# The role of seafood* for human health

By

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*Denotes freshwater and marine fish as well as shellfish.

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# 1. Preface

Dietary fat research is currently to a large extent focussed on effects of individual fatty acids as related to health. This includes the essential omega-3 and omega-6 fatty acids from plant origin and the very long-chain omega-3 polyunsaturated fatty acids (VLCn-3PUFAs) of marine origin. The individual dietary fatty acids have distinctive functions and physiological and other effects with consequences for health and disease. With the recent discovery that fatty acids are modulators of nuclear transcription factors influencing genes and gene products this research has attained a new dimension. In addition, the focus is now pointed towards the food chain from feed resources, food production and the impact of food on human health. This report reviews the scientific evidence for the beneficial effects of VLCn-3PUFAs and seafood consumption with respect to human health.

## 2. Summary

The very long-chain n-3 polyunsaturated fatty acids (VLCn-3PUFAs) found in seafood have been extensively studied, and along with seafood they have been shown to have a positive effect on a number of diseases including chronic diseases like cardiovascular diseases, cancer, and immune and inflammatory diseases. However, much less attention has been paid to the original source of these important fatty acids, namely seafood itself. Seafood has been an important component of the human diet througout human evolution. Studies of existing hunter-gatherer populations and of archaeological dietary information suggests that the ratio of n-6 to VLCn-3PUFAs were about 1:1. This ratio changed little until the event of agricultural and industrial revolutions when cheap and plentiful vegetable oils (rich in n-6 fatty acids) were included in the diets of man and his livestock. Thus, intake of new foodstuffs concomitant with a reduced seafood intake has led to ratios between n-6 and n-3 fatty acids in the human diet closer to 10-15:1. In this ratio alfa-linolenic acid (ALA, 18:3n-3), which is found mainly in vegetable oils, is included. Thus, the current ratio between n-6 and VLCn-3PUFAs in our diet is much greater than 10-20:1. Seafood represents a good source of VLCn-3PUFAs in addition to other health promoting nutrients. An increased consumption of safe, nutritious, and high quality seafood can help to ensure a properly balanced diet and possibly improved human health. With respect to the diet and human health, more research is necessary to define how diet (particularly dietary fat and seafood) affects e.g. lifestyle disease (e.g. the metabolic syndrome). Thus, in addition to epidemiological studies, well designed, long-term multicenter dietary intervention studies must be undertaken if dietary guidelines are to be based on scientific valid data.

## 3. Introduction

The interaction of genes and environment, nature, and nurture is a main determinant for health and disease. During the last two decades, by use of techniques of molecular biology, it has been shown that genetic factors determine susceptibility to disease and environmental factors determine which genetically susceptible individuals will be affected [1]. Nutrition is an environmental factor of major importance. Whereas major changes have taken place in our diet over the past 10,000 years since the beginning of the Agricultural Revolution, our genes have not changed much as the spontaneous mutation rate for nuclear DNA is estimated at 0.5% per million years. Using the tool of molecular biology and genetics, research is defining the mechanisms by which genes influence nutrient absorption, metabolism and excretion, and the mechanisms by which nutrients influence gene expression. Dietary fatty acids have been, and probably are, the most important energy source for most humans but the role in gene regulation has just recently been addressed [2-5]. The rapid changes in our diet, particularly during the last 100 years, can be potent promoters of chronic diseases such as atherosclerosis, hypertension, diabetes, many cancers and lifestyle diseases (e.g. metabolic syndrome and obesity) causing great concern for health authorities worldwide [6].

The early literature describing the disease and dietary patterns among Arctic Inuits documents the unusually low frequency of diseases common in the more “civilised” temperate latitudes [7,8]. Early fatty acid analyses had uncovered ω-3 fatty acids and there were isolated reports in the medical literature of their effectiveness in lowering blood lipids [9-12]. It had been known since the 1940s that Greenland Eskimos did not develop heart disease despite their high fat consumption [13,14]. However, it was not until Danish scientists vigorously pursued this anomaly that the importance of the Eskimo diet was more widely recognised. The Inuit diet revealed not only a higher fat and cholesterol content than typical European diets, but also substantial amounts of VLCn-3 PUFAs which were virtually absent from many European and North American diets. This led Bang, Dyerberg and colleagues to hypothesise that VLCn-3 fatty acids were linked to low cardiovascular mortality [15-20].

## 4. Seafood: definition and nutritional characteristics

The definition of seafood in this report includes primarily marine fish as well as shellfish. Fresh water fish will be mentioned in some connections. In human nutrition, we are concerned mainly with fatty acid data based on the edible portion of foods. For fish that means mainly the fillets, whereas certain shellfish such as clams, oysters, and mussels are consumed whole. With crustaceans, shrimp, lobster, cray fish usually only muscle parts are eaten. As a category, fish vary greatly in their fat content, not only between species, e.g., salmon vs. cod, but also within species. For example, the total lipid in Atlantic mackerel ranges from 5% to 25% throughout the year [21]. Individual fatty acids also vary widely with the season, in contrast to terrestrial animals, especially those mass-produced for food. Fatty acid composition of fish differs from terrestrial animals in having a substantial portion of fatty acids with more than 20-carbon atoms. These consist of 20- and 22-carbon monoenes and very long-chain polyunsaturated n-3 fatty acids (VLCn-3PUFAs) [22]. The two major VLCn-3PUFAs in fish are eicosapentaenoic acid (EPA, 20:5n-3) and docosahexaenoic acid (DHA, 22:6n-3). EPA and DHA differ from the polyunsaturated fatty acids found in plants, being longer, more highly unsaturated and of the n-3 rather than the n-6 type. Fish and shellfish have less than 30% saturated fatty acids [22]. Fish also contain notable amounts of "unusual" fatty acids including; odd-chain [23] and branched-chain [24] fatty acids, monoenes [25] and wax esters [26]. The content of VLCn-3PUFAs in various foods has been summarised recently and fish and shellfish are by far the most abundant source of EPA and DHA in foods [27].

Fresh water fish and certain marine species such as cod, saithe and haddock represent lean fish with a low fat content whereas other species such as herring and mackerel represent oily or fatty fish rich in VLCn-3 PUFA. In addition, the amount of fat and VLCn-3 PUFA varies according to catch area, season and means of preparation [28]. Shellfish generally contain relatively low levels of fat but a major proportion of the fatty acids represent VLC n-3PUFA. Fish represent a rich source of valuable nutrients that may explain the health promoting effect. In addition to being rich in VLC n-3PUFA fish are an excellent source of protein, calcium, selenium, vitamins, taurine and coenzyme Q10 [29]. The vast majority of studies relating seafood intake to human health focus on the VLC n-3 PUFA and cardiovascular diseases and will be described in detail later. The content of VLC n-3 PUFAs in e.g., serum lipids or in red blood cell membranes are commonly used as biomarkers for habitual seafood intake [30,31]. Seafood is a complex matrix and some of the components other than VLCn-3, which have been linked to prevention of cardiovascular diseases, will be addressed first.

## 4.1 Calcium

Fish, particularly small and softboned fish may represent a good source of calcium [32,33] and with a newly developed dual radio- and stable-isotope method for measuring calcium absorption in humans [34], other calcium sources e.g. marine calcium, can be compared to more frequently used inorganic calcium sources like dolomite. Calcium is important for bone mineralisation but may also protect against cardiovascular disease by favourably influencing blood pressure. One meta-analysis of controlled randomised trials found evidence to indicate that dietary calcium supplementation lowers systolic but not diastolic blood pressure. The effect was greatest in those who had low dietary calcium intake to begin with [35].

### 4.2 Selenium

Selenium is an essential trace element [36] and epidemiological studies have reported an inverse relationship of selenium levels in serum with the risk of cardiovascular death [37,38]. Fish is rich in selenium and as selenium is important in the function of a number of anti-oxidant enzymes, such as glutathione peroxidase, it may potentially retard the development of cardiovascular disease via two pathways. One pathway offering protection would be through favourable action of antioxidant enzymes on oxidation of plasma lipids; thereby retarding development of atherosclerosis. The other pathway involves the production of eicosanoids. In selenium deficiency, the synthesis of thromboxane (an eicosanoid that enhances vasoconstriction and platelet aggregation) is favoured over the synthesis of prostacyclin (a vasodilatory eicosanoid) [39]. In a recent study the relationship between dietary intake of fish and non-fish selenium and serum lipids was addressed [40]. Dietary non-fish selenium had a positive correlation between high-density lipoprotein (HDL) cholesterol and an inverse correlation with the atherogenic index in all subjects. On the other hand, fish selenium had no relationship with any serum lipids. This absence of association between the intake of fish selenium and serum lipids could be due to contamination of heavy metals, mainly mercury, in the fish consumed. Selenium is important in the detoxification reactions (acting as an antioxidant) of ingested heavy metals [41,42].

### 4.3 Vitamin D

Fish, and especially fatty fish, is one of the few food commodities that contain vitamin D. It is the main source of vitamin D in the Japanese diet [43] and also in the Norwegian diet accounts for about one third of the intake. Vitamin D is required for normal calcium absorption in the gut and important in bone metabolism in order to prevent osteomalacia and osteoporosis. It is also important in cell differentiation [44]. Therefore, it may theoretically play a role in dampening down atherogenesis, a process that has proliferative features.

### 4.4 Taurine

Seafood is a rich source of taurine [45] and taurine excretion is sometimes used as a marker of seafood intake [46]. Animal studies suggest taurine may reduce serum cholesterol levels by altering the activity of certain enzymes that either influence cholesterol metabolism through bile acid synthesis or inhibits its absorption from the intestine [47]. From other animal studies, taurine has been demonstrated to have antihypertensive [48,49] and antiatherogenic effects [49,50]. Epidemiological studies also revealed that taurine intake correlates inversely with the incidence of coronary heart disease [51,52]. Hyperhomocysteiemia, an independent risk factor for atherosclerosis [53,54] was associated with oxidative stress leading to endothelial cell injury and/or dysfunction [55-57]. More recent papers reveal that homocysteine induces oxidative stress in the endoplasmatic reticulum (ER) of endothelial cells leading to accumulation of proteins and altered function [58-60]. Taurine has been shown to antagonise the effect of homocysteine and restores the secretion and expression of extracellular superoxide dismutase (EC-SOD), a glycoprotein secreted from vascular smooth muscle cells (VSMCs) that protects the vascular wall from oxidative stress [61]. In addition, taurine has been shown to restore the levels of nitric oxide and endothelin-1 to control levels indicating a beneficial impact on vascular endothelial function [62].

### 4.5 Coenzyme $Q_{10}$ (ubiquinone)

Ubiquinone is an important cofactor in the mitochondrial electron transport chain. The concentrations in fish range from 4 to 64 microgram per gram of fish [63]. Ubiquinone acts as an antioxidant and protects low-density lipoprotein (LDL) against oxidation *in vitro* and so may play a protective role against atherosclerosis [63].

## 4.6 Protein

Fish protein has a high nutritional value having the entire complement of essential amino acids and a high digestibility and in terms of nutritive value fish ranks above casein [64]. High intake of fish protein has been shown to be related to a reduced risk of microalbuminuria in young patients with diabetes type I [65].

## 5. Dietary fat and fatty acids: chemistry, nomenclature and essentiality

By far the most important component of dietary fat in quantitative terms is triacylglycerol, which in most diets constitutes > 95% of dietary fat. Each triacylglycerol molecule is composed of three fatty acid molecules esterified to a glycerol backbone, and so fatty acids are a major constituent of dietary fat. Because of the range of foodstuffs consumed, the human diet contains a great variety of fatty acids. The most abundant fatty acids have straight chains of an even number of carbon atoms. The chain lengths vary from 4 carbon atoms in milk fat to 30 in some fish oils. Fatty acids may contain double bonds; these are then termed unsaturated fatty acids, as opposed to saturated fatty acids, which do not contain any double bonds. The number and position of the double bonds differ among different unsaturated fatty acids; if there are two or more double bonds the fatty acid is termed polyunsaturated. It is the nature and the constituent fatty acids (their chain length and degree of unsaturation) that are responsible for the physical properties of fats, specifically determining the temperature at which the fat will melt. Thus, fats that contain a high proportion of long chain saturated fatty acids are solid at room temperature (e.g. lard, butter) while fats that contain a high proportion of polyunsaturated fatty acids are liquid at room temperature (e.g. olive oil, sunflower oil, fish oil).

