EVALUATION OF THE HEALTH ASPECTS OF PAPAIN

AS A FOOD INGREDIENT

1977

Prepared for

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

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

/Signature/
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 papain 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 June 3, 1977 (42 FR 28600 and 28601) 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 papain as a food ingredient. The Select Committee received no requests for such a hearing on papain.

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 Act and in the Code of Federal Regulations (2) [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. 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 (2) recognizes further [21 CFR 170.30] that it is impossible to provide assurance that any substance is absolutely safe for human consumption.

*The document (PB-228 540/1) 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 reconduted, 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 papain 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

Papain is obtained from the latex of unripe papaya, Carica papaya L. (1, 3, 4). The term is currently applied both to the crude dried latex available commercially, as well as the crystalline proteolytic enzyme (5, 6). The articles of commerce are white to light tan amorphous powders, or light brownish gray to reddish granules which are obtained from the dried and sometimes further purified latex. The protein-digesting action of the latex has been known for centuries (4, 5). There are four recognized proteases in the water soluble proteins of commercial papain: papain (about 5 percent), chymopapain (about 27 percent), papaya peptidase A (about 18 percent), and a fourth, uncharacterized enzyme (about 14 percent). These enzymes act upon similar substrates. Papain preparations also exhibit esterase activity (6).

The pure crystalline enzyme, papain, has a molecular weight of 21,000, and the sequence of amino acids in its structure has been determined (7). Chymopapain has been crystallized in two forms (5, 6).

The commercial product is prepared by slashing green papaya fruits, collecting the latex, and allowing it to evaporate to a granular residue (4, 5). About half the proteolytic activity is lost in drying. Purification is
accomplished by dissolving the crude papain in water, precipitating with alcohol, and drying the precipitate at a low temperature (4). The principal protein constituents present in varying amounts, are globulins, albumins, proteases, and peptones. The latex also contains coloring matter, hard and soft waxes, hard and soft resin, and pectose compounds (5).

The Food Chemicals Codex (3, 8) specifies that the commercial product shall have not less than 6000 N. F. units of papain activity per mg, with an arsenic concentration of not more than 3 ppm and heavy metals as lead, not more than 10 ppm. One N. F. unit of papain activity is the amount that releases the equivalent of 1 μg of tyrosine from a casein substrate under specified conditions (3). A milk-clotting assay also is used (5).

Papain is employed exclusively for its enzyme activity, for example, to reduce "chill haze" in beer or as a meat tenderizer (9). Food grade papain digests about 35 times its weight of lean meat (10). The range of optimum activity is between pH 6 and 7 but appreciable proteolysis occurs between pH 4 and 9 (11).

The Code of Federal Regulations (2) lists papain as a multiple purpose (GRAS) food substance (21 CFR 182.1585). Papain preparations are used in home cooking, in restaurants, and in meat packing for tenderizing meat, particularly beef. Annual papain imports approximate 500,000 pounds (9), and are included with brewers' yeast and ficin in foreign trade import statistics (12). About a third of the papain imported is used by consumers in the home (9); about a quarter to a third by food processors (13); the remainder is used for various other purposes, including use in restaurants. Antemortem tenderization is now practiced by meat packers who use specially purified papain at concentrations equivalent to 5 to 30 ppm of commercial papain based on the total weight of the animal (9). The enzyme is injected intravascularly into the cattle shortly before slaughter. Papain has considerable effect on connective tissue, mainly collagen and elastin and also some action on muscle fiber proteins. Meat must be refrigerated or, because the enzyme is inactivated by heat, promptly cooked after papain treatment to avoid over-tenderization (9).

