Fish Oil Research, 1920-87, in the National Marine Fisheries Service, NOAA

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ABSTRACT—Research on extracted fish oils carried out by the National Marine Fisheries Service and its predecessor laboratories from its early beginnings in 1921 to the present time are reviewed. The work, after a slow start, was greatly expanded during the decade beginning in 1955 when Saltonstall-Kennedy (S-K) funding allowed both inhouse and contract programs to be carried out, primarily based at the Seattle Technological Laboratory. After the decline in such work during the 1970's, such research has become important again during the 1980's at all three of the NMFS Utilization Laboratories. Projects concerning research on the nutritional and medical effects of long chain omega-3 fatty acids of fish oils are also discussed.

Introduction

Recently, a great deal of publicity has been and is being given to findings that long-chain omega-3 fatty acids (which occur almost exclusively in the oil of fish) may have beneficial effects in reducing the incidence of heart disease and certain other medical conditions (Stansby, 1985). These findings result from research carried out over many years, and part of the early research along these lines was done at laboratories financed by the National Marine Fisheries Service, NOAA, and its predecessor agencies. Other research has also been carried out by laboratories of this agency on other aspects of fish oils which have various industrial applications. This paper summarizes such research which began about 1920 and continues today.

Research is described here which took place not only in the National Marine Fisheries Service (NMFS) which started operation in 1970 but also at its predecessor organizations, the Bureau of Fisheries and Bureau of Commercial Fisheries (BCF). The research discussed here is largely devoted to work on fish oils occurring as oils themselves rather than with fish oils in fish flesh. Thus, not included here is any mention of the considerable research dealing with storage changes in frozen fish which involves, among others changes, alterations, especially rancidity development, of the oil within the fish.

While discussion is included here on various aspects of extracted fish oils, special attention and more detail is included on nutritional properties on such medical conditions as heart attacks.

Research on extracted fish oils can be divided into several time periods. The earliest work, carried out at several laboratories between 1921 and 1953, is designated as "Early Research." Research since 1953 has been carried out for the most part at the Seattle, Wash., College Park, Md., and Charleston, S.C., laboratories. This research is designated as "Modern Work on Fish Oil." It initially was carried out to a large extent at Seattle where, for about 10 years beginning in 1955, large amounts of Saltonstall-Kennedy (S-K) funds were available for research on fish oils. Such work tapered off about the middle of the 1960's at Seattle. Work on fish oils thereafter and up until about 1980 was concentrated largely at the College Park Laboratory and its successor, the Charleston Laboratory. Beginning in about 1980, modern fish oil research programs have been devoted largely to nutritional properties of fish oil and are here described in the section "Nutritional Aspects of Fish Oil."

Early Research, 1921-53

The first research within the Bureau of Fisheries on fish oils occurred in 1921. This is not surprising even though the NMFS dates back to 1871 when it was known as the U.S. Fish Commission. For just a few years in the 1870's and 1880's some research was carried out on technological aspects, especially composition of fish, which were felt by the agency's first Commissioner, Spencer F. Baird to be important. Baird died in 1887, and no more technological work was undertaken until 1918. At that time, new personnel believed that the agency, which had devoted all its attention to biological and statistical endeavors, ought also to include technological aspects. In 1921, chemical research was carried out at an agency laboratory, then located in Washington, D.C., to determine fat constants of fish oils. Although this work was never published, the results were passed on to companies who might be potential customers for fish oils.

From 1926 to 1930, research was carried out by Roger Harrison and associates at a laboratory at Reedville, Va., on fundamental aspects of the operation of the menhaden industry. Menhaden is used not for human food but rather for manufacture of fish oil, fish meal, and fish solubles, all industrial products. This 4-year study resulted in a 113-page publication (Harrison, 1931) giving voluminous detail of menhaden oil manufacture.

In 1933, a study was made at Gloucester, Mass., on oxidation of mackerel oil (Stansby and Lemon, 1941), as a part of a longer study on handling fresh mackerel. This was probably the first research on oxidation of fish oil carried out not only by our agency but anywhere else.