Fatty acids have systematic names but most also have common names. The systematic name used in the biochemical literature  (nomenclature) indicates the number of carbon atoms in the chain, the number of double bonds in the chain and the position of the first double bond from the methyl end of the molecule (for an overview see [66,67]). It is the position of the first double bond counted from the methyl end of the hydrocarbon chain that is indicated by n-3, n-6, n-7, n-9 or n-11 in the shorthand notation for a fatty acid. Thus, an n-3 fatty acid has the first double bond on carbon number 3 and an n-6 has the first double bond on carbon number 6 counted from the methyl terminus (distal end). The ”n-” notation is sometimes synonymously referred to as ω- or omega. If the position of a double bound is counted from the carboxyl end of the molecule this is indicated by Δ or delta.

Saturated fatty acids and most monounsaturated fatty acids can be made in mammalian tissues from non-fat precursors like glucose or amino acids. This does not usually occur in humans eating a Western diet since the consumption of fat in general, and of saturated and monounsaturated fatty acids in particular, is high. However, mammals cannot insert double bonds between the methyl terminus and carbon number 9 in oleic acid (OA, 18:1n-9). Thus, mammals cannot convert 18:1n-9 into linoleic acid (LA, 18:2n-6). The enzyme that catalyses this reaction is called a Δ-12-desaturase and is found only in plants and insects. Likewise, mammals cannot convert 18:2n-6 into α-linolenic acid (ALA, 18:3n-3). The enzyme that does this is called a Δ15-desaturase and again this is found only in plants and insects. Because mammals cannot make these two fatty acids they are termed essential fatty acids. Also, because mammalian tissues do not contain the Δ15-desaturase they cannot interconvert n-6 and VLCn-3PUFAs. Plant tissues and plant oils tend to be rich sources of 18:2n-6 and 18:3n-3. For example, 18:2n-6 contributes over 50% and often up to 80% of the fatty acids found in corn, sunflower, safflower and soybean oils. Rapeseed oil and linseed oil (also called flaxseed oil) are the richest sources of 18:3n-3, 15% and 60% of the total fatty acids, respectively.

## 5.1 Synthesis of long-chain polyunsaturated fatty acids

Once consumed in the diet 18:2n-6 can be converted via γ-linolenic acid (GLA, 18:3n-6) and dihomo-γ-linolenic acid (DGLA, 20:3n-6) to arachidonic acid (AA, 20:4n-6). Using the same pathway, dietary 18:3n-3 can be converted into eicosapentaenoic acid (EPA, 20:5n-3), docosapentaenoic acid (DPA, 22:5n-3) and docosahexaenoic acid (DHA, 22:6n-3). Thus, there is a competition between the n-6 and n-3 fatty acids for the enzymes that metabolise them. The conversion of 18:3n-3 into EPA and DHA appears to be limited in premature and new-born infants and also in adult humans the conversion into DHA is hardly detectable [68]. Because of the competition between the n-6 and n-3 fatty acid families for the same enzymes dietary intake of VLCn-3 fatty acids will increase production of eicosanoids derived from the n-3 family at the expense of those derived from arachidonic acid. This may have consequences on a number of regulatory mechanisms that will be discussed below. EPA and DHA are found in high proportions in the tissues of oily-fish (e.g. herring, mackerel, fresh tuna, sardines, salmon), in the liver of some lean fish (e.g. cod, saithe) and in commercially fish oils from either the body fat or the liver.

## 5.2 Changes in the pattern of consumption of dietary fat

Large changes in the pattern of consumption of individual fatty acids particularly among Western populations have occurred over the last decades [1,69]. In general the amount of saturated fat in the diet has declined and the amount of polyunsaturated fat increased. The driving force behind these changes was the realisation that plasma cholesterol concentrations is positively correlated with cardiovascular risk and with intake of some saturated fatty acids and that replacement of dietary saturated fatty acids with linoleic acid (18:2n-6) lowers plasma cholesterol concentrations. Thus, increased consumption of 18:2n-6 occurred because it became generally available in margarines and vegetable oils. One other change in the pattern of fatty acid consumption that has occurred in many countries over the last few decades is a reduction in the intake of VLCn-3PUFA as a result of decreased consumption of oily fish and decreased use of fish oil (cod liver oil). In the absence of significant consumption of oily fish or fish oil, 18:3n-3 is the major dietary n-3 fatty acid. The ratio of n-6 to n-3 polyunsaturated fatty acids in most Western diets is ca 10-15 with an average of 10. In the Nordic countries this ratio is lower, 4-8, because of a high consumption of soybean oil and rapeseed oil. Because the intake of VLCn-6PUFA and VLCn-3PUFA is low, this ratio effectively represents the ratio of 18:2n-6 to 18:3n-3. Since these fatty acids compete for the enzymes which convert them to their more unsaturated longer-chain derivatives, this ratio favours the conversion of 18:2n-6 over 18:3n-3, resulting in much lower levels of EPA and DHA than of AA in cells [68].

### 5.3 The ratio between n-6 and n-3 fatty acids

Given that VLCn-3PUFA have a range of health benefits (for overview see [1,28,69-71]), it has been argued that the current ratio of n-6 to n-3 polyunsaturated fatty acids of Western diets does not promote optimal health [1] whereas others focus on the n-6 fatty acids [72]. It is noteworthy that the dietary changes described above have been accompanied by remarkable decline in coronary heart disease mortality in most Western countries during the last generation. It has been demonstrated that wild animals contain five times more PUFAs than domestic livestock [73,74]. However, at this stage it is difficult to define an optimal n-6 to n-3 fatty acid ratio because in most cases it is 18:3n-3 and not the VLCn-3PUFAs that are consumed. Thus, in Norway (based on data from 1993) the ratio is around 5 but 12 when compared to VLCn-3PUFAs.

In a recent workshop report from the UK Food Standard Agency unlike the risk prevention by VLCn-3 fatty acids reservations were expressed about the evidence suggesting a beneficial effect of α-linolenic acid (18:3n-3) on secondary prevention of coronary heart disease [75]. Moreover, the possibility of feeding livestock 18:3n-3-rich oils to provide a means of increasing the dietary intake of EPA and DHA in humans was highlighted [75].

## 6. Cardiovascular diseases

Heart disease includes a host of specific medical conditions affecting the heart. Terms closely related to heart disease, having specific medical definitions, include cardiovascular disease (CVD), coronary heart disease (CHD), ischemic heart disease, myocardial infarction, angina pectoris, and atherosclerosis. The last term, atherosclerosis, is the underlying cause of heart disease and other cardiovascular diseases. People with elevated blood cholesterol and triacylglycerol levels and hypertension are at increased risk of developing heart disease.

The relationship between diet and coronary heart disease has been intensively studied for more than half a century. The past 3 decades have been a period of rapid expansion in the scientific knowledge of VLCn-3PUFAs in relation to CHD and it now appears that these dietary factors may be the most protective against death from CHD. Beginning with the studies of Bang and Dyerberg et al. [15-20] involving Greenland Eskimos in the late 1970s, the body of evidence supporting a role for VLCn-3PUFAs in the prevention of CHD has continued to grow. Epidemiological studies indicate a positive health effect from consuming fish and shellfish rich in VLCn-3PUFAs. For example, the Japanese have among the world's lowest rate of death from heart disease. According to the World Health Organisation, from 1984 to 1986, total mortality from ischemic heart disease in Japan was 29, whereas the corresponding rate for the United States was 197 deaths per 100,000 [76]. It was demonstrated that those who consumed the greatest amounts of fish had the lowest incidence of heart disease [77,78]. This finding is based on observations of mortality rates among mainland Japanese and those living on the island of Okinawa [77,79].

However, during the last decade the diet in Japan and in Asia has become more influenced by the Western way of living and the incidence of cardiovascular diseases in the big cities is now approaching that of Western countries. By 2020, non-communicable diseases including cardiovascular diseases (CVD) are expected to account for seven out of every 10 deaths in the developing countries compared with less than half this value today [80].

As a proportion of total deaths from all-causes, CVD in the Asia Pacific region ranges from less than 20% in countries such as Thailand, Philippines and Indonesia to 20-30% in urban China, Hong Kong, Japan, Korea and Malaysia. Countries such as New Zealand, Australia and Singapore have relatively high rates that exceed 30-35%. The latter countries also rank high for coronary heart disease (CHD) mortality rate (more than 150 deaths per 100,000). In contrast, death from cerebrovascular disease is higher among East Asian countries including Japan, China and Taiwan (more than 100 per 100,000). It is worth noting that a number of countries in the region with high proportions of deaths from CVD has undergone marked declining rates in recent decades. For example, in Australia, between 1986 and 1996, mortality from CHD in men and women aged 30-69 years declined by 46 and 51%, respectively. In Japan, stroke mortality dropped from a high level of 150 per 100,000 during the 1920s-1940s to the present level of approximately 100 per 100,000. Nonetheless, CVD mortality rate is reportedly on the rise in several countries in the region, including urban China, Malaysia, Korea and Taiwan. In China, CVD mortality increased as a proportion of total deaths from 12.8% in 1957 to 35.8% in 1990. The region is undergoing a rapid pace of urbanisation, industrialisation and major technological and lifestyle changes. Thus, monitoring the impact of these changes on cardiovascular risk is essential to enable the implementation of appropriate strategies towards countering the rise of CVD mortality [76].

## 6.1 Epidemiological evidence

In the1970s Bang and Dyerberg et al. [15-20] evaluated the dietary habits of Greenland Eskimos, a population known to have low mortality rate from CHD. This was one of the first epidemiological studies to explore the relationship between dietary VLCn-3PUFAs intake and the rate of CHD. Results of dietary surveys indicated that the Eskimo diet was not a low-fat diet and that approximately 39% of energy intake was from fat. Further analysis revealed the intake of saturated fat to be low (9% of total calories), whereas the dietary intake of VLCn-3PUFAs was high (4.2% of total calories). These findings contrasted sharply with the dietary habits of an ethnically similar population in Denmark with much higher rates of CHD. The Danish diet had a comparable amount of total fat (42% of total calories) but a much lower intake of VLCn-3PUFAs (< 1% of total calories) and a much higher intake of saturated fat (22% of total calories). A second similar study [81] followed inhabitants of Greenland and Denmark for 25 years; a 10-fold increase in myocardial infarction (MI) was noted in the Danish group.

In addition to cross-cultural epidemiological studies, results of various prospective observational cohort studies have suggested a cardioprotective effect of dietary VLCn-3PUFAs. Early important cohort studies include the Zutphen and Western Electric studies [82,83] that demonstrated an inverse relation between fish consumption and mortality from CHD.

In more recent studies [84,85], the US Physicians Health Study, more than 20,000 male US physicians who were free of cardiovascular disease were evaluated. These men were asked to complete food frequency questionnaires on fish consumption and were then followed up for

11 years. Consumption of at least 1 fish meal per week reduced the risk of sudden cardiac death by 52% compared to those consuming fish only monthly. All levels of fish consumption up to 1 meal per week were associated with decreased risk of sudden death. At levels of consumption greater than 1 fish meal per week the risk reduction did not change, indicating a threshold effect. More recent studies confirm the positive effect of seafood intake and the prevention of sudden cardiac death and total mortality, for details end reviews see [86-100]. Not all prospective cohort studies on the relationship between VLCn-3PUFA (fish) consumption and cardiovascular mortality rates have reported inverse associations [101-104] Three negative studies [101-103] involved cohorts with higher baseline intakes of VLCn-3PUF than as the cohort studies above. In addition, these studies had few participants who consumed less than 1 fish meal per week. A threshold effect, in which fish intake is cardioprotective in small amounts, could possibly explain these discordant results. Recently, a systematic review of 11 prospective cohort studies by Marckman and Grønbæk [105] examined the relationship between fish intake and CHD mortality rates. Four of these studies were judged to be of high quality in terms of study design. Two of the high-quality studies were performed on low risk populations and demonstrated no cardioprotective effect from fish consumption. The other two high-quality studies were performed on populations at higher risk for CHD and found an inverse association between fish consumption and CHD death. It was suggested that in these higher-risk cohorts, consumption of 40 to 60 g of fish per day could reduce the risk of CHD by 40% to 60%.

Cohort studies have also examined the effects of 18:3n-3 (plant origin) and in the Multiple Risk Factor Intervention Trial (MRFIT) [106] multivariate regression analysis was used to determine the effect of dietary 18:3n-3 on 101/2-year mortality rates. Significant inverse associations were found for intake of 18:3n-3 and mortality rates for CHD. In the Nurses Health Study [107] as well as in the National Heart, Lung, and Blood Institute Family heart study [108] a high intake of 18:3n-3 was associated with a lower risk of fatal CHD. In a more recent Dutch study no association was found between intake of 18:3n-3 and risk of CHD possibly because of covariation of ALA with trans fatty acids [109].