III. CONSUMER EXPOSURE DATA

A subcommittee of the National Research Council (NRC) surveyed manufacturers in 1970 concerning the addition of commercial papain to foods (13). Based upon information supplied, weighted means (Table I) were calculated for the levels of addition of papain to foods in several categories.
TABLE I

Level of Addition of Papain* to Foods by Food Categories (13)

<table>
<thead>
<tr>
<th>Food category</th>
<th>Weighted mean (^\text{b}) percent</th>
</tr>
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<tbody>
<tr>
<td>Baked goods, baking mixes</td>
<td>0.0025</td>
</tr>
<tr>
<td>Meat products</td>
<td>0.0009</td>
</tr>
<tr>
<td>Poultry products</td>
<td>0.0005</td>
</tr>
<tr>
<td>Condiments, relishes, salt substitutes</td>
<td>0.0625</td>
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<tr>
<td>Gelatins, puddings, fillings</td>
<td>(<em>\text{</em>**})</td>
</tr>
<tr>
<td>Beverages, alcoholic</td>
<td>0.0004</td>
</tr>
<tr>
<td>Reconstituted vegetable protein</td>
<td>0.0500</td>
</tr>
<tr>
<td>Gravies, sauces</td>
<td>0.1860</td>
</tr>
<tr>
<td>Seasonings, flavorings</td>
<td>1.0145</td>
</tr>
</tbody>
</table>

* Papain refers to commercial preparations which contain inert components of the latex inactivated enzyme, and the proteases referred to in the text.

b The weighted mean was calculated from the levels reported by manufacturers as their usual addition to one or more products in a food category. For discussion of weighted mean see Section X and Exhibit 50 of reference 13.

\(*\text{***}\) Asterisks mean that data were insufficient to permit estimation of a weighted mean.

The NRC subcommittee also estimated the possible average daily intakes of papain from Market Research Corporation of America data on the mean frequency of eating foods by food category, U.S. Department of Agriculture data on mean portion size of foods in these categories, and the assumption that all food products within a category contained papain at the levels shown in Table I. For individuals over 2 years old, the average intake estimated in this manner was 25.5 mg per day. The NRC subcommittee has recognized that such an assumption is likely to lead to overestimates of intake, often by considerable margins. Because of factors detailed in Section XI of the subcommittee's report, it was stated that the average total dietary intakes estimated by this method are likely to be much higher than would be the intakes achieved through consumption of a diet consisting totally of processed foods to which the substance had been added at maximum levels. However, the Select Committee considers that this latter statement may not be applicable to papain. It seems likely that a relatively small percentage of the population may account for a large percentage of the
consumption of papain in such items as condiments, seasonings and gravies. An average intake of 25 mg papain per day might be achieved by such individuals.

Such estimates should be viewed in the light of the total amount of papain used in foods, data that are provided in the NRC subcommittee report (13). Food processors surveyed reported the use of 159,000 pounds (72,300 kg) of papain in 1970. The NRC subcommittee report indicates that this amount probably represents 60 percent of the total actually used. Converting this annual poundage to 100 percent and dividing by a population of 205 million, shows that the per capita daily disappearance of papain in 1970 was about 1.6 mg. This figure can be considered typical of per capita daily intake for most adults, but it is evident that even this figure will exceed actual dietary intake because of wastage and other factors. It is recognized, for the reason indicated above, that although per capita consumption of papain added to foods is probably less than 1.6 mg per day, some individuals may consume about 25 mg per day.

It is noted that the total amount of papain used by the food industry in 1970 was about 1.8 times that used in 1960 (13).

IV. BIOLOGICAL STUDIES

Animal studies

No animal studies have been reported on the acute, short-term, or long-term effects of ingesting pure papain. The studies of concern to the Select Committee relate to the effects of various commercial preparations of papain as an anthelmintic agent, as a digestant for protein when instilled into the gastrointestinal tract or mixed with food, or as an agent for eliciting various physiological effects. Because papain preparations used in many of these studies are characterized, if at all, in terms of enzyme activity, dose calculations based on weight of preparation used have limited significance.

