EVALUATION OF THE HEALTH ASPECTS OF PROPYL GALLATE
AS A FOOD INGREDIENT

JANUARY 1973

Prepared for

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

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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 of evaluations of the health aspects of the Generally Recognized as Safe (GRAS) food substances that are being made by the Life Sciences Research Office of the Federation of American Societies for Experimental Biology under contract with the Food and Drug Administration of the U.S. Department of Health, Education, and Welfare. The Federation recognizes that the safety of GRAS substances is of national significance, and its resources are particularly suited to marshalling the opinions of knowledgeable scientists to assist in these evaluations. The Life Sciences Research Office, established in 1962 to make scientific assessments in the biomedical sciences, is conducting these studies.

Qualified scientists were selected as consultants to make a continuing review, analysis, and evaluation of the available information on each of the GRAS substances. These scientists, designated the Select Committee on GRAS Substances, were chosen for their competence and judgment with due consideration for balance and breadth in the appropriate professional disciplines. Members of the Select Committee on GRAS Substances who have contributed to this report are named in Section VII. The Select Committee’s evaluations are being made independently of FDA or any other governmental or non-governmental group.

These reports are approved by the Select Committee prior to submission to FDA. Although most LSRO consultants are members of FASEB constituent societies, the reports do not necessarily reflect the views of the Federation as a corporate body or carry the endorsement of the members of its constituent societies.

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FASEB
CONTENTS

I. Introduction ........................................... 1
II. Background information .............................. 2
III. Consumer exposure data ............................. 3
IV. Biological studies .................................... 4
V. Opinion ................................................ 7
VI. References cited ..................................... 9
VII. Scientists contributing to this report .......... 13
I. INTRODUCTION

Under terms of FDA Contract 72-85, FASEB's Life Sciences Research Office was requested to evaluate the health aspects of using propyl gallate as a food ingredient, primarily on the basis of information contained in a monograph furnished by FDA (1), summarizing the world's scientific literature from 1920 through 1970, and in certain supplemental documents available as of January 1973. Propyl gallate is one of the food substances that has been generally recognized as safe (GRAS) under the provisions of Section 121.101 of the Code of Federal Regulations (21 CFR 121.101, revised January 1, 1972).

As indicated in the Food, Drug and Cosmetic Act [21 USC 321 (s)], GRAS substances are exempt from the requirement of pre-marketing clearance for food additives. It is stated in 21 CFR 121.1 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. It is recognized further (21 CFR 121.3) that is 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 decisions the Select Committee, with the concurrence of FDA, is relying primarily on the absence of substantive evidence indicating the existence of a significant risk to the public health, and realizes that a decision, based on reasoned judgment, is expected even in instances where the available information is qualitatively or quantitatively limited.

In this context, the LSRO Select Committee on GRAS Substances has reviewed the available information on propyl gallate and submits its interpretation and assessment in this report, which is intended for the use of FDA in determining the future status of propyl gallate under the Federal Food, Drug and Cosmetic Act.
II. BACKGROUND INFORMATION

Propyl gallate is the normal propyl ester of 3, 4, 5-trihydroxybenzoic acid. Natural occurrence of propyl gallate has not been reported, the commercial product being synthesized by esterification of trihydroxybenzoic acid (1, 2).

The Food Chemicals Codex (3) specifies that the food grade product should contain not less than 98 percent propyl gallate, not more than 3 ppm arsenic, and not more than 10 ppm of heavy metals as lead.

Propyl gallate is among several phenolic compounds that have been used in foods since 1948 because of their antioxidant properties. Most fats, oils and fat-containing foods are naturally susceptible to rapid rancidification and other oxidative reactions that produce compounds having objectionable taste and odor, making foods containing them unpalatable. Lipid oxidation is autocatalytic and proceeds as a complex of chain reactions the nature and speed of which vary with the substrate, temperature, light, availability of oxygen and the presence or absence of oxidation catalysts. Antioxidants like propyl gallate act as "chain breakers" in the autoxidation processes, and retard the development of objectionable oxidation products under the usual conditions of processing, storage and use of fat-containing foods. Propyl gallate appears to be particularly effective in inhibiting the formation of peroxides which, when formed, are believed to generate additional chain-propagating radicals that increase the rate of autoxidation (2).

Propyl gallate is present in amounts ranging from 0.01484 to 0.00001 percent in the following categories of foods arranged in decreasing order of propyl gallate content: Fats and oils, meat products, snack foods (0.003%), baked goods, nut products (0.001%), other grain products, frostings, chewing gum (0.0001%), soft candy, frozen dairy products, gelatin puddings, non-alcoholic beverages, and alcoholic beverages (4).