## 6.2 Secondary prevention studies

Evidence from recent intervention trials [92, 110-112] in patients with previous myocardial infarction (MI) indicates that intake of VLCn-3PUFAs from marine sources prevents cardiac death and nonfatal myocardial infarction. A recently published metaanalysis of randomised controlled secondary prevention studies concludes that VLCn-3PUFAs reduce total mortality, mortality from MI as well as sudden death [113]. One study from Norway [114] was not included in the analysis. In that study no effect was seen after18 months follow up in postinfarction pasients given 3.5 g EPA/DHA pr day.

In the Lyon diet heart study it was shown that a Mediterranean type diet with increased intake of 18:3n-3 decreased significantly mortality in patients with a previous myocardial infarction [115-117]. As mentioned above also other modifications of the diet occurred in this trial such as increased intake of fruit, vegetables and increased fish consumption. It is thus not proven that the effect can be solely ascribed to the increased intake of α-linolenic acid. However, there is good systematic review evidence that dietary advise to those with CVD can reduce mortality [118,119].

## 6.3 Case – control studies

At least three case – control studies have shown that increased intake of VLCn-3 fatty acids is associated with reduced risk of a first myocardial infarction [98,120,121]. These results further indicate that not only mortality but also the incidence is favourably influenced by intake of VLCn-3 fatty acids.

## 6.4 Stroke

The relationship between fish consumption and stroke is controversial. The reason may be that not all studies have differentiated thrombotic (ischemic) and hemorrhagic stroke. (The first category makes up about 80-85% and the second 15-20% of all strokes). High fish consumption levels have been associated with reduced stroke mortality [83,122,123] and possible mechanisms include a blood pressure lowering effect from VLCn-3PUFAs by a modulating effect on baroflex functions, reduced blood viscosity, reduced pressure responses and increased $PGI_2$ formation [124]. In contrast, other observational studies have failed to demonstrate any effect [84,125] and an intervention study could not demonstrate any effect of VLCn-3PUFAs on the prevention of stroke [111]. More recent papers do not elucidate the story. In a community case – control study (440 incident cases and 473 controls) from the Asturias, (Spain) it was concluded that a high fish consumption was associated with an increased risk of stroke and vertebral infarction [126] whereas data from the epidemiological follow-up to the first National Health and Nutrition Examination Survey (NHANES) failed to provide any evidence that eating fish once per week over long periods is sufficient to reduce the incidence of hypertension [127]. However, recent data on the association between seafood intake and stroke from two very large prospective cohort studies in women and men, the Nurses Health Study and the Health Professional Follow-up study, respectively, indicate that fish consumption is associated with reduced risk of thrombotic stroke. In women, it was reported that a high consumption of fish and VLCn-3PUFAs was associated with a reduced risk of cerebral thrombotic infarction, primarily among women who did not take aspirin regularly, but was not related to risk of hemorrhagic stroke [128]. In men, compared to persons who ate fish less than once per month, the multivariate relative risk of ischemic stroke was significantly lower among those who consumed fish one to three times per month. An even higher frequency of fish intake was not associated with further risk reduction [129]. In contrast, a higher consumption of fish and VLCn-3PUFAs was associated with a lower CHD incidence and total mortality among diabetic women [130].

## 6.5 Mechanisms for the protective cardiovascular effects of VLCn-3PUFAs

VLCn-3PUFAs (and fish consumption) may reduce risk of CHD by multiple mechanisms but their role as potential antiarrhythmics has gained major attention recently. This mechanism may in particular explain the marked effect of VLCn-3PUFAs on reduced risk of sudden death found in several studies [131,132]. It is believed that VLCn-3PUFAs stabilise the electrical activity of cardiac myocytes by inhibiting sarcolemmal ion channels, resulting in prolonged relative refractory period and preventing intracellular calcium overload [133-135]. This may possibly also be related to the increased oxygen utilisation and work efficiency seen in hearts of rats given fish oil as compared to saturated fat [136]. In a recent study by Geelen at al. [137], the effect of VLCn-3PUFAs on the standard electrocardiogram (ECG) was studied in healthy men and women. They did not find any effect of VLCn-3PUFAs on the ECG indicating that VLCn-3PUFAs prevent arrhythmia through electrophysiological effects on myocyte membranes. However, this study had few participants and as mentioned involved healthy subjects, thus, an effect on the ECG in more susceptible populations cannot be ruled out.

TheVLCn-3PUFAs also have significant antithrombotic properties. EPA has been shown to inhibit the synthesis of thromboxane $A_2$, a prostaglandin that causes platelet aggregation and vasoconstriction [138]. Similar beneficial effects have been reported from intake of both marine fish and freshwater fish [139-142]. Other antithrombotic effects reported include reductions in fibrinogen and increases in tissue plasminogen activator [143-145].

Endothelial function is also favourably affected by VLCn-3PUFAs and fish intake increases flow-mediated brachial artery dilation [146-148],

## 6.6 Hypolipidemic effects

The hypolipidemic effects of VLCn-3PUFAs have been extensively studied in humans [149-154]. Omega-3 fatty acids lower plasma triacylglycerol by reducing the hepatic production and secretion of lipoprotein particles rich in triacylglycerol, e.g., very low density protein [155,156]. VLCn-3PUFAs also markedly reduce postprandial lipemia, which typically occurs after consumption of a fatty meal [157], and postprandial lipoproteins are atherogenic. Postrandial lipemia is also thrombogenic because it increases levels of activated factor VII, a procoagulant[157]. Unlike vegetable oils rich in n-6 fatty acids VLCn-3PUFAs do not lower high-density lipoprotein (HDL) cholesterol levels. In contrast, they have been shown to result in a favourable change in HDL cholesterol metabolism. It seems that VLCn-3PUFAs and fish intake cause an increase in the large $HDL_2$ subtype while decreasing the smaller triacylglycerol-enriched $HDL_3$ subtype [158,159]. HDL2 is considered to be the most antiatherogenic HDL subtype. Some concerns have been raised about potential atherogenic changes in lipid metabolism caused by dietary VLCn-3PUFAs. LDL cholesterol levels have been shown to occasionally increase with VLCn-3PUFA supplementation; however, this effect was not evident in fish intake [159]. Also, some concern has been raised about *in vitro* studies that demonstrate that VLCn-3PUFA supplementation might increase LDL susceptibility to oxidation. It has been demonstrated that this oxidation can be reduced by supplementation with antioxidants (e.g. vitamin E) [160]. In a recent study habitual fish intake was associated with decreased LDL susceptibility to *ex vivo* oxidation [161]. Recently an inverse correlation between the acute-phase reactant C-reactive protein (CRP), an independent risk factor for CVD and DHA, was demonstrated in patients with stable coronary heart disease (CHD) [162]. This might indicate an anti-inflammatory effect of DHA and suggests a novel mechanism by which seafood consumption may decrease the risk for CHD.

## 6.7 Recommended intake in relation to CHD

The American Heart Association has recently issued a statement on the cardioprotective effects of fish consumption, fish oil and VLCn-3PUFAs [163,164]. In that connection recommendations have been issued on desirable intake of omega-3 fatty acids [165]. According to these, adults should consume fish, preferably fatty fish, at least two times a week. Also n-3 fatty acids from vegetable sources should be included in the diet. For patients with CHD one gram of DHA + EPA pr day is recommended. If this amount is difficult to obtain through fish consumption supplements of fish oil should be taken. For patients with hypertriglyceridemia a supplement of 2-4 grams of DHA + EPA per day may be useful.

## 7. Immune and inflammatory responses

The effects of dietary fatty acids on the immune system and inflammatory diseases have been reviewed by others [166-168]. Less is known, however, of the effects of seafood intake. Consumption of VLCn-3PUFAs and seafood alter the eicosanoid production. Dietary EPA and DHA reduce thromboxane $A_2$ ($TXA_2$) production and lead to the formation of the inactive or weakly aggregatory $TXA_3$ and the antiaggregatory prostaglandin $I_3$ ($PGI_3$) [169]. Thus, consumption of fish oil leads to a shift from the production of pro-aggregatory prostanoids to antiaggregatory prostanoids.

Leukotrienes (LT) are potent pro-inflammatory agents [170]. They enhance immune response by attracting infection/antigen-fighting cells (leukocytes and macrophages) and stimulating their activity at the host site. The consumption of EPA and DHA in fish oils suppresses the formation of leukotriene $B_4$ ($LTB_4$) [171]. VLCn-3PUFAs are given as dietary supplements to patients with rheumatoid arthritis (RA), the most common systemic inflammatory rheumatic disease [172]. The effects of dietary fish oil supplements in patients with RA have been studied in several investigations and improvement in the number of tender joints on physical examinations is most often observed [168,173,174]. Fish consumption has been shown to prevent RA [175]. In a recent study a positive effect of dietary VLCn-3PUFAs on patients with atopic dermatitis was demonstrated [176]. Subsequent to the reports of benefits of fish and fish oil supplementation in patients with RA, fish oil has been employed with some reported benefit in patients with inflammatory bowel disease [177] and in IgA nephropathy [178]. In a recent cohort study the association of fish intake and survival of incident dialysis patients revealed a 50% reduction of fatal outcome during the study period of one year [179]. Concerning psoriasis, VLCn-3PUFAs (1-18 g/d) have been reported to have no to excellent improvement in scaling, itching, lesion thickness and erythema in the majority of patients, reviewed by Gil [168]. There are some epidemiological findings to support a protective role of VLCn-3PUFAs in allergic diseases [180] but the effect of seafood on asthma is a controversial issue. Several studies indicate that seafood and VLCn-3PUFAs intake have a positive effect on asthma [181-185] and respiratory symptoms [186] but other studies have shown no effect [187-189]. In a recent non-interventional epidemiological study the relationship between fish intake and the prevalence of asthma indicated that fish intake was positively related to the prevalence of asthma [190]. In this study 1,673 currently asthmatic Japanese school children and 22,109 controls (age range 6-15 years old) were included. A significantly higher prevalence of asthma was noted among subjects that ate fish one to two times a week than those who ate fish one to two times a month (adjusted odds ratio: 1.117; 95% confidence interval: 1.005-1.241; $P = 0.041$). Since the study was cross-sectional the causative effects cannot be inferred from the results. Thus, the need for further studies in which the subjects are examined at specific intervals with respect to asthma including the use of objective measures e.g., respiratory function test. In a prospective study (1970-1990) diet and 20-year chronic obstructive pulmonary disease mortality in middle-aged men from three European countries (Finland, Italy and The Netherlands) was investigated, and the results suggested a positive effect from fruit but no effect was observed for intake of vitamin C, beta-carotene, vegetables and fish [191].

## 8. Neural development

The question of whether VLCn-3PUFAs are essential nutrients in human development has been reviewed recently and it seems that these fatty acids are essential for the optimum development of neural tissues during foetal development [192-195]. Particularly DHA is specifically incorporated into the phospholipids of brain and retina [196] and is the preferred fatty acid for the development of these tissues [197]. In brain, DHA is associated with synaptosomes, synaptic vesicles, myelin, endoplasmatic reticulum and mitochondria [198,199]. In retina, DHA is found in the photoreceptor cells, especially the outer segments of the rods where it may constitute as much as half of the total fatty acids, and in association with rhodopsin, the visual pigment of the photoreceptors [200-202]. Retinitis pigmentosa (RP) is a family of inherited retinal degeneration characterised by progressive loss of rod photoreceptors resulting in night blindness. As the rod cells detoriate, adjacent cone photoreceptors responsible for daytime and colour vision are affected. This occurs in the rod-rich peripheral retina and progresses toward the macula at the center resulting in tunnel-vision and leading to functional and legal blindness. There is no cure for the disease and treatment of symptom is limited. The first evidence for beneficial nutritional intervention in RP was reported by Berson et al. [202] who found a small but significant reduction in the progress of RP with dietary supplementation of the lipid-soluble vitamin A.

Evidence to support the concept of lipid influences in RP has accumulated over the past two decades, as numerous investigations have reported abnormal levels of VLCn-3PUFAs, particularly DHA in plasma lipids of patients with RP [204-207]. In preterm infants, delayed maturation of rod electroretinographic responses was associated with reduced blood levels of

DHA in infants receiving commercial formula (VLCn-3PUFA deficient) compared to those fed breast milk or DHA-enriched formula [208,209]. In a recent study it was demonstrated that fish intake prevented the development of age related maculopathy (leads to irreversible blindness) [210].