In a study of analgesic and anti-inflammatory activity, a highly purified extract of papain (Prolase 300, Wallerstein Laboratories) was administered orally as a suspension in one percent gum tragacanth to groups of 10 adult female rats that had inflammation of the paws induced by prior injection of brewers' yeast (14). Administration of doses ranging from 200 to 600 mg per kg (twice a day for two days and once on the third day) produced a decrease in the inflammation and raised the pain threshold as measured one hour after the fourth and fifth doses. Pain threshold was measured in a special apparatus in terms of the mm of mercury pressure applied to
the inflamed paw requisite to induce removal of the paw from the pressure applicator. The oral analgesic $ED_{50}$ (dose at which there was a 50 percent increase in pain threshold) was 540 mg per kg and the anti-inflammatory $ED_{50}$ (dose at which there was a 50 percent decrease in circumference of the inflamed foot) was 610 mg per kg. No adverse effects of papain at these doses were reported.

Studies with young adult male and female rats weighing about 200 g were carried out with a test meal containing 1 g of casein, 330 mg of glucose and either 1.25 or 5 mg of papain (15, 16). The animals that consumed the entire test meal within 20 minutes were sacrificed two hours later and the contents of the stomachs were analyzed for free amino groups as a measure of the extent of protein digestion. Control animals received the same meal except that the papain added was heat inactivated. Papain was found to increase the extent of protein digestion in vivo about 1.8-fold.

Papain was added to the diet of nine adult, parasite free, mongrel dogs (6 to 11 kg body weight) in which the protein was provided by unheated, defatted soybean meal (17). The papain content of the diet was 0.2 percent, amounting to 250 to 400 mg of papain powder per dog per day (about 35 to 40 mg per kg body weight). In feeding tests lasting two to three weeks, animals receiving active papain showed a 15.5 percent improvement in digestive efficiency (measured by nitrogen balance determinations) as compared to controls receiving heat inactivated papain.

Sheep were given a commercial preparation of papain, Nematolyt (not otherwise characterized) as an anthelmintic against the intestinal nematode Haemonchus contortus (18). The dose ranged from 5 to 10 g (about 85 to 170 mg per kg body weight) in water given by mouth or by injection into the abomasum. The treatment was effective in destroying worms and eggs; no side effects were noted.

As part of a study on the role of papain (not characterized) in hematopoiesis (19), oral doses up to 200 mg of an unspecified papain preparation were given to 2.5 kg rabbits for 12 to 15 days. The animals were made anemic by bleeding prior to the test period. The hemoglobin level of the controls rose 2.6 percent during the test period while the increase for papain-treated animals averaged 4.2 percent. The effect was not proportional to the papain dose but was improved by addition of ascorbic acid and/or iron to the diet. No deleterious effects were noted in animals receiving as much as 200 mg papain (80 mg per kg body weight) per day.

Five male rats, 60 to 90 days old, were given 400 mg per day (about 2.5 g per kg body weight) of papain (powder, crude) in the diet or by stomach tube for 3 days after which the animals were sacrificed and the
submaxillary and major sublingual salivary glands were removed and weighed. The results showed that to have an effect on the salivary glands (sialadenotrophic action), the papain must come into contact with the oral cavity. Surgical intervention showed that 1 percent papain in the diet had maximum sialadenotrophic action but only if both autonomic nerve branches of the gland were intact. In another part of the study, 200 mg of papain per day for three days were intubated without adverse effect to rats with sectioned glossopharyngeal or lingual nerves (20).

Groups of six young male Long-Evans rats were fed papain (Purified Standard, Hathaway Allied Products) at levels of 5 and 10 percent in the diet (about 5 to 10 g per kg body weight) for 12 days (21). Marked hypertrophy of the submaxillary glands occurred at both papain levels. Similar results were obtained with trypsin and chymotrypsin, but not with pepsin.

