (50).

Lehman et al. (51) reported that when young male rats were fed gum guaiac as 0.5 percent of the diet (about 500 mg per kg body weight) for six months, the mean growth rate was 80 to 85 percent of the rate for control rats.

The effect of gum guaiac ingestion was studied in 11 adult dogs over a period of 62 to 103 weeks (50). Five dogs received 0.5 to 1 g of gum guaiac daily, in addition to a standard diet. Three dogs received 1 g daily (about 100 mg per kg body weight), and three dogs served as controls. At the end of the test, all but one dog had gained weight, and in the exception, the loss apparently was not significant. Histological examination of intestines, lungs, kidneys, livers, and spleens from three dogs fed 1 g gum guaiac daily for 75 weeks showed that these tissues and organs were normal. Red cell and white cell counts were normal, as were hemoglobin levels.

A similar experiment was conducted with eight adult cats for 34 to 117 weeks (50). Three received no gum guaiac, and five were fed 0.5 to 1.0 g of gum guaiac daily (about 600 mg per kg body weight). Only one cat, receiving 1 g of gum guaiac daily, failed to gain weight. Gross and histological examination of the lungs, kidneys, livers and spleens revealed no untoward effects. The intestinal mucosa was not inflamed.

Four women and seven men ingested 0.05 or 0.10 g of gum guaiac (about 1 to 2 mg per kg of body weight) mixed in chocolate pellets, daily for periods of 18 to 104 weeks (50); five subjects continued for another 90 weeks. Red and white blood cell counts, hemoglobin determinations, and Fishberg's (1930) modification of Volhard's urine-concentration test for kidney function were performed each month. Stool consistency and body weight were noted. No abnormalities in these parameters were detected and all subjects remained healthy.
Lehman et al. (51) cited an unpublished two-year feeding study of R. N. Bieter in which one group of 10 rats was fed a diet containing 0.5 percent gum guaiac (about 500 mg per kg of body weight), and another group of 10 rats received no gum guaiac. There was no discernible difference between the two groups as determined by mortality and pathological examination.

In a lifetime study, four groups of 10 rats each were fed a basal diet containing 0.005, 0.05, or 0.5 percent (estimated to be in the range of 5 to 500 mg per kg body weight) of gum guaiac (50). The second- and third- generation descendants (80 in number) of the original rats were maintained throughout their lives on the same diet as their parents. No differences were observed between the experimental groups and the controls in regard to body weight, growth rate, life span, reproduction, or pathological examination. In all three generations, there were no significant differences between the treated and control groups with respect to number of pregnancies, number of young born, and number of young weaned.

No reports on the teratogenicity, mutagenicity, carcinogenicity, or allergic reactions due to gum guaiac have come to the attention of the Select Committee.

V. OPINION

The literature on the biological activity of gum guaiac indicates that it is a substance of very low acute toxicity. A number of short- and long-term feeding studies in experimental animals at levels orders of magnitude greater than those to which humans might be exposed indicate the absence of chronic effects. Daily ingestion by human subjects for nearly four years resulted in no observable adverse effects.

The Select Committee has found no indication that gum guaiac is currently used as a food ingredient.

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

There is no evidence in the available information on gum guaiac that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public if it is used as an antioxidant at levels compatible with current limitations.
VI. REFERENCES CITED


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<th>July 14, 1976</th>
<th>George W. Irving, Jr. Chairman</th>
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