## 9. Infant development

Human milk is the only infant food containing fatty acids of 20 or more carbon atoms. It is also the only infant food containing DHA, the amount depending largely on the mother's diet and, more specifically, her consumption of fish. Studies in both premature infants and in healthy term infants revealed that addition of 18:3n-3 in the formula did not provide the equivalent amount of DHA for neural tissue development compared to preformed DHA from breast milk or fish-oil supplemented formula [208,209,211-213]. Low consumption of seafood in early pregnancy has been shown to be a risk factor for preterm delivery [214]. Supplementation with cod liver oil during pregnancy has been shown to be related to gestational length and cerebral maturation [215] and an increased cognitive function in the infant [216]. The breast-milk content of VLCn-3PUFAs is not regulated by the mammary gland but, rather, reflects the concentrations of VLCn-3PUFAs in maternal plasma lipids, that, in turn, are dependent of maternal diet and, probably, maternal activities of the desaturases and elongases involved in converting LA and ALA to AA and VLCn-3PUFAs [217]. In a recent workshop addressing the role of VLCn-3PUFAs in maternal and child health, it was concluded that it seems prudent for pregnant and lactating women to include seafood or other sources of VLCn-3PUFAs in their diet in view of their assumed increase in VLCn-3PUFA demand and the relationship between maternal and foetal DHA status [218].

## 10. Diabetes

Omega-3 fatty acids have been shown to possess positive effects in patients with insulin-dependent diabetes mellitus (IDDM) [135, 219-221] and non-insulin-dependent diabetes mellitus (NIDDM) [145,222-224]. In a recent review by Sirtori and Galli [225] they conclude that fish and dietary VLCn-3PUFAs may be beneficial in the treatment of diabetic patients.

## 11. Multiple sclerosis

Multiple sclerosis (MS) is an inflammatory, degenerative disease of the central nervous system characterised by demyelination of the white matter of nervous tissue and MS occurs in many scattered areas of the brain, spinal cord, and optic nerves. Some studies have revealed that n-3 fatty acids may be of use as a therapy in MS patients [226,227] whereas a recent study did not find a link between dietary fat and MS [228].

## 12. Psychological disorders

There is now substantial evidence that major depression is associated with VLCn-3PUFA depletion [229-235]. Severity of depression correlated negatively with both VLCn-3PUFAs content in red blood cell membrane and dietary intake of these VLCn-3PUFAs [230]. A significantly increased omega-6/omega-3 ratio together with a significantly lower total VLCn-3PUFAs was found in major depressed patients compared to minor drepressed and healthy controls [236,237]. In a recent review, the role of VLCn-3PUFAs as a possible missing link between myocardial infarction, cardiac death and depression was proposed, and the relationship appears to be a common pathophysiological patway involving immunological factors [238]. The immune system appears to influence serotonin (5-HT) turnover, availability and metabolism as pro-inflammatory cytokines such as IL-1 and IFN induce the enzyme indoleamine-2,3 – dioxygenase (IDO), which converts the essential amino acid tryptophan, the precursor of 5-HT, to kynurenic acid and guinolinic acid [239]. In the brain dietary fatty acids, in particularly VLCn-3PUFAs, modify membrane structure and function by changing the index of viscosity, fluidity, and by modulating the activity of tryptophan hydroxylase, the rate limiting enzyme in serotonin synthesis [237,240,241]. Animal studies have shown accumulation of brain tryptophan, followed by an increase of brain serotonin after feeding with VLCn-3PUFAs [242]. Among healthy volunteers, low levels of plasma DHA predicted low concentrations of 5-hydroxy-indoleacetic acid (5-HIAA), a marker of brain serotonin turnover [243]. In a recent cross-sectional study it was demonstrated a significant relationship between fish intake and self-reported mental health status, thus offering indirect support for the hypothesis that dietary VLCn-3PUFAs may act as mood stabilisers [244,245]. Thus, seafood consumption may maintain normal or increase the serotonergic nervous system function and thereby possible prevent major depression.

In animals it has been demonstrated that changing the dietary n-6/n-3 ratio effectively modifies the fluidity of phospholipid membranes [246]. The influence of dietary VLCn-3PUFA composition are, however, not restricted to structural changes in the plasma membranes but can also be reflected in behavioral and cognitive performance [247-249]. In humans, dietary VLCn-3PUFAs have been shown to improve cognitive functioning [216,250,251] and reduced risk for dementia [251,252]. In a recent paper it was demonstrated that purified ethyl EPA did not affect cognitive impairment in patients with schizophrenia [253] whereas seafood intake (rather than capsules containing VLCn-3PUFAs) results in an improved cognitive functioning [251,252].

## 13. Cancer

Dietary seafood intake and cancer is a subject of interest. The evidence for a protective effect from seafood is less extensive than for CVD. Still, several studies have shown an inverse relationship between fish consumption and cancer incidence [254-262]. Inverse associations with the risk of various cancers i.e., oral cavity and upper digestive tract [263-265] stomach [266,267], colorectal [257,268-271], lung [272,273], pancreas [274], gallbladder [275], breast [256,270,276-278], endometrial [279], ovary [280-282], prostate [281,283,284], bladder [285], kidney [286], and thyroid [287,288] have been reported from case-control, cohort or intervention studies. A recent panel report concluded, based on a comprehensive review of epidemiological studies, that fish consumption may possibly protect against cancers of the colon, rectum and ovary [289].

## 14. Osteoporosis

Recent in vitro experiments suggest that VLCn-3PUFAs may favourably affect the balance beween the activities of osteoclasts and osteoblasts thereby reducing bone resorption [290]. The explanation offered is that EPA inhibits cyclooxygenase-2 the enzyme that converts arachidonic acid into $PGE_2$, the latter increase the activity of the osteoclasts while decreasing that of the osteoblasts. The possibility that VLCn-3PUFAs may retard osteoporosis has so far not been tested in humans.

## 15. Life style diseases

The so called life style diseases include cardiovascular disease, immune system disorders, metabolic disorders, Type II diabetes, and mental disorders. The name reflects the simple fact that life styles have changed, particularly in theWestern world but, and the diet an dietary fat, has been discussed as causative factor. Moreover, during the last decade a new syndrome has emerged, i.e. the metabolic syndrome, a cluster of disorders including abdominal obesity, dyslipidemia, increased blood pressure and insulin resistance is associated with a high risk of cardiovascular disease and premature death also linked primarly to dietary fat [291]. It is reassuring that the patterns of dietary fatty acids that appear to be beneficial for insulin action and energy balance are also the patterns that would seem appropriate in the fight against thrombosis and cardiovascular disease [292,293]. It has been shown that incorporation of a daily fish meal into a weight-loss regimen in overweight hypertensive subjects was the most efficient way to improve glucose-insulin metabolism and dyslipidemia [158]. Thus, by increasing the seafood consumption in order to achieve a more balanced diet, it is possible to improve the health and well-being as well as preventing disorders occurring in the first place. The latter has been addressed by the National Cholesterol Education Program's Adult Treatment Panel in USA with the emphasis of the health promoting effects of fish and VLCn-3PUFAs to prevent or treat the metabolic syndrome, and improve the overall health of the patient [294]. Moreover, the effect of dietary quality for elderly people has been evaluated in Europe [295] and in America [296] showing a clear relationship between poor nutritional quality and increased mortality risk. Thus, factors like e.g. a high nutritional quality that include seafood and physical activity are important for improved health for the elderly. However, these are two of many important factors that most likely apply for the general population in order to maintain good health.

## 16. Seafood safety

The role of seafood in ensuring nutritional security to an increasing global population has been emphasised by several international organisations e.g. Food and Agriculture Organisation (FAO). However, efforts to increase seafood intake by the population must recognice that global supplies of wild fish are stagnant if not declining, with some traditional fisheries close to collapse due to persistent over fishing driven by increasing demand for fish as a human food. Food allergy and foodborne diseases are challenges that are linked to all foodstuffs, including seafood, and the marine environment has unquestionably become contaminated with industrial pollutants such as heavy metals and “persistant organic pollutants” including dioxins and PCBs. The latter is mainly a problem with wild fish caught in particularly contaminated areas but will affect the customers attitude towards all kinds of seafood. Thus, it is difficult to sustain the seafood intake, far less increase it, unless seafood producers can ensure all aspects of food safety for the consumers. Food must be free from pathogens, contain minimal levels of dioxins and other contaminants and provide a balanced input of nutrients for varying and changing human needs including demographic changes and population movements. In Europe, the latter is highligted in the “White Paper on Food Safety” and by the establishment of the European Food Safety Authority (EFSA) as well as an increased focus from national bodies as well as the industry itself. Therefore, it is important to continue to reduce the contamination of the open seas as well as ensure sustainable management of the wild fish stocks. Traditionally, the aquaculture industry has relied heavily on fish meal and fish oil, but it has been predicted that the global demand for fish oils in farmed fish feeds will exceed supply in little more than 5 years. However, it is encouraging that scientifically based aquaculture has recently demonstrated the feasibilty of replacing fish oil and fish meal with alternative vegetable, microbial, or other ingredients not utilised today, including some unexploited fisheries resources. Aquaculture can in principle expand without constraint by using sustaiable resources, principally from terrestrial production, albeit supplemented by specialised marine resources. Thus, aquaculture can ensure a safe, nutritious, healthy and high quality seafood product through the whole food chain, i.e. from feed resources to the final product, thereby providing a properly balanced diet for the consumers. Clearly, consumer trust can only be achieved by parallel evidence on the potential health benefits and the lack of risks consuming seafood. Thus, epidemiological studies adressing both positive and negative endpoints of specific populations i.e. high-, medium-, and low seafood consumption from areas known to have low and high amounts of contaminants are needed in order to assess the extent to which seafood consumption as part of the regular diet influences, whether positively or negatively human health.

An in debt review of the literature regarding contaminants, allergy and foodborne disease are beyond the scope of this report, but some general remarks are given below.

## 16.1 Contaminants

Seafood contamination is frequently a subject of public debate, and the markets (consumers) react immediately to the slightest suspicion that food consumption represents possible hazards to human health.

### 16.1.1 Chlorinated hydrocarbons

Chlorinated hydrocarbons (dioxins, PCBs, DDTs, HCBs, etc.) represent a group of very heterogenous compounds, but they share several common properties. They are hydrophobic and accumulate in the food chain, particularly in the marine food chain, and they are very persistent, i.e. have long halflife. Generally, lean fish species like cod, saithe or Alaska pollock are less contaminated than fat fish species like herring, Greenland halibut and sardine [297]. Moreover, the dioxin content is related to the fish ground, e.g. low concentrations are found in the North Sea compared to the Baltic Sea [297]. The toxicity varies among these compounds and their different metabolites but generally they have been linked to i.e. neurotoxic effects, cancer, and fecundability [298,299].

### 16.1.2 Toxic elements

Elements that contribute significantly to the human intake by consuming seafood, are e.g. cadmium, arsenic and mercury. Of these elements mercury has received most attention. The major physical forms of mercury to which humans are exposed are inorganic (mercury vapor) and organic (methylmercury) compounds [300]. Mercury vapour emitted from both natural and anthropogenic sources is globally distributed in the atmosphere. It is returned as water-soluble form in precipitation and finds its way into bodies of fresh and ocean water. Land run-off also accounts for further input into lakes and oceans. Inorganic mercury, present in water sediments, is subject to bacterial conversion to methylmercury compounds that are bioaccumulated in the aquatic food chain to reach the highest concentration in the predator fish. Human exposure to mercury vapor is from dental amalgam and industries using mercury. Methylmercury compounds are found exclusively in seafood and freshwater fish [301]. The health effects of mercury vapor have been known since ansient time and severe exposure results in a triad of symptoms, erethism, tremor, and gingvitis [300] and neurotoxic effects [302]. Methylmercury in high doses is a neurological poison affecting primarily brain tissue, and today there is concern regarding brain development and cognitive changes in children. Studies of seafood eating populations have not found a consistent pattern of exposures and outcomes. Two recent reports have been unable to confirm any relationship between maternal exposure to dietary methylmercury during pregnancy and adverse developmental outcomes [303,304]. The early effects of mercury on the central nervous system due to occupational exposure to low levels of inorganic mercury revealed alterations of motor function and neuroendocrine secretion at very low exposure levels, whereas an inverse association between most neurophysiological symptoms and seafood consumption, indicationg a beneficial effect from eating seafood [302].

Generally, seafood intake is associated with a reduced mortality from coronary heart disease (see section 4). However, in some countries e.g. Finland no such association has been found and it has been concluded that high intake of mercury from nonfatty freshwater fish and the consequent accumulation of mercury in the body are associated with an excess risk of acute myocardial infarction as well as death from coronary heart disease and cardiovascular disease [305]. However, in a prospective case-control study in Sweden there was a strong inverse association between the risk of a first myocardial infarction and the biomarkers of fish intake, mercury and VLCn-3PUFAs in red blood cells, and this association was independent of traditional risk factors [121].