Papain was fed to depancreatized dogs as a dietary supplement twice daily in doses of 0.5 or 1.0 g (100 to 200 mg per kg body weight per day) for periods of 18 to 21 weeks (22). The papain feeding prevented the fatty livers generally observed in depancreatized dogs. The effect was ascribed to a restoration by papain of lost digestive function in the depancreatized animal.

The oral toxicity and other effects of Vermizym (a commercial tableted anthelmintic preparation containing papain but otherwise uncharacterized) were studied by Takaoka (23). An emulsion of the powdered product was administered to fasted, male, 10 to 15 g mice by stomach tube in single doses ranging from 125 to 375 mg. The animals exhibited "goose flesh," breathing difficulties, diarrhea with bloody stools, weakness, and death in some animals due to respiratory failure. The LD<sub>50</sub> of this papain preparation was about 12.5 to 18.7 g per kg. Animals which died within 24 hours after administration had hemorrhagic spots in the serous membrane of the small intestine, especially the jejunum. Survivors for longer periods had generalized hemorrhagic involvement which disappeared after one week. When the papain activity of the preparation was destroyed by heating, a dose of 250 mg (about 25 g per kg body weight) elicited different toxic signs characterized chiefly by clonic and tonic spasms. Dogs were administered Vermizym (1 g per kg body weight) by stomach tube and sacrificed five hours later. No gross change in the stomach mucous membrane was observed but small white spots and slight loss of luster were found in the gastric mucous membranes of some dogs.

Human studies

Vermizym was administered to five men aged 27 to 58 years as a treatment for round worms. A dose of 2.5 g was given each hour for five consecutive hours (total dose equivalent to about 200 mg per kg body weight). The treatment was effective in removing round worms and no side effects were noted in any of the patients (23).
Caroid, a proprietary digestant containing papain, caused perforation of the esophagus when used to treat esophageal obstruction due to meat impaction in a 27-year-old woman (24). In subsequent animal tests, anesthetized dogs were treated with a 33 percent aqueous solution of Caroid dripped onto an esophageal impaction consisting of a bolus of meat. Doses varied from a single dose of 3.3 g of Caroid to 4 to 11 doses of 1.6 g each over periods of one to five hours. When dead animals were necropsied or surviving animals were sacrificed and examined 3 to 16 hours after treatment, almost every dog receiving Caroid was found to have some damage to the esophageal wall. In addition the lungs of each dog showed hemorrhage and edema, which was in some instances sufficient to cause death. It was postulated that stretching and compression of the esophageal wall caused sufficient ischemia to permit papain to digest it. In another report (25), 28 patients treated with papain for meat impaction, suffered some esophageal damage from the treatment, especially if there were pre-existing esophageal disease or abnormality; in one patient, treatment resulted in perforation and destruction of the entire esophagus. In the latter case, the dose of papain was 1.2 g over a 12-hour period.

Five young adult men were given one 7.5 mg papain tablet every half hour for six doses (26). This slightly reduced (from 146 to 94 minutes) fibrin formation time and prolonged (from 180 to 277 minutes) clot formation time.

Papain may have a sensitizing effect on individuals who are exposed to the air-borne powdered product (3). Osgood (27), for example, reviewed the cases of six individuals who had dispensed papain and thus received inhalation exposures that would be unlikely to occur in normal food use of papain. They developed allergies characterized by such symptoms as rhinitis, skin reactions, asthma, cramps, and diarrhea. He also described a case in which a young woman developed an allergy to papain after its use to clear leg wounds that sloughed open following vein ligations for varicosities. Osgood concluded that papain is an active antigen and that sensitization may possibly occur from the ingestion. However, only slight reactions were elicited in 11 of 40 patients tested intradermally, even though six of these admitted to the use of tooth powder containing papain.

Milne and Brand (28), Marchioli et al. (29), and Tarlo et al. (30) have reported the development of occupational asthma by workers who inhaled dust containing papain resulting from processing the enzyme. In no case did emphysema develop and symptoms abated on permanent withdrawal of the sensitized individuals from the exposure area.