From 1932 to 1950, many studies were carried out on vitamin A content of fish oils. This research began in Gloucester,

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Mass., in 1932 and was carried out by Harrison and Anderson who comprised the agency's authorities on fish oils. When they were transferred to Seattle in 1933, this work was continued. Eventually a fairly extensive series of research studies were carried out by Sanford (1945); Sanford et al. (1946); Sanford and Bonham (1947); and McKee et al. (1944). This vitamin A in fish oil work ceased in 1950 when synthetic vitamin A became available. At least in the United States, it was so much less expensive to use the synthetic vitamin A than to process fish livers that that industry was no long feasible.

In 1937, a research project was started by Harrison to develop an improved method for extracting fish oil from fish meal. Initially, the oil content may run, for example 10 percent, but owing to the oil somehow complexing with the protein, conventional ethyl ether extraction methods used for fish meal stored for some time may give as little as 1 percent oil. Many methods were tried by Harrison from 1937 to 1942. When he was transferred to Washington, D.C., the work was continued by Stansby up to 1953, and a modified acid hydrolysis ether extraction method was developed (Stansby, 1948) which was adopted by the Association of Official Agriculture Chemists for inclusion as an official procedure in their book of methods. The work as described above covers all the work carried out by the Seattle NMFS Laboratory on fish oils up to 1953.

Modern Work on Fish Oil, 1953-87

Research at Seattle

In 1953, the Seattle Technological Laboratory initiated a research program to learn more about the chemistry of fish oils. For 2 years some small-scale research was carried out on fractionation of fatty acids by urea complexes. Work also got underway on methods for preparation of new compounds such as alcohols, amines, and silicones.

The work on fish oil chemistry was expanded between 1955 and 1967 owing to availability to the laboratory in Seattle of relatively large amounts of S-K funds. Several new chemists were added to the staff, and many research contracts with other laboratories were funded. The extent of research under this expanded program was so great that it is not feasible to describe it to any significant extent here. From 1955 through 1965, 107 research papers on the chemistry and nutritional value of fish oils were published as a result of the availability of S-K funds to the Seattle Laboratory. These included 56 papers by Seattle authors on research in the Seattle Technological Laboratory as well as papers by contractors for the Seattle Laboratory. The contractors were largely either the University of California (primarily the Department of Food Science and Technology and the Institute of Marine Technology both at Davis) and the University of Minnesota (Hormel Institute at Austin and the School of Mines and Metallurgy at Minneapolis). The extent of research on fish oils during this 10-year period was greater than that which has been carried out either before or since that time. Much of the research of this program has been documented in papers by Stansby and Butler (1958) and Karrick (1965). The book by Stansby (1967) on fish oils, now out of print, remains the most modern book on this subject.

In 1967, the large, expanded fish oil program at the Seattle Technological Laboratory ceased shortly after (1 July) when most of the laboratory came under its new director, Maynard Steinberg. A portion of this laboratory, however, became the Food Science Pioneer Research Laboratory under Stansby, and a major portion of its program dealt with oxidation of fish oil. Actually, this new laboratory remained in existence for only about 3 years, because in 1970 a massive reorganization took place with the Bureau of Commercial Fisheries in the Department of Interior being moved to the Department of Commerce under the new name of the National Marine Fisheries Service. At about that time, the personnel of the Food Science Pioneer Research Laboratory became the first unit called the Environmental Conservation Division of the Northwest Fisheries Center. Thus only a small amount of work was accomplished on the fish oil oxidation project.

Perhaps the most important finding of this short-lived laboratory was that fish oils while in the flesh of freshly caught fish, oxidized very slowly during storage of such fish in ice. As long as such fish remained unfrozen, the oxidation rate was very small. But as soon as anything was done to eliminate bacterial spoilage (e.g., freezing) the rate then increased tremendously. It appeared as if the microorganisms used most of the oxygen leaving little for reaction with the oils. Unfortunately, this project had to be terminated before this matter could be further investigated.

At Seattle no more work on fish oils was undertaken until the early 1980's. At that time considerable work was undertaken by the Seattle Utilization Laboratory to investigate the possibility of carrying out fractionation of fish oil fatty acids employing supercritical carbon dioxide extraction. A very successful fractionation is possible by this procedure especially when partially fractionated fatty acids are employed (Nilsson et al., 1988). Such methods make possible the preparation of eicosapentaenoic acid (EPA) or docosahexaenoic acid (DHA) at purity levels well over 90 percent. Two U.S. patents were awarded to two staff members on this process (Stout and Spinelli, 1987; Spinelli et al., 1987).