A European Prospective Investigation into Cancer and Nutrition (EPIC) cohort in Spain has estimated and validated the relationship between seafood consumption and mercury intake, as well as seafood consumption and mercury in red blood cells, indicating that no individual from the cohort would exceed the provisional tolerable weekly intake [306]. In other populations with a high intake of fish like some Native American populations exceed the tolerable daily intake of mercury [307]. Two recent papers have addressed dietary intake of mercury as a function of mercury in toenails and the effects on the risk of myocardial infarction and coronary heart disease. One report found no significant association between total mercury exposure and the risk of coronary heart disease [308], whereas the other study found that the toenail mercury level was directly accociated with the risk of myocardial infarction, and that adipose-tissue DHA (VLCn-3PUFA) level was inversely associated with the risk [309]. Thus, the risk of various diseases in a population related to contaminants may depend on the balance between positive nutrients (e.g. VLCn-3PUFAs) and contaminants (e.g. methylmercury) in the seafood consumed.

## 16.2 Allergy

A comprehensive analysis of food allergens resulted in the purification and characterisation of the major codfish allergen, Gad c1 [310]. Gad c1 (originally designated allergen M) belongs to a group of muscle tissue proteins known as parvalbumins controlling the flow of calcium in and out of the cells and are found in the muscles of amphibians and fish. The existence of structurally related parvalbumins in different fish species may explain why a close cross-reactivity exists within different species such as herring, plaice and mackerel [311]. Other fish allergens have been described as well as shrimp allergens [312]. Workers involved in either manual or automated processing of seafood are commonly exposed to various constituents of seafood have led to more frequent reporting of allergic reactions in occupational and domestic settings [313]. Studies in both children and adults indicate that symtomatic reactivity to food allergens is often lost over time, except possibly reactions to peanuts, tree nuts and seafood [314]. Thus, once the diagnosis of food allergy is established, the only proven therapy is the strict elimination of the food from the patient’s diet. Data from the occurrence of severe food allergies in the EU, conducted in four countries (France, The Netherlands, UK and Sweden) revealed 535 cases of anaphylaxis, of which 5% was caused by fish and 8% was caused by shellfish [312].

## 16.3 Foodborne diseases

Most parasites of marine animals are of little public health concern. Some helminths, however, such as anisakis nematodes are capable of infecting humans (zoonotic infections) by consumption of raw or undercooked seafood [315-317]. This is mainly a problem in developing countries [318] and also in countries with a lack of adequate inspection of food products [319]. Fish and shellfish poisoning occur through the natural event of the food chain. Fish and shellfish consume algae that contain toxin-producing dinoflagellates. As a result they become contaminated and the toxin is concentrated as it moves up the food chain. Fish and shellfish can tolerate high levels of toxins, thereby appearing healthy while posing a significant danger to man. There are several types of poisoning that can occur through fish and shellfish consumption, including ciguatera and scombroid fish poisoning; and paralytic, diarrheic, neurotoxic, and amnesic shellfish poisoning [320,321]. Microorganisms such as bacteria and fungi have been extensively studied in fish products found on the different markets [322,323]. During processing of fish i.e. slaughter, refrigerating and processing, there is a possibility that bacteria are introduced that are zoonotic in nature. One exampel is *Listeria monocytogenes*, which is distributed widely in nature and grows at refrigerated temperatures under aerobic, micro-aerophilic and anaerobic conditions. This implies that bacteria could be present in fish products which are processed and refrigerated for extended periods., for example vacuum packed smoked salmon. The seafood industry and government authorities apply various programmes to reduce this risk, including good manufacturing practices (GMPs) and hazard analysis and critical control point (HACCP) systems. These programmes are very effective, and in the Western world as demonstrated by the United States, only 10% of all foodborne diseases are attributed to seafood, thus, making seafood a relatively safe commodity [324].

## 17. Future perspectives

Consumers of seafood world wide are becoming increasingly concerned over the safety and nutritional quality of their food. This occurs at a time where food production in general has become increasingly efficient with food surplus, particularly in the Western world. Life styles have changed and during the last decade(s) a new syndrome has emerged, i.e. the metabolic syndrome. Interestingly, the metabolic syndrome is not restricted to the Western world, and is now rapidly increasing world wide, including developing countries. Diet, particularly dietary fat, has been said to be a risk factor. This has led to a great interest in functional foods, i.e. foodstuffs enriched with certain nutrients (e.g. vitamins, VLCn-3PUFAs, etc.) in order to achieve an addtional health beneficial effect besides being a nutrient. In this respect, safe seafood represents a natural food source that contain some of the most health promoting nutrients known and can in many ways be defined as "functional food" *per se*. Moreover, fish protein has a high nutritional value having the entire complement of essential amino acids and a high digestibility and in terms of nutritive value fish ranks above casein. In order to assess the role of nutrition and health in Europe, a huge research programme started more than a decade ago finansed by the EU. This study is known as the European Prospective Investigation into Cancer and Nutrition (EPIC) which is a multicenter European study, cordinated by the International Agency for Research on Cancer (Lyon, France) and more than 450,000 volunteers are recruited. However, the data on seafood consumption is in many respects not optimal and in some countries not sufficient to make any conclutions regarding the impact of seafood consumption and outcomes of end points. Thus in the new 6th framework programme within EU, a strong link between the EPIC study(ies) and research projects within food quality and safety should be made, ensuring maximum data in order to assess the link between food intake (particularly seafood) and human health. With respect to the diet and human health, more research is needed to define how diet (particularly dietary fat and seafood) affect e.g. the metabolic syndrome and other chronic diseases. Thus, in addition to epidemiological studies,well designed, long-term multicenter dietary intervention studies must be undertaken if dietary guidelines are to be based on scientific valid data.

## 18. References

[1] Simopoulos AP (2002) The importance of the ratio of omega-6/omega-3 essential fatty acids. *Biomed Pharmacother* **56**, 365-379.

[2] Clarke SD & Jump DB (1993) Regulation of gene transcription by polyunsaturated fatty acids. *Progress in Lipid Research* **32**, 139-149.

[3] Clarke SD & Jump DB (1994) Dietary polyunsaturated fatty acid regulation of gene transcription. *Annual Review of Nutrition* **14**, 83-89.

[4] Jump DB & Clarke SD (1999) Regulation of gene expression by dietary fat. *Annu Rev Nutr* **19**, 63-90.

[5] Sessler AM & Ntambi JM (1998) Polyunsaturated fatty acid regulation of gene expression. *Journal of Nutrition* **128**, 923-926.

[6] The World health report 2002. *Reducing risks, promoting healthy life.* World Health Organisation, Geneva, Switzerland. ISBN 92 4 156207 2, ISSN 1020-3311.

[7] Urquhart JA (1935) The most northerly practice in Canada. *Can. Med. Assoc. J.* **33**, 193-196

[8] Rabinowitch IM (1936) Clinical and other observations on Canadian Eskimos in the Eastern Arctic. *Can Med Assoc J* **34**, 487-501.

[9] Burr GO (1942) Significance of the essential fatty acids. *Fed Proc* **1**, 224-233.

[10] Bronte-Steward, B., Antonis, A., Eales, L., and Brock, J.F. 1956. Effects of feeding different fats on serum cholesterol level. *Lancet* **1:** 521-527.

[11] Keys, A., Anderson, J.T., and Grande, F. 1957. “Essential” fatty acids, degree of unsaturation and effect of corn (maize) oil on the serum-cholesterol level in man. *Lancet* **1:** 66-68.

[12] Ahrens, Jr., E.H., Insull, Jr., W., Hirsch, J., Stoffel, W., Peterson, M.L., and Farquhar, J.W. 1959. The effect on human serum-lipids of a dietary fat, highly unsaturated, but poor in essential fatty acids. *Lancet* **1:** 115-119

[13] Ehrstrøm, M.C. 1951. Medical studies in North Greenland, 1948-1949. *Acta Med. Scand.* **140**, 416-422.

[14] Sinclair, H.M. 1953. The diet of Canadian Indians and Eskimos. *Proc. Nutr. Soc.* **12:** 69-82.

[15] Bang HO & Dyerberg J (1972) Plasma lipids and lipoproteins in Greenlandic west-coast Eskimos. *Acta Med Scand* **192**, 85-94.

[16] Dyerberg, J., Bang, H.O., and Hjørne, N. 1975. Fatty acid composition of the plasma lipids in Greenland Eskimos. *Am. J. Clin. Nutr.* **28:** 958-966.

[17] Dyerberg, J. & Bang, H.O. 1978. Dietary fat and thrombosis. *Lancet* **1:** 152.

[18] Dyerberg J, Bang HO, Stoffersen E, Moncada S & Vane JR (1978) Eicosapentaenoic acid and prevention of thrombosis and atherosclerosis. *Lancet* **2**, 117-119.

[19] Dyerberg, J. And Bang, H.O. 1979. Haemostatic function and platlet polyunsaturated fatty acids in Eskimos. *Lancet* **2:** 433-435.

[20] Bang HO, Dyerberg J & Sinclair HM (1980) The composition of the Eskimo food in northwestern Greenland. *American Journal of Clinical Nutrition* **33**,2657-2661.

[21] Sidwell, V.D., Foncannon, P.R., Moore, N.S., and Bonnett, J.C. 1974. Composition of the edible portion of raw (fresh or frozen) crustaceans, finfish, and mollusks. I. Protein, fat, moisture, ash, carbohydrate, energy value, and cholesterol. *Mar. Fish. Rev.* **368:** 21-35.

[22] Ackman, R.G. 1989. Nutritional composition of fats in seafoods. *Prog. Food Nutr. Sci.* **13:** 161-241.

[23] Ackman, R.G. 1976. Fish oil composition. In: *Objective Methods for Food Evaluation.* Washington, DC: National Academy of Sciences. pp 103-131.

[24] Young, F.R. 1986. *The chemical and Physical Properties of Crude Fish Oils for Refiners and Hydrogenators,* Fish Oil Bulletin No. 18. Hertfordshire, U.K.: International Association of Fish Meal Manufacturers.

[25] McGill, A.S. and Moffat, F.H. 1992. A study of the composition of fish liver and body oil triglycerides. *Lipids* **27:** 360-370.

[26] Mori, M., Saito, T., Nakanishi, Y., Miyazawa, K., and Hashimoto, Y. 1966. The composition and toxicity of wax in the flesh of castor oil fishes. *Bull. Jpn. Soc. Sci. Fish.* **32:** 137-145.

[27] Nettleton, J.A. 1991. Omega-3 fatty acids: Comparison of plant and seafood sources in human nutrition. *J. Am. Dietet. Assoc.* **91:** 331-337.

[28] de Lorgeril M & Salen P (2002) Fish and n-3 fatty acids for the prevention and treatment of coronary heart disease: nutrition is not pharmacology. *Current Opinion in Cardiology* **15**, 364-370.

[29] Savige GS (2001) Candidate foods in the Asia-Pacific region for cardiovascular protection: fish, fruit and vegetables. *Asia Pacific Journal of Clinical Nutrition* **10**, 134-137.

[30] Amiano P, Dorronsoro M, de Renobales M, Ruiz de Gordoa JC & Irigoien I: EPIC group of Spain (2001) Very-long chain omega-3 fatty acids as markers for habitual fish intake in a population consuming mainly lean fish: the EPIC cohort of Gipuzkoa, European Prospective Investigation into Cancer and Nutrition. *European Journal of Clinical Nutrition* **55**, 827-832.

[31] Li D, Zhang H, Hsu-Hage BH-B, Wahlqvist ML and Sinclair AJ (2001) The influence of fish, meat and polyunsaturated fat intakes on platelet phospholipid polyunsaturated fatty acids in male Melbourne Chinese and Caucasian. *European Journal of Clinical Nutrition* **55**, 1036-1042

[32] Hansen M, Thilsted SH, Sandström B, Kongsbak K, Larsen T, Jensen M & Sörensen S.S. (1998) Calcium absorption from small soft-boned fish. *J Trace Element Med Biol* **12**: 148-154.

[33] Larsen T, Thilsted SH, Kongsbak K & Hansen M (2000) Whole small fish as a rich calcium source. *Brit. J. Nutr.* **83**: 191-196.

[34] Beck AB, Bugel S, Sturup S, Jensen M, Molgaard C, Hansen M, Krogsgaard OW & Sandstrom B (2003) A novel dual radio- and stable-isotope method formeasuring calcium absorption in humans: comparison with the whole-body readioisotope retention method. *Am J Clin Nutr* **77**, 399-405.

[35] Bucher HJ, Cook RJ, Guyatt GH; Lang JD, Cook DJ, Hatala R & Hunt DL (1996) Effects of dietary calcium supplementation on blood pressure –a meta analysis of randomised controlled trials. *Journal of the American Medical Association* **275**, 1016-1022.