Tarlo et al. (30) found that seven of 330 subjects, who were receiving routine allergy skin tests, reacted to papain. Of 19 Red Cross blood bank workers who were exposed to papain, only two demonstrated a positive radio-immunoelectrophoresis test. One of the two exhibited symptoms of irritation.
of the eyes and nasal mucosa and also developed a positive radioallergo-
sorbent test.

The possible antigenicity of heat-inactivated papain has apparently
not been studied.

Special studies

Solutions of crystalline papain, when injected intraperitoneally
in a dose of 2.5 ml per kg of body weight, caused a significant dose related
increase in the number of mitotic figures in the livers of male rats. The
enzyme concentration of each dose was measured by spectrophotometric
absorbency and varied from 1.1 to 11.6 units. No pathological changes
were observed after 48 hours and all mitotic figures were of normal configuration.
Smaller increases in the mitotic index in the epithelial cells of kidney prox-
imal convoluted tubules and cardiac myofibers were observed, but no changes
occurred in the small intestines or adrenal glands (31).

Papain was found to display no teratogenicity to the developing
chicken embryo. Doses used were 10 to 200 mg per kg injected into the air
cell or yolk of unincubated eggs, or 5 to 100 mg per kg injected into the air
cell or yolk at 96 hours incubation. There was slight toxicity under all con-
ditions of test but it was significant only for the yolk treatment at 96 hours
when the LD₅₀ was calculated to be 2.4 mg per kg (32).

The oral administration of up to 1,080 mg per kg to pregnant
mice (day 6 through day 15 of gestation), and up to 820 mg per kg to preg-
nant rats (day 6 through day 15 of gestation) had no clearly discernible effect
on nidation or on maternal or fetal survival. The number of abnormalities
seen in either soft or skeletal tissues of the test animals did not differ from
the number occurring spontaneously in the sham-treated controls (33).

Intraperitoneal injection of papain (NF VIII, Difco Laboratories)
in mice induced a nonspecific resistance to a variety of bacterial challenge
infections, evident within 24 to 48 hours after papain injection and persist-
ing for at least 36 days. Doses of papain ranged from 0.125 to 2 mg and
the response was dose related. The protective activity of the papain prepara-
tion was not related to its enzymatic activity since crystalline papain did not
induce bacterial resistance (34).

No reports dealing with carcinogenic effects of papain have come
to the attention of the Select Committee.

V. OPINION

No studies of the acute, short-term, or long-term effects from
ingestion or oral administration of the pure enzyme papain have been found
by the Select Committee. The acute oral LD$_{50}$ of a commercial preparation of papain has been reported to be more than 10 g per kg for mice. The apparent acute oral toxicity is low when compared with the usual levels of human exposure which appear to be of the order of 2 to 25 mg per day. Commercial papains are only standardized for their proteolytic activity and the various methods of preparation may result in the presence of other macromolecules, such as protein and carbohydrate, as well as minerals. The relationship between food grade papain and that used by the investigators in the biological studies evaluated in this report is not known but their gross similarity can be assumed.

The proteolytic activity of papain is destroyed by extremes of pH and by heat. Cooking converts the enzyme to an inactive protein. Little is known about the nature and properties of the inactivated enzyme, or the other protein and non-protein portions of commercial preparations, but there is no evidence that they produce deleterious effects when ingested with food.

Allergies to papain have been reported but the incidence is low and the slight reactions reported appear to be confined to workers exposed to papain in air-borne dust.

In common with other proteolytic enzymes, papain digests the mucosa and the musculature of tissues in contact with the active enzyme for an appreciable period. Because there is no food use of papain that could result in the enzyme preparation occurring in sufficient amount in foods to produce these effects, this property does not pose a dietary hazard.

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

There is no evidence in the available information on papain 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.
VI. REFERENCES CITED


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