Most of the work was carried out on menhaden oil. Several Pacific Coast species were tested for EPA and DHA content. These included Alaska pollock liver oil and Pacific whiting oil, both high in EPA, and several tuna oils very high in DHA (23-29 percent).

Work was also carried out on storage of fish oils or fish oil fatty acid concentrates in pressurized cans under inert gas and with provision for metering out predetermined amounts of the contents. Such a procedure precludes any loss from oxidation for an indefinite period of time.

Research at College Park, Md., and Charleston, S.C., Laboratories

When S-K funds became available in 1955, the Technological Laboratories at Seattle and College Park received financing from them for research on fish meal and fish oil. After about 3 years, how-

ever, the BCF headquarters directed the College Park Laboratory to work on fish meal and the Seattle Laboratory to work on fish oil. There was, however, about a 3-year period when College Park carried out, largely on contract, work on uses of fish oils. For example, one such contract dealt with uses of fish oil in the leather industry (Matei and Roddy, 1958).

Later, toward the end of the 1960's and after the Seattle Technological Laboratory had discontinued its fish oil program, the College Park Laboratory began research (Kifer and Miller, 1969). Much of the work at this period dealt with feeding of fish oil to poultry (Miller et al., 1969) but some involved feeding it to animals (Kifer et al., 1971).

During this period, research was also carried out by George Knobl and Preston Smith at College Park, Md., on adapting the chloroform-methanol extraction procedure to determination of the oil content of fish meal.

During the 1980's the Charleston Utilization Laboratory carried out considerable research on fish oils, especially menhaden oils. They prepared a very exhaustive literature search on fish oils (Bauersfeld and Winemiller, 1985). The laboratory set up complete analytical facilities for running fish oil fatty acid content studies and made analyses of many fishery samples, especially of menhaden (Joseph, 1985). Research was also carried out on rates of oxidation of lipids in fish (Joseph and Seaborn, 1982). Additional Charleston Laboratory research relating to an FDA petition to permit menhaden oil to be used in food for human consumption and to its major role in omega-3 fatty acids research (jointly with the National Institutes of Health) is described in the section on "Nutritional Aspects of Fish Oils."

Research at the Gloucester Laboratory

Not until 1980 did the Gloucester Laboratory become involved in fish oil research. That year a small program was initiated, including looking into variations in cholesterol and fatty acids content of different fishes, especially those of the New England area (Krzynowek and Murphy, 1987). Considerable study was also made into separation of fish oil fatty acids by High Performance Liquid Chromatography (HPLC), particularly at a scaled-up level.

Nutritional Aspects of Fish Oils

Most of the material in this section relates to the nutritional aspects dealing with the effects of the polyunsaturated fatty acids in fish oils upon serum cholesterol levels and particularly upon alleviating certain diseases. To help put the NMFS research into perspective, it is important to include references to some of the studies carried out in this field by other investigators.

During the 1940's and early 1950's it was learned that polyunsaturated fatty acids in the diet lowered serum cholesterol levels. At this early period it was believed that the best measurement of the effects of different oils in this respect was to determine the ratio of polyunsaturated to saturated fatty acids in the oil. It was supposed that this ratio was directly proportional to the ability of the oil, when used in the diet, to lower serum cholesterol levels. Many vegetable oils had a very high such ratio. On the other hand, fish oils had a low ratio, often around one; i.e., there were often as many (sometimes even more) saturated than polyunsaturated fatty acids in fish oils. Because of this fact in the early period of research in this field, fish oils were never used. In 1956, however, a paper appeared (Bronte-Stewart et al., 1956) which showed that fish oils were as effective (and usually a great deal more effective) than vegetable oils in lowering serum cholesterol levels when taken in the diet.

While Norway was occupied by Nazi forces during World War II, the diet changed because of a scarcity of certain foods including meat. Medical records showed that during this period there was a definite decrease in the incidence of heart attacks (Strom and Jensen, 1951). There was very little known about this and what few publications appeared gave no insight into how diet might have been involved. In 1946-47 Averly Nelson, a Seattle physician, interrupted his practice to take a year of courses at the University of California at Los Angeles (UCLA) which led to a degree in Medical Science. At that time, several of his professors at UCLA who knew about the decrease in heart disease during the Nazi occupation of Norway discussed these ideas in detail among themselves and with Nelson.