[36] Schwarz K & Folts CM (1957) Selenium as an integral part of factor 3 against dietary necrotic liver degeneration. *J Am Chem Soc* **79**, 3292-3293.

[37] Salonen JT, Alfthan G, Huttunen JK, Pikkrainen J & Puska P (1982) Association between cardiovascular death and myocardialinfarction and serum selenium in a matched-pair longitudinalstudy. *Lancet* **2**, 175-179.

[38] Jackson ML (1988) Selenium: geochemical distribution and associations with human heart and cancer death rates and longlivety in China and the United States. *Biol Trace Elem Res* **15**, 13-21.

[39] Rayman MP (2000) The importance of selenium to human health. *Lancet* **356**, 233-241.

[40] Miyazaki Y, Koyama H, Nojiri M & Suzuki S (2002) Relationship of dietary intake of fish and non-fish selenium to serum lipids in Japanese rural coastal community. *Journal of Trace* Elements in Medicine and Biology **16**, 83-90.

[41] Burk RF, Jordan HE Jr & Kiker KW (1977) Some effects of selenium status on inorganic mercury in the rat. *Toxicology & Applied Pharmacology* **40**, 71-82.

[42] King LJ & Soares JH Jr (1978) Mercury metabolism in Japanese quail, II.The effects of dietary mercury and selenium on blood and liver glutathione peroxidase activity and selenium concentration. *Poultry Science* **57**, 1286-1292.

[43] Nakamura K, Nashimoto M, Okuda Y, Ota T & Yamamoto M (2002) Fish as a major source of vitamin D in the Japanese diet. *Nutrition* **18**, 415-416.

[44] Kato S (2000) The function of vitamin D receptor in vitamin D action. *J Biochem* **127**, 717-722.

[45] Laidlaw SA, Grosvenor M & Kopple JD (1990) The taurine content of common foodstuffs. *J Parenter Enteral Nutr* **14**, 183-188.

[46] Liu LJ, Mizushima S, Ikeda K, Hattori H, Miura A, Gao M, Nara Y & Yamori Y (2000) Comparative studies of diet-related factors and blood pressure among Chinese and Japanese. Results from the China-Japan Cooperative Research of the WHO-CARDIAC Study. *Hypertens Res* **23**, 413-420.

[47] Murakami S, Yamagishi I, Asami Y, Ohta Y, Toda Y, Nara Y & Yamori Y (1996) Hypolipidemic effect of taurine in stroke-prone spontaneously hypertensive rats. *Pharmacology* **52**, 303-313.

[48] Nara Y, Yamori Y & Lovenberg W (1978) Effect of dietary taurine on blood pressure in spontanously hypertensive rats. *Biochem Pharmacol* **27**, 2689-2692.

[49] Huxtable RJ (1992) Physiological actions of taurine. *Physiol Rev* **72**, 101-163.

[50] Petty MA, Kintz J & DiFrancesco GF (1990) The effects of taurine on atherosclerosis development in cholesterol-fed rabbits. *Eur J Pharmacol* **180**, 119-127.

[51] Yamori Y, Nara Y, Ikeda K & Mizushima S (1996) Is taurine a preventive nutritional factor of cardiovascular disease or just a biological marker of nutrition?. *Adv Exp Med Biol* **403**,623-629.

[52] Yamori Y, Liu L, Ikeda K, Miura A, Mizushima S, Miki T & Nara Y (2002) Distribution of twenty-four hour urinary taurine excretion and association with ischemic heart disease mortality in 24 populations of 16 countries: results from the WHO-CARDIAC study. *Hypertens Res* **24**, 453-457.

[53] Refsum H, Ueland PM, Nygård O & Vollset SE (1998) Homocysteine and cardiovascular disease. *Annu Rev Med* **49**, 31-62.

[54] Eikelbom JW, Lonn E, Genest J Jr., Hankey G & Yusuf S (1999) Homocyst(e)ine and cardiovascular disease: a critical review of the epidemiological evidence. *Ann Intern Med* **131**, 363-375.

[55] Harker LA, Ross R, Slichter SJ & Scott CR (1976) Homocysteine-induced arteriosclerosis: the role of endothelial injury and platelet response in its genesis. *J Clin Invest* **58**, 731-741.

[56] Wall RT, Harlan JM, Harker LA & Striker GE (1980) Homocysteine-induced cell injury in vitro: a model for the study of vascular injury. *Thromb Res* **18**, 113-121.

[57] Loscalzo J (1996) The oxidant stress of hyperhomocyst(e)inemia. *J Clin Invest* **98**, 5-7.

[58] Kokame K,Kato H & Miyata T (1996) Homocysteine-respondent genes in vascular endothelial cells identified by differential display analysis: GRP78/BiP and novel genes. *J Biol Chem* **271**, 29659-29665.

[59] Outinen PA, Sood SK, Liaw PC,Sarge KD, Maeda N, Hirsh J, Ribau J, Podor TJ, Weitz JI & Austin RC (1998) Characterization of the stress-inducing effects of homocysteine. *Biochem J* **332**, 213-221.

[60] Kaufman RJ (1999) Stress signalling fromthe lumen of the endoplamatic reticulum: coordination of gene transcriptional and translational controls. *Genes Dev* **13**, 1211-1233.

[61] Nonaka H, Tsujino T, Watari Y, Emoto N, Yokoyama M. (2001) Taurine prevents the decrease in expression and secretion of extracellular superoxide dismutase induced by homocysteine: amelioration of homocysteine-induced endoplasmic reticulum stress by taurine. *Circulation* **104**,1165-1170.

[62] Fennessy FM, Moneley MB,Wang JH, Kelly CJ & Bouchier-Hayes MB (2003) Taurine and Vitamin C modify monocyte and endothelial dysfunction in young smokers. *Circulation* 107, 410-415.

[63] Weber C, Bysted A & Holmer G (1994) The coenzyme $Q_{10}$ content of the average Danish diet. *Int J Vitam Nutr Res* **67**, 123-129.

[64] Simopoulos AP (1997) Nutritional aspects of fish, In “Seafood from producer to consumer; an integrated approach to quality”. *Developments in Food Science* **38**, 589-607. Eds. Luten JB, Børresen T, Oehlenschläger J. Elsevier, Amsterdam.

[65] Mollsten AV, Dahlquist GG, Stattin EL & Rudberg S (2001) Higher intakes of fish protein are related to a lower risk of microalbuminuria in young Swedish type I diabetic patients. *Diabetes Care* **24**, 805-810.

[66] Calder PC (2001) Fatty acid metabolism and eicosanoid synthesis. *Clinical Nutrition* **20**, Suppl. 4, 1-5.

[67] Schmidt EB, Christensen JH, Aardestrup I, Madsen T, Riahi S, Hansen VE & Skou HA (2001) Marine n-3 fatty acids: basic features and background. *Lipids* **36**, S65-S68.

[68] Burdge GC, Jones AE & Wootton SA (2002) Eicosapentaenoic acid and docosahexaenoic acid are the principal products of α-linolenic acid metabolism in young men. *British Journal of Nutrition* **88**, 355-363.

[69] Lichtenstein AH (1999) Dietary fat: a history. *Nutrition Reviews* **57**, 11-14.

[70] Harper CR & Jacobsen TA (2001) The fats of life. The role of omega-3 fatty acids in the prevention of coronary heart disease. *Arch Intern Med* **161**, 2185-2192.

[71] Hu FB & Willett WC (2002) Optimal diets for prevention of coronary heart disease. *Journal of the American Medical Association* **288**, 2569-2578.

[72] Berry EM (2001) Who’s afraid of n-6 polyunsaturated fatty acids? Methodological considerations for assessing whether they are harmful. *Nutr Metab Cardiovasc Dis* **11**, 181-188.

[73] Crawford MA (1968) Fatty acid ratios in free-living and domestic animals. *Lancet* **I***,* 1329-1333.

[74] Crawford MA, Gale MM & Woodford MH (1969) Linoleic and linolenic acid elongation products in muscle tissue of Syncerus caffet and other ruminant species. *Biochemical Journal* **115**, 25-27.

[75] Sanderson P, Finnegan YE, Williams CM, Calder PC, Burdge GC, Wootton SA, Griffin BA, Millward, DJ, Pegge NC & Bemelmans WJE (2002) UK Food Standards Agency α-linolenic acid workshop report. *British Journal of Nutrition* **88**, 573-579.

[76] World Health Organisation. 1989. *World Health Statistics Annual Report, 1989.* World Health Organisation, Geneva, Switzerland.

[77] Kagawa, Y., Nishizawa, M., Suzuki, M., Miyatake, T., Hamamoto, T., Goto, K., Motonaga, E., Izumikawa, H., Hirata, H., and Ebihara, A. 1982. Eicosapolyenoic acids of serum lipids of Japanese Islenders with low incidence of cardiovascular diseases. *J. Nutr. Sci. Vitaminol.* **28:** 441-453.

[78] Yamori, Y., Nara, Y., Iritani, N., Workman, R.J., and Inagami, T. 1985. Comparison of serum phospholipid fatty acids among fishing and farming Japanese populations and American inlanders. *J. Nutr. Sci. Vitaminol.* **31:** 417-422.

[79] Hirai, A., Hamazaki, T., Terano, T., Nishikawa, T., Tamura, Y., and Kumagai, A. 1980. Eicosapentaenoic acidand platelet function in Japanese. *Lancet* **2:** 1132-1133.

[80] Khor GL (2001) Cardiovascular epidemiology in the Asia-Pacific region. *Asia Pac J Clin Nutr* **10**, 76-80.

[81] Kroman N & Green A (1980) Epidemiological studies in the Upermauik District, Greenland. *Acta Med Scand* **208**, 401-406.

[82] Kromhout D, Bosschieter EB & Coulander CEL (1985) The inverse relation between fish consumption and 20 year mortality from coronary heart disease. *New England Journalof Medicine* **312**, 1205-1209.

[83] Davilgus ML, Stamler J, Orencia AJ, Dyer AR, Liu K, Greenland P, Walsh MK, Morris D & Shekell RB (1997) Fish consumption and the 30-year risk of fatal myocardial infarction. *New England Journal of Medicine* **336**, 1046-1053.

[84] Morris MC, Manson JE, Rosner B, Buring JE, Willett WC & Hennekens CH (1995) Fish consumption and cardiovascular diseases in the Physicians' Health Study: a prospective study. *American Journal of Epidemiology* **142**, 166-175.

[85] Albert CM, Hennekens CH, O'Donnell CJ, Ajani UA, Carey VJ, Willett WC, Ruskin JN & Manson JE (1998) Fish consumption and risk of sudden cardiac death. *Journal of the American Medical Association* **279**, 23-28.

[86] Albert CM, Campos H, Stampfer MJ, Ridker PM, Manson JE, Willett WC & Ma J (2002) Blood levels of long-chain n-3 fatty acids and the risk of sudden death. *New England Journal of Medicine* **346**, 1113-1118.

[87] Nagata C, Takatsuka N & Shimizu H (2002) Soy and fish intake and mortality in a Japanese community. *American Journal of Epidemiology* **156**, 824-831.

[88] Gillum RF, Mussolino M & Madans JH (2000) The relation between fish consumption, death from all causes, and incidence of coronary heart disease: the NHANES I epidemiologic follow-up study. *Journal of Clinical Epidemiology* **53**, 237-244.

[89] Hu FB, Bronner L, Willett WC, Stampfer MJ, Rexrode KM, Albert CM, Hunter D & Manson JE (2002) Fish and omega-3 fatty acid intake and risk of coronary heart disease in women. *Journal of the American Medical Association* **287**, 1815-1821.

[90] Kromhout D (1993) Epidemiological aspects of fish in the diet. *Proc Nutr Soc* **52**, 437-439.

[91] Kromhout D (1999) Fatty acids, antioxidants, and coronary heart disease from an epidemiological perspective. *Lipids* **34**, S27-S31.

[92] Ness AR, Hughes J, Elwood PC, Whitley E, Smith GD & Burr ML (2002) The long-term effect of dietary advice in men with coronary disease: follow-up of the Diet and Reinfarction trial (DART). *European Journal of Clinical Nutrition* **56**, 512-518.

[93] Nordøy A (2001) Fish consumption and cardiovascular diseases. *European Heart Journal* **3**, Suppl. D, D4-D7.

[94] Oomen CM, Feskens EJ, Räsänen L, Fidanza F, Nissinen AM, Menotti A, Kok FJ & Kromhout D (2000) Fish consumption and coronary heart disease mortality in Finland, Italy, and The Netherlands. *American Lournal of Epidemiology* **151**, 999-1006.

[95] Rodriguez BL, Sharp DS, Abbott RD, Burchfiel CM, Masaki K, Chyou PH, Huang B, Yano K & Kurb JD (1996) Fish intake may limit the increase in risk of coronary heart disease morbidity and mortality among heavy smokers. *Circulation* **94**, 952-956.