The Food and Drug Administration's GRAS list indicates a limitation with respect to the total content of antioxidants in food (5). The tolerance for total antioxidant (including propyl gallate) is 0.02 percent of the fat or oil content of the food, including essential (volatile) oil content.
Propyl gallate, among other antioxidants, has been declared by the U.S. Department of Agriculture as acceptable for use in meat products within specified limits (30). A level of 0.02% of combinations of propyl gallate, butylated hydroxyanisole, butylated hydroxytoluene, glycine, nordihydroguaiaretic acid and resin guaiac is acceptable to retard rancidity in rendered animal fat or a combination of animal and vegetable fat.

The total poundage of propyl gallate used in foods did not change significantly between 1960 and 1970, the two years for which comparable figures are available (4). However, there is no information now available to the Select Committee that permits it to determine the extent to which there has been significant change in the propyl gallate content of any of the foregoing food categories over the past decade.

III. CONSUMER EXPOSURE INFORMATION

A National Research Council subcommittee (4) has supplied the following information on the possible daily human intake of propyl gallate in the total diet, by individuals in various age groups. The Select Committee has converted these figures to possible intakes per kilogram of body weight.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Possible daily intake</th>
<th>Per kilogram of body weight*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Average</td>
</tr>
<tr>
<td>0-5 mos.</td>
<td>0.07</td>
<td>0.014</td>
</tr>
<tr>
<td>6-11 mos.</td>
<td>0.91</td>
<td>0.114</td>
</tr>
<tr>
<td>12-23 mos.</td>
<td>1.49</td>
<td>0.135</td>
</tr>
<tr>
<td>2-65+ yrs.</td>
<td>3.88</td>
<td>0.065</td>
</tr>
</tbody>
</table>

*Calculations based on an average weight of 60 kg for an adult (6) and the following estimated weights of infants by age groups: 0-5 mos., 5 kg; 6-11 mos., 8 kg; and 12-23 mos., 11 kg (7).
It is recognized that the figures calculated for the daily intake of propyl gallate per kg of body weight in the age group 2-65+ years could be low for some since individuals from age 2 to maturity will obviously weigh less than 60 kg; thus the daily intake of propyl gallate per kg for a 20 kg child, for example, could be higher by a factor of 3 than the figures indicated in the table.

The NRC subcommittee has pointed out (4) that its calculations of intakes of GRAS substances are overstated, in most cases, often by considerable margins. In the case of propyl gallate, however, the intakes indicated in the foregoing table may be only slightly overstated as is borne out by the following calculation: Other NRC data show that the use of propyl gallate for food purposes in the United States was 137,146 pounds or 62,339 kg in 1970. It is stated that this reported figure comprises between 60 and 70 percent of the total actual poundage used as food. On the basis of 60 percent adjusted to 100 percent (103,898 kg) and a U.S. population of 200 million, the per capita per day average intake would be 1.42 mg of propyl gallate rather than 3.88 mg as given in the table.

In the light of these considerations the Select Committee concludes that the figures given in the foregoing table reflect fairly accurately the actual levels of consumption of propyl gallate by the several age groups.

An acceptable daily intake of propyl gallate for man has been estimated by the Joint FAO/WHO Expert Committee on Food Additives (23) to be 0.2 mg per kg body weight (unconditional) and 0.2 to 0.5 mg per kg (conditional).

IV. BIOLOGICAL STUDIES

Orally administered propyl gallate and other alkyl esters of gallic acid undergo cleavage of the ester linkage and the gallic acid portion is metabolized and excreted mainly (about 72 percent) as the glucuronide of 4-O-methyl gallic acid (8). The main pathway of metabolism appears to be the initial methylation of the hydroxyl group in the 4 position as previously demonstrated (9) followed by conjugation with glucuronic acid. Other excretion products include
4-0-methyl gallic acid, gallic acid and pyrogallol accounting for some 80 percent of the administered propyl gallate in rabbits (8). It has been suggested that the nature and relative amounts of the excretion products may depend on the availability of methyl donors in the diet (9, 29).

The oral LD50 of propyl gallate in mice is reported to be in the range of 2,000 mg per kg (10) to 3,500 mg per kg (11); in the rat 3,000 (12) to 3,800 (13); in the hamster 2,480 (12); in the rabbit 2,750 (12).

The following short-term studies (extending for less than half of the life span of the species) are relevant, although conflicting and difficult to interpret.

Diets containing 0.002 percent or 0.004 percent propyl gallate were fed to rats for 13 weeks (15). No differences were noted in protein and fat utilization or in survival time for the experimental animals as compared to the controls.

A delayed increase in weight in rats and mice was reported when the animals were fed propyl gallate at levels of 1/5 and 1/10 of the LD50 for 2.5 months. There was also reduced blood catalase, peroxidase and cholinesterase activity (16).