One aspect concerned the fact that considerably more fish was used in the Norwegian diet during the period when the incidence of heart disease declined. Nelson was very much impressed by these ideas. In 1953, he began to specialize in treatment of patients referred to him for his interest in recommending diet change for individuals who had suffered one or more heart attacks. He therefore suggested to his patients, beginning in 1953, that they eat fish at least three times per week as the main course of a meal. Because the evidence at that time had led to the idea that fish oil was of no value in the diet for reducing serum cholesterol levels, Nelson did not mention this aspect in some of his very early publications of his results.

Nelson's final paper covered all of his 19 years of study (Nelson, 1972). It clearly showed that individuals who had suffered at least one heart attack and then went on a diet including use of fish as the main course at a minimum of three times per week had considerably fewer subsequent heart attacks. In this long-term study involving several hundred patients, those who did not include fish in their diet suffered 4.5 more heart attacks than those who did follow the recommendation of fish (which became a mandatory part of the diet for the last 15 years of the test). Nelson died in 1973 and possibly because his paper was published in a journal not ordinarily read by those interested in coronary disease, his work was almost unknown. A summary of its findings, however, has been published more recently (Stansby, 1982).

In 1953, at the same time that Nelson began his work on diet for heart patients, the Seattle Fishery Technological Laboratory of the Bureau of Commercial Fisheries began its work on fish oil research. Nelson, soon learning of the interest of laboratory staff, contacted Stansby on many occasions by phone and talked at great length about his project. He invited Stansby on several occa-

sions during subsequent years to talk to his patients about fish and fish oils.

In 1955, with the advent of greatly expanded research by the Seattle Laboratory for fish oil investigation, some work was begun on looking into effect of ingestion of fish oil among the laboratory staff members, and correlating its effect on serum cholesterol levels. It was decided, however, not to pursue such work further in-house. Instead, beginning in 1957 a series of research contracts were begun at the Hormel Institute of the University of Minnesota. Walter Lundberg, director of that laboratory, was the first to head such research on nutrition of fish oils. Soon, however, James Peifer of that laboratory continued the contract research. Many papers resulted from this research which greatly strengthened proof that fish oils could, better than any other oils, act as serum cholestrol depressants. Much of the results of this research was published by Peifer (1967) as a chapter in a new book on fish oils. This and some later work is also summarized elsewhere (Stansby, 1969). This publication is probably the first to ascribe some of the important potential medical effects of fish oil to its content of omega-3 fatty acids (Stansby, 1969:88-90).

During the 1970's, almost no research was carried out within NMFS laboratories on nutritional properties of fish oils. The one exception was at the College Park Laboratory. This laboratory had specialized for many years on programs involving the nutritional properties of fish and fishery products. Included in such studies during the 1970's were a few small projects in which menhaden oil was fed to animals.

The College Park Laboratory was transferred to Charleston, S.C., during 1978. One of the projects in which fish oil was involved had been discussed shortly before this transfer was made from College Park to Charleston. This stemmed from the interest at that time by the menhaden industry in the possibility of selling some of their menhaden oil for partial hydrogenation and use in the United States for adding to margarine. For many decades the menhaden industry had been shipping most of their fish oil to Europe where it was partially hydrogenated and then added to margarine or shortening for human consumption. Regulations of the U.S. Food and Drug Administration had precluded such use in the United States pending establishment by lengthy feeding tests proof that such oil was safe[1]. Upon the transfer of the laboratory from College Park to Charleston one of the first new programs which was being requested by the menhaden industry was the undertaking of such work using S-K funds. During the first part of the 1980's much of the attention of the Charleston Laboratory's staff went into this program. At present, the data from such contract research on menhaden oil is being studied by the Food and Drug Administration.

During the current decade, all three of the NMFS utilization laboratories have become involved in several aspects of determining the nutritional value of the long-chain omega-3 fatty acids in fish oils. Present indications are that these omega-3 long chain fatty acids probably are involved in minimizing incidence of heart disease for reasons which go beyond the mere lowering of serum cholesterol levels. There also are indications that the long-chain omega-3 fatty acids may be useful in minimizing the incidence or severity of several other human diseases.