[96] Siscovick DS, Raghunathan TE, King I, Weinmann S, Wicklund KG, Albright J, Bovbjerg V, Arbogast P, Smith H, Kushi LH, Cobb L, Copass MK,Psaty BM, Lemaitre R, Retzlaaff B, Childs M & Knopp RH (1995) Dietary intake and cell membrane levels of long-chain n-3 polyunsaturated fatty acids and risk of primary cardiac arrest. . *Journal of the American Medical Association* **274**, 1363-1367.

[97] Siscovick DS, Raghunathan TE, Lemaitre R, King I & Cobb LA (2001) Long-chain n-3 polyunsaturated fatty acids and out-of-hospital primary cardiac arrest: clinical and public health implications of observational studies and clinical trials. *European Heart Journal* **3**, Suppl. D, D70-D74.

[98] Tavani A, Pelucchi C, Negri E, Bertuzzi M & La Vecchia C (2001) n-3 Polyunsaturated fatty acids, fish, and nonfatal acute myocardial infarction. *Circulation* **104**, 2269-2272.

[99] Yuan JM, Ross RK, Gao YT & Yu MC (2001) Fish and shellfish consumption in relation to death from myocardial infarction among men in Shanghai, China. *Am J Epidemiol* **154**, 809-816.

[100] Jones PJ & Lau VW (2002) Effect of n-3 polyunsaturated fatty acids on risk reduction of sudden death. *Nutr Rev* **60**, 407-409.

[101] Vollset SE, Heuch I & Bjelke E (1985) Fish consumption and mortality from coronary heart disease. Letter *New England Journal of Medicine* **313**, 820-821.

[102] Simonsen T, Vartun A, Lyngmo V & Nordøy A (1987) Coronary heart disease, serum lipids, platelets and dietary fish in two communities in northern Norway. *Acta Med Scand* **222**, 237-245.

[103] Ascherio A, Rimm EB, Stampfer MJ, Giovanucci EL & Willett WC (1995) Dietary intake of marine n-3 fatty acids, fish intake, and risk of coronary disease among men. *New England Journal of Medicine* **332**, 978-982.

[104] Piettinen P, Ascherio A, Korhornen AM, Willett WC, Albanes D & Virtamo J (1997) Intake of fatty acids and risk of coronary heart disease in a cohort of Finnish men. The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. *Am J Epidemiol* **145**, 876-887.

[105] Marckman P & Grønbæk M (1999) Fish consumption and coronary heart disease mortality. A systematic review of prspective cohort studies. *European Journal of Clinical Nutrition* **53**, 585-590.

[106] Dolecek TA & Grandits G (1991) Dietary polyunsaturated fatty acids and mortality in the Multiple Risk Factor Intervention Trial (MRFIT). *World Rev Nutr Diet* **66**, 205-216.

[107] Hu FB, Stampfer MJ, Manson JE, Rimm EB, Wolk A, Colditz GA, Hennekens CH & Willett WC (1999) Dietary intake of alpha-linolenic acid and risk of fatal ischemic heart disease among women. *American Journal of Clinical Nutrition* **69**, 890-897.

[108] Djoussé L, Pankow JS, Eckfeldt JH, et al. (2001) Relation between dietary linolenic acid and coronary artery disease in the National Heart, Lung, and blood Institute Family Heart Study. *Am J Clin Nutr* **74**: 612-619.

[109] Oomen CM, Ocké MC, Feskens EJM, et al. (2001) Alfa-Linolenic acid intake is not beneficially associated with 10-y risk of coronary artery disease incidence: the Zutphen elderly Study. *Am J Clin Nutr* **74**:457-463.

[110] Burr ML, Fehily AM, Gilbert JF, Rogers S, Holliday RM, Sweetnam PM, Elwood PC & Deadman NM (1989) Effects of changes in fat, fish,fiber intakes on death and myocardial infarction: Diet and Reinfarction Trial (DART). *Lancet* **2**, 757-761.

[111] GISSI-Prevenzione Investigators (1999) Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico. *Lancet* **354**, 447-455.

[112] Marchioli R et al. (2002) Early protection against sudden death by n-3 polyunsaturated fatty acids after myocardial infarction. Time-course analysis of the results of the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Prevenzione. *Circulation* **105**, 1897-1903.

[113] Bucher HC, Hengstler P, Schindler C, Meier G. (2002) N-3 polyunsaturated fatty acids in coronary heart disease: A meta-analysis of randomized controlled trials. *Am J Med* **112**: 298-304.

[114] Nilsen DW, Albrektsen G, Landmark K, et al.(2001) Effects of a high-dose concentrate of n-3 fatty acids or corn oil introduced early after an acute myocardial infarction on serum triacylglycerol and HDL cholesterol. *Am J Clin Nutr.* **74**: 50-56.

[115] de Lorgeril M, Renaud S, Mamelle N, Salen P, Martin JL,Monjaud I, Guidollet J, Touboul P & Delaye J (1994) Mediterranen alpha-linolenic acid-rich diet in secondary prevention of coronary heart disease. *Lancet **343**,* 1454-1459.

[116] de Lorgeril M, Salen P, Martin JL, Monjaud I & Delaye J (1999) Mediterranen diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. *Circulation* **99**, 779-785.

[117] de Lorgeril M & Salen P (2000) Diet as preventive medicine in cardiology. *American Journalof Medicine* **112**, 316-319.

[118] Hooper L (2001) Dietetic guidelines: diet in secondary prevention of cardiovascular disease. *Journal of Human Nutrition and Dietetics* **14**, 297-305.

[119] Hooper L (2001) Survey of UK dietetic departments: diet in secondary prevention of myocardial infarction. *Journal of Human Nutrition and Dietetics* **14**, 307-318.

[120] Pedersen, J.I., Ringstad, J., Almendingen K., Haugen, T.S., Stensvold, I. and Thelle D. (2000) Adipose tissue fatty acids and risk of myocardial infarction – a case-control study. *Eur J. Clin. Nutr.* **54**,618-625.

[121] Hallgren CG, Hallmans G, Jansson J-H, Marklund SL, Huhtasaari F, Schütz A, Strömberg U, Vessby B & Skerfving S (2001) Markers of high fish intake are associated with decreased risk of a first myocardial infarction. *British Journal of Nutrition* **86**, 397-404.

[122] Keli SO, Feskens EJM & Kromhout D (1994) Fish consumption and risk of stroke. *Stroke* **25**, 328-332.

[123] Gillum RF, Mussolino M & Madans J (1996) The relationship between fish consumption and stroke incidence and death. The NHANES I epidemiologi follow-up study. *Arch Intern Med* **156**, 537-542.

[124] Knapp HR (1994) Fatty acids and hypertension. *Wld Rev Nutr Diet* **76**, 9-14.

[125] Orencia AJ, Daviglus ML, Dyer AR, Shekelle RB & Stamler J (1996) Fish consumption and stroke in men: 30-year findings of the Chicago Western Electric Study. *Stroke* **27**, 204-209.

[126] Caicoya M (2002) Fish consumption and stroke: A community case-control study in Asturias, Spain. *Neuroepidemiology* **21**, 107-114.

[127] Gillum RF, Mussolino M & Madans JH (2001) Fish consumption and hypertension incidence in African americans and whites: the NHANES I epidemiologic follow-up study. *J Natl Med Assoc* **93**, 124-128.

[128] Iso H, Rexrode KM, Stampfer MJ, Manson JE, Colditz GA, Speizer FE, Hennekens CH & Willett WC (2001) Intake of fish and omega-3 fatty acids and risk of stroke in women. *Journal of the American Medical Association* **285**, 304-312.

[129] He K, Rimm EB, Merchant A, Rosner BA, Stampfer MJ, Willett WC & Ascherio A (2002) Fish consumption and risk of stroke in men. *JAMA* **288**,3130-3136.

[130] Hu FB, Cho E, Rexrode KM, Albert CM, Manson JE. (2003) Fish and long-chain omega-3 fatty acid intake and risk of coronary heart disease and total mortality in diabetic women. *Circulation*, **107**, 1852-1857

[131] Marchioli R, Barzi F, Bomba E, et al. (2002) Early protection against sudden death by n-3 polyunsaturated fatty acids after myocardial infarction. Time-course analysis of the results of the Gruppo Italiano per lo Studiodella Sopravvivenza nell´Infarto Miocardico (GISSI)-Prevenzione. *Circulation*;**105**:1897-1903.

[132] Albert CM, Campos H, Stampfer MJ, et al. (2002) Blood levels of long-chain n-3 fatty acids and the risk of sudden death. *N Engl J Med*;**346**:113-8.

[133] Kang JX & Leaf A (1996) Antiarryhthmic effects of polyunsaturated fatty acids: recent studies. *Circulation* **94**, 1774-1780.

[134] Nair SSD, Leitch JW, Falconer J & Garg ML (1996) Prevention of cardiac arrhythmia by dietary (n-3) polyunsaturated fatty acids and their mechanism of action. *Journal of Nutrition* **127**, 383-393.

[135] Christensen JH, Skou HA, Madsen T, Tørring I & Schmidt EB (2001) Heart rate variability and n-3polyunsaturated fatty acids in patients with diabetes mellitus. *Journal of Internal Medicine* **249**, 545-552.

[136] Pepe S & McLennan PL (2002) Cardiac membrane fatty acid composition modulated myocardial oxygen consumption and postischemic recovery of contractile function. *Circulation* **105**, 2303-2308.

[137] Geelen A, Brouwer IA, Zock PL, Kors JA, Swenne CA,Katan MB & Schouten EG (2002) (n-3) Fatty acids do not affect electrocardiographic characteristics of health men and women. *Journal of Nutrition* **132**, 3051-3054.

[138] Connor SL & Connor WE (1997) Are fish oils beneficial in the prevention and treatment of coronary artery disease. *American Journal of Clinical Nutrition* **66**(suppl) 1020S-1031S.

[139] Bradlow BA, Chetty N, van der Westhuyzen J, Mendelsohn D & Gibson JE (1983) The effects of a mixed fish diet on platelet function, fatty acids in serum lipids. *Thromb Res* **29**, 561-568.

[140] van Houwelingen AC, Hennissen AA, Verbeek-Schippers F, Simonsen T, Kester AD & Hornstra G (1988) Effect od a moderate fish intake on pletelet aggregation in human platelet rich plasma. *Thromb Haemost* **59**, 507-513.

[141] Hanninen O & Agren JJ (1989) Effects of moderate freshwater fish diet on lipid metabolism in Finnish students. *J Intern Med Suppl* **225**, 77-81.

[142] Nelson GJ, Schmidt PC & Corash L (1991) The effect of a salmon diet on blood clotting, platelet aggregation and fatty acids in normal adult men. *Lipids* **26**, 87-96.

[143] Mehta J, Lawson D & Saldeen TJ (1988) Reduction in plasminogen activator inhibitor-1 (PAI-1) with omega-3 polyunsaturated fatty acid (PUFA) intake. *Am Heart J* **116**, 1201-1206.

[144] Brown AJ & Roberts DC (1991) Fish and fish oil intake: effect on haematological variables related to cardiovascular disease. *Thromb Res* **64**, 169-178.

[145] Dunstan DW, Mori TA, Puddey IB, Beilin LJ, Bruke V, Morton AR & Stanton KG (1999) A randomised controlled study of the effects of aerobic excercise and dietary fish on coagulation and fibrinolytic factors in type 2 diabetics. *Thromb Haemost* **81**, 367-372.

[146] Vogel RA, Corretti MC & Plotnick GD (2000) The postprandial effect of components of the Mediterranean diet on endothelial function. *J Am Coll Cardiol* **36**, 1455-1460.

[147] Goodfellow J, Bellamy MF, Ramsey MW, Jones CJH & Lewis MJ (2000) Dietary supplementation with marine omega-3 fatty acids improve systemic large artery endothelial function in subjects with hypercholesterolemia. *J Am Coll Cardiol* **35**, 265-270.

[148] Leeson CPM, Mann A, Kattenhorn M, Deanfield JE, Lucas A & Muller DPR (2002) Relationship between circulating n-3 **fatty** acid concentrations and endothelial function in early adulthood. *European Heart Journal* **23**, 216-222.

[149] Harris, W.S., Connor, W.E., and McMurry, M.P. 1983. The comparative reductions of the plasma lipids and lipoproteins by dietary polyunsaturated fats: Salmon oil versus vegetable oils. *Metabolism* **32:** 179-184.

