EVALUATION OF THE HEALTH ASPECTS OF CERTAIN
RED AND BROWN ALGAE AS FOOD INGREDIENTS

DECEMBER, 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 (LSRO) of the Federation of American Societies for Experimental Biology (FASEB) under contract with the Food and Drug Administration (FDA) 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 experience 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 nongovernmental 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.

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

Under terms of FDA Contract 72-85, FASEB's Life Sciences Research Office was requested to evaluate the health aspects of using certain red and brown algae as food ingredients, 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, including current literature citations obtained through Toxline* and Medline*, available as of December, 1973. Certain red and brown algae are food substances that have been generally recognized as safe (GRAS) under the provisions of Title 21, Section 121.101 of the Code of Federal Regulations (revised April 1, 1973).

As indicated in the Food, Drug, and Cosmetic Act [21 USC 321(s)], GRAS substances are exempt from the requirement of premarketing 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 it is impossible to provide assurance that any substance is absolutely safe for human consumption.

The Select Committee on GRAS Substances of LSRO is making its evaluations of these substances in full recognition of the foregoing provisions. In reaching its conclusions on safety the Select Committee, in accord 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, and realizes that a conclusion, based on such reasoned judgment, is expected even in instances where the available information is qualitatively or quantitatively limited. The Committee is also aware that biological testing, like all of science, is dynamic. Accordingly, the Committee's conclusions, based as they are on the information now available, cannot anticipate and be guided by experiments

*Nationwide online bibliographic retrieval systems initiated by the National Library of Medicine, Bethesda, Maryland.
not yet done or by the results of tests that may be reconducted, using new technologies that are continually being evolved. 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 certain red and brown algae and submits its interpretation and assessment in this report, which is intended for the use of FDA in determining the future status of these substances under the Federal Food, Drug, and Cosmetic Act.

II. BACKGROUND INFORMATION

Algae constitute a major group of nonvascular plants (Thallophyta) found in salt and fresh water. They are characteristically photosynthetic but diverse in morphology and physiology. Numerous algal species have been harvested and used for livestock and human food and as sources of medicinals, since before the Christian era (2). Various polysaccharide gums have been isolated or prepared from species of algae, including laminarin, algin, alginic acid, alginites, agar-agar, carrageenan, agaroid, iridophycin, funorin, fucoidin, and furcelleran (1).

Among the GRAS substances included in the Code of Federal Regulations [21 CFR 121.101 (e) (3) and (4)], the algae are listed as natural substances or as their extractives that are used with spices, seasonings, and flavorings. The term "algae" refers to materials derived from two genera of brown algae (Phaeophyceae), Laminaria sp. and Nereocystis sp., and two red algae (Rhodophyceae), Porphyra sp. and Rhodymenia palmata (L.) Grev. The latter species also is listed as GRAS under the entry, "dulse" [21 CFR 121.101 (e) (3) and (4)]. Kelp, a synonym for brown algae, is listed separately [21 CFR 121.101 (e) (3) and (4)] and, in addition, is listed as a source of iodine in foods for special dietary use [21 CFR 121.1149]. In this latter section, kelp is specifically identified as the dehydrated, ground product prepared from Macrocystis pyrifera, Laminaria digitata, L. saccharina, and L. cloustoni. Furcelleran and its salts are listed as food additives [21 CFR 121.1068] and [21 CFR 121.1069] and are reported to be structurally and functionally similar to κ-carrageenan (2).

The alginates, agar-agar, and carrageenan are listed separately in the Code of Federal Regulations [21 CFR 121.101 (d) (7)] and have been reviewed by the Select Committee on GRAS Substances in separate reports (3, 4, 5). Furcelleran and its derivatives will be the subject of a subsequent report by the Select Committee on GRAS Substances.
The Food Chemicals Codex (6) provides specifications for kelp obtained from *M. pyrifera* and related species. These specifications limit ash to not more than 35 percent, iodine content to between 0.15 and 0.22 percent, and loss on drying to not more than 13 percent. Limitations on impurities are set for arsenic (3 ppm), heavy metals as lead (40 ppm), and lead (10 ppm). Dried algae meal is included among color additives listed for food use and exempt from certification (7). It is used in chicken feed to enhance yellow skin and egg color. The Codex does not give specifications for other algae.

In general, the substances isolated from the red algae are hydrocolloids, most of which are polymers of galactose. Many of these polymers are distinctive sulfated polysaccharides characteristic of the particular species from which they are isolated. The hydrocolloids extracted from the brown algae are mainly salts of mannuronic and guluronic acids. These substances as a group are known as algins (2, 3).

The only products considered in this report are the brown algae (*Laminaria* sp. and *Nereocystis* sp.), also referred to as kelp, and the red algae, *Porphyra* sp. and *Rhodymenia palmata* (L.) Grev., also referred to as dulse, and the materials derived from these species.