These ideas originated from research carried out during the 1970's by investigators in Denmark. They had noted beliefs that Eskimos living in remote areas of Greenland seldom suffered from heart attacks. Several trips were made to such areas of Greenland by competent Danish medical statisticians who confirmed that those beliefs were well founded. Then several researchers, notably Bang and J. Dyerberg and their staffs, carried out studies which indicated that the beneficial effects stemmed from the presence of long-chain omega-3 fatty acids in the diet of Eskimos who ate almost nothing except the flesh of fish and marine mammals. The omega-3 fatty acid, eicosapentaenoic acid (C20:5), was studied especially. It was shown that its presence in the diet promoted altered prostaglandin formation and diminished the tendency toward blood platelet aggregation. Research by Hamberg et al. (1975) showed that such aggregation was promoted by the presence of the prostaglandin thromboxane-A_2 (TXA_2). Other research by Moncada et al. (1976) showed that the reverse action of inhibiting blood platelet aggregation was induced by the presence of another prostaglandin, prostacyclin (PGI_2). The Danish investigators suggested that the effectiveness of the omega-3 long chain fatty acid, eicosapentaenoic acid (C20:5), was caused by the alteration in the amounts of these two prostaglandins such that the ratio of PGI_2 to TXA_2 was increased. The research of these workers is very well summarized by Dyerberg (1982).

After publication of several of the papers of Danish scientists in this field, analogous research began in other countries, especially Great Britain, Germany, the United States, and Japan. Probably the first individuals in the United States to begin work in this field were William E. M. Lands and coworkers at the University of Michigan. They made studies during the late 1970's on effects of fish oils fed to cats on strokes (Black et al., 1979) and effects when fed to dogs (Culp et al., 1980). Lands, now at the University of Illinois Medical School in Chicago, has also written several articles and books on the general aspects of these effects of fish oil omega-3 fatty acids (Lands, 1982, 1986; Lands and Bimbo, 1983).

Many research papers have also been published by staff members of the University of Oregon Health Sciences Center, Portland, especially by W. E. Connor, S. H. Goodnight, W. S. Harris, and D. R. Illingworth. In this work, salmon oil has been the major fish oil used for tests with human subjects (Goodnight et al., 1982; Harris and Connor, 1980).

By far the largest portion of research carried out to date has related the effects

[1]Hydrogenated California sardine oil was used in margarine for many years when there were no Food and Drug Standards for margarine. About 1940, the California sardine disappeared, and shortly after the Food and Drug Administration began hearings on standards for margarine. Since no one appeared from the then-defunct sardine oil industry, nor from the menhaden oil industry, no consideration was given to blanket in fish oil (after hydrogenation) as an acceptable component. Had anyone then appeared, such fish oil would have probably been accepted as a generally regarded as safe (GRAS) ingredient.

of the long-chain, omega-3 fatty acids which occur primarily in fish, to effects on coronary diseases. The effect of aspirin (closely related to the mechanism of the omega-3 fatty acids effects) applies not only to coronary diseases but also to a variety of inflammatory diseases such as arthritis. It is, therefore, not surprising that some limited research indicates similar beneficial effects of omega-3 fatty acids on a number of inflammatory diseases. Furthermore, a relatively small number of investigations have suggested that fish oil omega-3 fatty acids may be effective in treatment of several other medical conditions such as breast cancer. Much more research must be published, however, before these preliminary findings can be established on as firm a basis as is the beneficial effects upon coronary diseases.

Very little research had been conducted by the National Marine Fisheries Service on the role of long chain omega-3 fatty acids in fish during the 1970's. A conference on the nutritional evaluation of long chain fatty acids in fish oils was held in London in 1981 (Barlow and Stansby, 1982). This conference consisted mostly of papers aimed at determining whether or not the fatty acids in partially hydrogenated fish oil contained sufficient harmful fatty acids (i.e., erucic acid) to make them unsafe for use in margarine. However, three papers were also presented on some of the newer ideas about beneficial effects of fatty acids in connection with heart disease. These three papers by individuals with different backgrounds raised considerable attention and brought up the question as to whether more widespread research was needed along these lines.