Rats fed a diet containing a mixture of 50 mg per kg of propyl gallate and 100 mg per kg of butylated hydroxytoluene daily for 2.5 months showed normal weight gains (14). Decreased blood cholinesterase, catalase and glucose levels were noted after 3 weeks but they returned to normal by the end of the experimental period.

Some investigators have stated that indices of fertility and physical endurance as well as weight increments were unaffected when female albino rats were fed propyl gallate at a level of 202 mg per kg per day (27). The authors indicate that this dosage amounts to about 35 times the level of human intake.

Daily administration of a mixture of propyl gallate (10 mg per kg) and butylated hydroxyanisole (20 mg per kg) was reported to increase male rat mortality and sterility with a decrease in blood ketone bodies and no change in blood sugar level or in blood catalase or cholinesterase activity (17).
Male albino rats, fed a diet consisting of sunflower seed oil and animal fat to which 0.02 percent of propyl gallate was added, showed markedly lower weight gains and delayed development; the nutritional value of the fat tended to be lower than in the controls (19).

Propyl gallate, fed at a level of 0.1 percent for six weeks to weanling male and female Norway Hooded rats, elicited no effect on serum cholesterol level (22).

Male albino rats, fed 4 mg of propyl gallate daily in lard, showed somewhat lower assimilation of fat than the control animals (18).

Propyl gallate and certain other antioxidants are reported to inhibit the liberation of fatty acids from adipose tissue as measured by examination of the epididymis of Wistar rats, starved for 16 hours and treated with adrenaline to activate fatty acid mobilization (20).

In studies to test for teratogenicity, pregnant Walter Reed-Carworth Farms rats, fed 500 mg of propyl gallate, showed 18.3 percent of implantations terminating in resorptions compared to 10.6 percent in control animals (21). In the same report, resorptions due to feeding ascorbic acid, glutathione and butylated hydroxytoluene at equivalent levels, were 15.3, 13.9 and 2.4 percent, respectively. The feeding of 0.025 to 0.075 percent propyl gallate to vitamin E deficient rats resulted in decreased incidence of congenital abnormalities in the offspring (28).

The following significant longer-term studies have been reported.

Rats, fed diets containing as much as 0.117 percent, and guinea pigs and dogs as much as 0.0117 percent propyl gallate for 1 to 2 years showed no adverse changes in gross appearance, growth, hemoglobin reproduction (guinea pig), renal function (dog), erythrocyte and leucocyte levels (rat), or in the histology of the liver, kidneys, spleen, stomach, gonads, lungs, or heart (rat and guinea pig) (13). Feeding of higher levels (1.17 percent or more) of propyl gallate to rats led to some growth inhibition, lowered hemoglobin levels and kidney damage.

Rats, fed 1 percent propyl gallate in the diet for their entire life span showed no adverse effects (11).
Young Wistar rats were fed for as long as a year on diets to which propyl gallate, butylated hydroxyanisole and chlorine dioxide were added at levels 50 times those normally used in bread ingredients (24, 25). No adverse effects were noted on growth, mortality, organ weights or histopathology of tissues.

In one report a man ingested 0.5 g of propyl gallate daily for six consecutive days (10). Examination of the urine during this period and for an additional six days thereafter revealed the presence of no albumin, blood or abnormal sediments or casts.

Feeding studies to test for carcinogenicity or mutagenicity of propyl gallate have not been reported. A number of reports record observations on the in vitro effects of propyl gallate on DNA and on cell cultures but the relevance of these studies to the in vivo oral effects of propyl gallate in humans is not clear (31). However, the intraperitoneal administration of a single 180 mg dose of propyl gallate to mice with Ehrlich ascites tumor and hepatomas was reported to inhibit tumor growth (26).

V. OPINION

Although interpretation of some reports is difficult, particularly where propyl gallate has been studied in mixtures with other antioxidants, it is evident that the no effect level of propyl gallate for the rat exceeds 100 mg per kg per day, and no effect levels of this order have also been reported for mice, guinea pigs and dogs. The Select Committee regards as reasonable the estimate of the FAO/WHO Expert Committee on Food Additives of 100 mg per kg per day as the level of propyl gallate that causes no significant toxicological effect when fed to the rat (23). Using this estimate and the consumer exposure data in Section III, the highest no effect level of orally administered propyl gallate is more than 1,500 fold that usually present in an adult's daily diet and more than 400 fold that which would obtain if his diet were to consist only of those foods containing the maximum amount of propyl gallate. Moreover, the highest no effect level is some 200 fold the maximum reported levels of consumption of the children who, according to the data in Section III, consume propyl gallate at the highest rates.
In the light of the foregoing the Select Committee concludes that:

There is no evidence in the available information on propyl gallate that demonstrates it to be a hazard to the public when used at levels that are now current or that might reasonably be expected in future.
VI. REFERENCES CITED


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Report submitted by:

March 16, 1973

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