III. CONSUMER EXPOSURE DATA

A National Research Council subcommittee has provided information on the possible daily human intake of such algal products as agar-agar, alginates, and carrageenan (8). However, the report contains no information on the consumption of algae, kelp, or dulse as such, or of materials derived from them. The Select Committee has found no consumption data that would provide an adequate basis for determining the level of consumer exposure to these products in the United States. However, since they appear to be used, if at all, exclusively in connection with spices, seasonings, and flavorings, it is presumed that human consumption of these substances is small.

IV. BIOLOGICAL STUDIES

Apart from related substances already evaluated in other reports of the Select Committee (3, 4, 5), most of the relevant work on algae has been carried out with *Laminaria* sp. and substances derived from them.
Laminine mononitrile, [(5-amino-5-carboxypentyl-trimethyl ammonium) mononitrile], isolated from L. augustata (Kjellman), has been studied in some detail. Ozawa et al. (9) reported the intravenous LD$_{50}$ for mice to be 394 mg per kg and the subcutaneous LD$_{50}$ to be about 3 g per kg. They also reported that intraperitoneal injections of 500 mg per kg produced no characteristic change in mice other than weak tremor of the hind legs and hypomobility; 200 mg per kg by the same route exerted no effect. These investigators studied the pharmacologic effects of laminine mononitrile and concluded that it had anti-histaminic properties and exerted a musculotropic relaxing effect on excised smooth muscles of mice and guinea pigs. In addition, they found that laminine mononitrile depressed toad cardiac function in situ and in vitro in concentrations above $10^{-4}$ Molar. The effects seemed to be dissociated from the action of the citrate moiety. Transitory hypotensive effects on blood pressure were observed in rabbits at doses of 10 to 30 mg per kg administered intravenously.

Laminarin sulfate is recognized as an antilipemic heparinoid that does not exhibit anticoagulant effects (10). Rabbits fed cholesterol and administered subcutaneous injections of 7.5 mg of laminarin sulfate per kg of body weight daily, exhibited fewer atherosclerotic lesions than rabbits fed cholesterol diets alone (10). Ellis (11) reported that 0.4 mg per ml or more of laminarin sulfate was fatal to young developing frog larvae before they reached the phase of incipient metamorphosis. With sublethal doses, metamorphosis and skeletal development were normal. Sodium heparin and sodium dextran sulfate at the same dosage level caused similar effects. Laminarin sulfate, injected at a dose of 50 mg per kg per day, was reported to induce hepatosplenomegaly and hyperphagocytosis in rats (12).

Fomina et al. (13) have reported that a chemically unidentified laminarin has some antibiotic activity against Staphylococcus aureus and S. albus when injected intraperitoneally in mice. Preobrazhenskaya and Kuznetsova (14) reported laminarin had antibiotic activity in mice infected with Escherichia coli but Fomina et al. (13) observed no activity against E. coli. However, dosage regimens were not specified in either study.

Solarino (15) found that laminarin did not alter the onset or growth of 3,4-benzpyrene sarcomas in rats but accelerated the onset and growth of a transplantable reticulosarcoma in rats. Intraperitoneal or intravenous administration showed no antitumor activity in mice with either Ehrlich ascites tumor or Sarcoma-180 (13).
McCandless (16) studied the effects of several polysaccharides on connective tissue growth in the abdominal wall of the guinea pig. Subcutaneous administration of laminarin from L. longicurris did not stimulate collagen production or fibroblast proliferation. In contrast, agar, agarose, carrageenann, and furcelleran did stimulate connective tissue growth.

There has been considerable interest in the use of algae and dried algal meals as animal feeds and supplements for animal feed. Lunde (17) reviewed a number of feeding experiments on rats, poultry, hogs, and horses in which algal meal prepared from Ascophyllum sp. and Laminaria sp. were fed at various levels. He concluded that the addition of 5 to 10 percent algal meal to the diet did not alter its feed value. Much larger amounts were recommended with caution, because of the iodine and mineral salt content of the algae. Black (18) in a review of the literature concerning the use of brown algae as feed for pigs, sheep, cows, horses, and poultry, had reported that when the diet contained 10 to 20 percent Ascophyllum or Laminaria meal, ruminants were more capable of utilizing the meal than other animals. When 20 percent of this type of algal meal was added to the feed of hens, the mineral metabolism was upset, although 10 to 15 percent was acceptable.

MacIntyre (19) has studied the effects of dried ground seaweed meal made from Fucus sp., Vasciculosus sp., and A. nodosum. Hens were given rations containing 10 to 50 percent seaweed meal for periods of 4 to 8 days. The seaweed was poorly digested by the hens even at the 10 percent level. In another study, pullets were fed rations containing 10 to 20 percent of L. cloustoni, A. nodosum or L. saccharina for periods of 14 to 16 days (20). The high chloride content of all three algae caused greatly increased water consumption and excessive excretion of water and chloride. While this did not appear to affect the general health of the birds, there was weight loss and reduced egg production. This was attributed to the lower feed value of the meal. Similar results were obtained when L. cloustoni and A. nodosum were fed at levels of 10 and 15 percent for 100 days (20).