The NMFS then set up an outside committee to look into this matter and to recommend whether NMFS should carry out research in this field. The committee recommended that the NMFS should first aid in the sponsoring of research meetings in this field. Two such meetings were held. The first one entitled "n-3 Fatty Acids" was held at the University of Reading, England, in 1981. It was jointly sponsored by the National Marine Fisheries Service, the International Association of Fish Meal Manufacturers, General Mills Co., Merck Co., Sharp and Dohm Co., the Seven Seas Health Care Co., and the R.P. Scherer Corp. A second somewhat similar meeting was held in 1985 in Washington, D.C., entitled "Health Effects of Polyunsaturated Fatty Acids in Seafoods," and was cosponsored by the National Institutes of Health and the NMFS. At both meetings many papers were presented on research at various laboratories investigating the effects of omega-3 fatty acids on various medical conditions.

More recently a cooperative program has been undertaken between the National Institutes of Health (NIH), the Alcohol, Drug Abuse and Mental Health Administration (ADAMHA) and the NMFS for research on effects of long-chain omega-3 fatty acids in fish or fish oil and its components upon medical effects in humans. Under this project, the NIH will contract out research programs to clinical and other laboratories. The NMFS, using its Utilization Laboratories at Charleston, S.C., Gloucester, Mass., and Seattle, Wash., will conduct research on methods of preparing omega-3 concentrates or highly purified fatty oils. Research is going on at Gloucester and Seattle to develop procedures for preparing small-scale amounts of such material. The Charleston Laboratory has set up facilities to prepare the large quantities which will be required for the NIH contractors.

Future Research

Much research is already well under way in the area of the biochemistry and metabolism of omega-3 fatty acids in the diet. This long-term research is required before recommendations can be made to make any drastic changes in diet involving large omega-3 fatty acid intake. There are, however, several other aspects about which very little is currently known.

One such need is to learn how small an amount of long-chain omega-3 fatty acid in the diet could make any meaningful effect. The Greenland Eskimos studied ate largely marine flesh foods. They thus got very large amounts of such fatty acids. In most of the biochemical investigations to date, the individuals or animals received still fairly high dietary amounts, though not as much long-chain omega-3 fatty acids as the Greenland Eskimos. This has been done to insure that enough omega-3 is present so the biochemical and metabolic changes will take place and can be studied. Thus, we can not yet say either how much fatty fish needs to be eaten or how much fish oil needs to be consumed to obtain even a minimal benefit. Quantitative investigation is much needed to resolve this problem.

By far most of the research to date has concentrated on the fish oil long chain C20:5 fatty acid, eicosapentaenoic acid. Very little work has been done with the other major long-chain fatty acid of fish, the C22:6 docosahexaenoic acid. The few studies made show that the C22:6 omega-3 fatty acid does have some benefit. More attention should be paid to it, and, perhaps also, to some of the other long chain omega-3 fatty acids which occur in smaller amounts in fish oil (e.g., C22:5 omega-3 fatty acid).

Perhaps most important is the need to study the range of fatty acid values within the oil of different species of fish (Stansby, 1981; 1986). Originally, it was not realized that there is a very large variation in the fatty acid make-up of the oils of the same species of fish, from one individual to another, from season to season, from year to year, and from one catching area to another. Because this was not understood many papers have appeared giving what purports to be the fatty acid make up of the oil from a given species. If one examines the data it is apparent that in most every case the values reported relate only to the few fish included in the research but have little or nothing to do with the values for the species as a whole. Unfortunately, however, tables of such values are being published which often give very misleading results.

This situation is analogous to the early studies on fat content of fish. The first investigation in the United States of the proximate composition of fish was that of Atwater (1888). Of the various items analyzed in a proximate composition of fish, the component showing the greatest range of values is the fat or oil content. Early investigators did not realize this. Thus, they often analyzed

only one or two or sometimes a few more individual fish. To give an example of how erroneous such results can be, the oil content of the common mackerel, *Scomber scombrus*, ranges from about 2 percent for fish caught in the early spring to 12-25 percent for fish caught in the summer. Atwater's investigation used mackerel caught in the spring and reported the fat content to range from 2.3 to 7.7 percent, with an average of 7.1 percent. Since most mackerel are taken in the summer months, the results of Atwater are far lower (less than half) than what is typical for this species. Nevertheless, Atwater's value of 7.1 percent was quoted in tables of food value in books for over 50 years. Unless some adequate investigations of the fatty acid content of the oils of different species of fish are made soon, the same situation could easily develop with tables of omega-3 fatty acid content of fish oils.

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