Tsujimuro et al. (21) fed rats a flavin-deficient diet which was supplemented with powdered L. japonica at levels of 1 g per day. The animals on the flavin-deficient diet without supplement showed poor growth and roughing of the fur; some animals died. However, the flavin-treated and algae-fed groups both showed normal growth and smooth fur. Further, the L. japonica group grew more rapidly than the flavin group, indicating that L. japonica contained nutritional factors in addition to flavin.
Carrazzoni et al. (22) fed female sheep on rations containing 100 to 300 g of dried ground unwashed M. pyrifera per day for a period of 60 days and observed no toxic effects. No variations were found in the blood concentrations of calcium, magnesium, phosphorus, urea, total protein, red blood cell count, or hemoglobin values. No digestive disturbances occurred. Conception, gestation, and parturition of all animals were normal. No significant differences were observed in the quality of wool derived from the sheep. The authors concluded that the use of this form of algae in the feed was completely harmless to the health of the animals.

No effect upon the milk yield was reported to occur in cows fed 10 percent of meals consisting of A. nodosum and L. cloustoni (23). A further study was carried out by Berry and Turk (24) on 74 heifers fed kelp meal at four percent of the feed mixture. The animals were maintained on this feed through completion of their first gestation period and 52 of the animals were followed through completion of their second gestation period. No significant adverse effects on weight gain, calving, lactation or milk yield resulted from feeding the kelp meal.

Studies have been carried out on the effects of L. japonica and Porphyridia sp. on thyroidal uptake of iodine in man (25). The authors indicate that these two algae are ingested by many people in Japan as everyday foodstuffs. In 10 normal subjects ingesting 7 to 16 g of L. japonica (0.31 percent iodine) for 1 to 14 days, a marked decrease occurred in the 24-hour thyroidal uptake of $^{131}$iodine. Preingestion values returned within two weeks after termination of the intake of algae. When 1.2 to 3.2 g of baked Porphyridia (0.03 percent iodine) were consumed per day for 2 to 14 days, no effect was observed on thyroid uptake. When 10 g of L. japonica was ingested per day by four patients with exophthalmic goiter, the thyroidal uptake of $^{131}$iodine was markedly suppressed. This response returned to preingestion values within two weeks. These results are consistent with and can be explained on the basis of the iodine content of the algae ingested.

In the Far East, seaweeds have been an accepted food for humans for centuries, constituting up to 25 percent of the diet (2, 26).

Jones et al. (27) have shown recently that mercury is present in several species of algae in an estuary in Scotland and have reported that other investigators have observed significant quantities of mercury in algae in other parts of the world.
Aside from the study of Solarino (15) on the effects of parenteral administration of laminarin on certain tumors, the Select Committee is not aware of data in the literature which pertain to the carcinogenic, mutagenic, or teratogenic effects of algae, kelp, or dulse. Also, the Select Committee has no information on the wholesomeness of agaroid, fucoidin, funorin, or iridophycin.

V. OPINION

The term, "algae", is too ill-defined to be a meaningful term in the context of the GRAS list. The uncertainty with respect to the source and the nature of these materials makes it imprecise to attempt to evaluate the health aspects of the use of substances that simply bear the designation brown algae, red algae, or algae. This is particularly pertinent because of the variation in the chemical constituency of the several species of algae that have been reported to be used in food. In addition, the fact that there are no data available on the usage or consumption of algae, kelp and dulse, raises a question as to whether or not any of these materials are now being used in foods in the United States.

The Select Committee believes that the extent of actual use of algae, kelp, and dulse in food should be ascertained. If they are found to be used to any considerable extent, it would be advisable to identify them more definitely for regulatory purposes. Further, in view of the probable absorption of metals by algae from polluted waters, permissible levels of mercury and other heavy metals should be specified for the materials so identified.

However, within this context, and in the light of available biological data, an interim conclusion can be drawn. The biological information available with respect to algae, dulse, and kelp and certain substances derived from them, is limited to studies on laminine monocitrate and laminarin sulfate, and to feeding trials involving fodder containing dehydrated algal meals and dried seaweed prepared from several species of brown and red algae. These investigations, involving several animal species have revealed no evidence of adverse effects from the feeding of the algal species tested or their derived products at levels that are orders of magnitude above those presumed to be used in foods in this country as ingredients of spices, seasonings, and flavorings.
The Select Committee has weighed the foregoing and concludes that:

There is no evidence in the available information on the brown algae (Laminaria sp. and Nereocystis sp.), also referred to as kelp, and the red algae, Porphyra sp. and Rhodymenia palmata (L.) Grev., also referred to as dulse, and the materials derived from these species, that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when they are used at levels that now seem to be current or that might reasonably be expected in future if their use is confined to ingredients of spices, seasonings, and flavorings as is now stated in the Code of Federal Regulations.
VI. REFERENCES CITED


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Report submitted by:

January 23, 1974
Date

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