[150] Philipson, B.E., Rothrock, D.W., Connor, W.E., Harris, W.S., and Illingsworth, R.D. 1985. Reduction of plasma lipids, lipoproteins, and apoproteins by dietary fish oil in patients with hypertriglyceridemia. *N. Engl. J. Med.* **312:** 1210-1216.

[151] Sanders, T.A.B., Sullivan, D.R., Reeve, J., and Thompson, G.R. 1985. Triglyceride-lowering effect of marine polyunsaturates in patients with hypertriglyceridemia. *Arteriosclerosis* **5:** 459-465.

[152] Harris, W.S. 1989. Fish oils and plasma lipids and lipoprotein metabolism in humans: A critical review. *J. Lipid Res.* **30:** 785-807.

[153] Schmidt, E.B. and Dyerberg, J. 1994. Omega-3 fatty acids. Current status in cardiovascular medicine. *Drugs* **47:** 405-424.

[154] Gustafsson I-B, Ohrvall M, Ekstrand B & Vessby B (1996) Moderate amounts of n-3 fatty acid enriched seafood products are effective in lowering serum triglycerides and blood pressure in healthy subjects. *Journal of Human Nutrition and Dietetics* **9**, 135-145.

[155] Davis, R.A. and Boogaerts, J.R. 1982. Intrahepatic assembly of very low density lipoproteins. *J. Biol. Chem.***257:** 10908-10913.

[156] Nestel, P.J., Connor, W.E., Reardon, M.F., Connor, S., Wong, S., and Boston, R. 1984. Suppression by diets rich in fish oil of very low density lipoprotein production in man. *J. Clin. Invest.* **74:** 82-89.

[157] Harris WS, Connor WE, Alam N % Illingsworth DR (1988) The reduction of postprandial triglyceriemia in humans by dietary n-3 fatty acids. *J Lipid Res* **29**, 1451-1460.

[158] Mori TA, Bao DQ, Bruke V, Puddey IB, Watts GF & Beilin LJ (1999) Dietary fish as a major component of a weight-loss diet: effect on serum lipids, glucose, and insulin metabolism in overweight hypertensive subjects. *American Journal of Clinical Nutrition* **70**, 817-825.

[159] Mori TA, Bruke V, Puddey IB, Watts GF, O'Neal DN, Best JD & Beilin LJ (2000) Purified eicosapentaenoic and docosahexaenoic acids have differential effects on

serum lipids and lipoproteins, LDL particle size, glucose, and insulin in mildly hyperlipidemic men. *American Journal of Clinical Nutrition* **71**, 1085-1094.

[160] Nestel PJ (2000) Fish oil and cardiovascular disease: lipids and arterial function. *American Journal of Clinical Nutrition* **71**(suppl), 228S-231S.

[161] de Ruiz Gordoa, de Renobaldes M, del Cerro A, de Fernandez LE, Amiano P & Dorronsoro M (2002) Habitual fish intake is associated with decreased LDL susceptibility to ex vivo oxidation. *Lipids* **37**, 333-341.

[162] Madsen T, Skou HA, Hansen VE, Fog L, Christensen JH,Toft E & Schmidt EB (2001) C-reactive protein, dietary n-3 fatty acids, and the extent of coronary artery disease. *Am J Cardiol* **88**, 1139-1142.

[163] Kris-Etherton PM, Harris WS, Appel LJ. (2002) AHA Scientific Statement: Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. *Circulation* **106**, 2747-2757.

[164] Kris-Etherton PM, Harris WS, Appel LJ. (2003) AHA Scientific Statement: Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. *Arterioscler Thromb Vasc Biol* 23:e20-e31.

[165] Kris-Etherton PM, Harris WS, Appel LJ. (2003) Omega-3 fatty acids and cardiovascular disease. New recommendations from the American heart Association. *Arterioscler Thromb Vasc Biol* **23**, 151-152.

[166] Miles EA & Calder PC (1998) Modulation of immune function by dietary fatty acids. *Proceedings of the Nutrition Society* **57**, 277-292.

[167] Calder PC (2001) Polyunsaturated fatty acids, inflammation and immunity. *Lipids* **36**, 1007-1024.

[168] Gil A (2002) Polyunsaturated fatty acids and inflammatory diseases. *Biomed Pharmacother* **56**, 388-396.

[169] Siess, W., Roth, P., Scherer, B., Kurzmann, I., Bohlig, B., and Weber, P.C. 1991. *Health effects of polyunsaturated fatty acids in seafoods.* Basel: Karger.

[170] Brain, S.D. and Williams, T.J. 1990. Leukotrienes and inflammation. *Pharmacol. Ther.* **46:** 57-66.

[171] Lee, T.K., Hoover, R.L., Williams, J.D., Sperling, R.I., Ravalese, III, J., Spur, B.W., Robinson, D.R., Corey, E.J., Lewis, R.A., and Austen, K.F. 1985. Effect of dietary enrichment with eicosapentaenoic and docosahexaenoic acids on in vitro neutrophil and monocyte leukotriene generation and neutrophil function. *New. Engl. J. Med.* **312:** 1217-1224.

[172] Kremer, J.M., Bigaouette, J., and Michalek, A.U. 1985. Effects of manipulating dietary fatty acids on clinicalmanifestations of rheumatoid arthritis. *Lancet* **1:** 184.

[173] Kremer JM (2000) N-3 fatty acid supplements in rheumatoid arthritis. *Am J Clin Nutr* **71** (Suppl) 349S-351S.

[174] Fortin, P.R., Liang, M.H., Beckett, L.A., Wright, E.A., Kremer, J.M., Chalmers, T.C., and Sperling, R.I. 1992. A meta-analysis of the efficacy of fish oil in rheumatoid arthritis. *Arth. Rheum.* **35:** S201.

[175] Shapiro JA, Koepsell TD, Voigt LF, Dugowson CE, Kestin M & Nelson L (1996) Diet and rheumatoid arthritis in women: a possible protective effect of fish consumption. *Epidemiology* **7**, 256-263.

[176] Barth GA, Weigl L, Boeing H, Disch R & Borelli S (2001) Food intake of patients with atopic dermatitis. *Eur J Dermatol* **11**, 199-202.

[177] Stenson, W.F., Eirt, D., Rodgers, J., Burakoff, R., De Schryver-Keckemeti, K., Gramlich, T.L., and Beeken, W.1992. Dietary supplementation with fish oil in ulcerative colitus. *Ann. Int. Med.* **116:** 609-614.

[178] Donadio, J.V., Bergstrath, E.J., Offord, K.P., Spenser, D.C., and Holley, K.E. 1994. A controlled trial of fish oil in IgA nephropathy. *New. Engl. J. Med.* **331:** 1194-1199.

[179] Kutner NG, Clow PW, Zhang R & Aviles X (2002) Association of fish intake and survival in a cohort of incident dialysis patients. *Am J Kidney Dis* **39**, 1018-1024.

[180] Calder PC, Yakoob P,Thies F, Wallace FA & Miles EA (2002) Fatty acids and lymphocyte function. *Br J Nutr* **87** (Suppl), S31-S48.

[181] Arm JP, Horton CE, Spur BW, Mencia-Huerta JM, & Lee TH (1989) The effects of dietary supplementation with fish oil lipids on the airways response to inhaled allergen in bronchial asthma. *Am Rev Respir* **139**, 1395-1400.

[182] Dry J & Vincent D (1991) Effect of a fish oil diet on asthma: results of a 1-year double blind study. *Int Arch Allergy Immunol* **95**, 156-157.

[183] Peat KJ, Salome CM & Woolcock AJ (1992) Factors associated with bronchial hyperresponsiveness in Australian adults and children. *Eur Respir J* **5**, 921-929.

[184] Hodge L, Salome CM, Peat KJ, Haby MED MER, Xuan W & Woolcock AJ (1996) Consumption of oily fish and childhood asthma risk. *Med J Aust* **164**, 137-140.

[185] Nagakura T, Matsuda S, Shichijyo K, Sugimoto H & Hata K (2000) Dietary supplementation with fish oil rich in omega-3 polyunsaturated fatty acids in children with bronchial asthma. *Eur Respir J* **16**, 861-865.

[186] Fluge Ø, Omenaas E, Eide GE & Gulsvik A (1998) Fish consumption and respiratory symptoms among young adults in a Norwegian community. *European Respiratory Journal* **12**, 336-340.

[187] Stenius-Aarniala B, Aro H, Hakulinen A, Ahola I, Seppaelae E & Vapaatalo H (1989) Evening primrose oil and fish oilare ineffective as supplementary treatment of bronchial asthma. *Ann Allergy* **62**, 534-537.

[188] Thien FCK, Mencia-Huerta JM & Lee TH (1993) Dietary fish oil effects on seasonal hay fever and asthma in pollen-sensitive subjects. *Am Rev Respir Dis* **147**, 1138-1143.

[189] Hodge L, Salome CM, Hughes JM, Liu-Brennan D, Rimmer J, Allmann M, Pang D, Armour C & Woolcock AJ (1998) Effectf dietary intake of omega-3 and omega-6 fatty acids on severity of asthma in children. *Eur Respir J* **11**, 361-365.

[190] Takemura Y, Sakurai Y, Honjo S, Tokimatsu A, Gibo M, Hara T, Kusakari A & Kugai N (2002) The relationship between fish intake and the prevalence of asthma: the Tokorozawa childhod asthma and pollinosis study. *Prev Med* **34**, 221-225.

[191] Walda IC, Tabak C, Smit HA, Rasanen L, Fidanza F, Menotti A, Nissinen A, Feskens EJ & Kromhout D (2002) Diet and 20-year chronic obstructive pulmonary disease mortality in middle-aged men from three European countries. *European Journal of Clinical Nutrition* **56**, 638-643.

[192] Innis, S.M. 1991. Essential fatty acids in growth and development. *Prog. Lipid Res.* **30:** 39-103.

[193] Nettleton, J.A. 1993. Are omega-3 fatty acids essential nutrients in fetal and infant development? *J. Am. Dietet.Assoc.* **93:** 58-64.

[194] Innis SM (2002) The role of dietary n-6 and n-3 fatty acids in the developing brain. *Dev Neurosci* **22**, 474-480.

[195] Wainwright PE (2002) Dietary essential fatty acids and brain function: a developmental perspective on mechanisms. *Proc Nutr Soc* **61**, 61-69.

[196] O’Brien, J.S., Fillerup, D.L., and Mean, J.F. 1964. Quantification of fatty acid and fatty aldehyde composition of ethanolamine, choline and serine glycerophosphatides in human cerebral grey and white matter. *J. Lipid Res.* **5:** 329-330.

[197] Anderson, G.J., Connor, W.E., and Corliss, J.D. 1990. Docosahexaenoic acid is the preferred dietary n-3 fatty acid for the development of the brain and retina. *Ped. Res.* **27:** 89-97.

[198] Cotman, C., Blank, M.L., Moehl, A., and Snyder, F. 1969. Lipid composition of synaptic plasma membranes isolated from rat brain by zonal ultracentrifugation. *Biochemistry* **8:** 237-247.

[199] Youyou, A., Durand, G., Pascal, G., Picotti, M., Dumont, O., and Bourre, J.M. 1986. Recovery of altered fatty acid composition induced by a diet devoid on n-3 fatty acids in myelin, synaptosomes, mitochondria and microsomes of developing rat brain. *J. Neurochem.* **46:** 224-227.

[200] Wheeler, T.G., Benolken, R.M., and Anderson, R.E. 1975. Visual membranes: Specificity of fatty acid precursors for the electrical response to illumination. *Science* **188:** 1312-1314.

[201] Fliesler, S.J. and Anderson, R.E. 1983. Chemistry and metabolism of lipids in the vertebrate retina. *Prog. Lipid Res.* **22:** 79-131.

[202] Anderson, R.E., O'Brien, P.J., Wiegand, R.D., Kountz, C.A., and Stinson, A.M. 1992. Conservation of docosahexaenoic acid in the retina. *Adv. Exp. Med. Biol.* **318:** 285-294.

[203] Berson EL, Rosner B, Sandberg MA, Hayes KC, Nicholson BW, Weigel-DiFranco C, Willett W (1993) A randomized trial of vitamin A and vitamin E supplementation for retinitis pigmentosa. *Arch Ophthalmol* **111**, 761-772.

[204] Converse, C.A., Hammer, H.M., Packard, C.J., and Shepard, J. 1983. Plasma lipid abnormalities in retinitis pigmentosa and related diseases. *Trans. Ophtalmol. Soc.* **103:** 508-512.

[205] Bazan, N.G., Scott, B.L., Reddy, T.S., and Pelias, M.Z. 1986. Decreased content of docosahexaenoate and arachidonate in plasma phospholipids in Usher's syndrome. *Biochem. Biophys. Res. Commun.* **141:** 600-604.

[206] Anderson, R.E., Maude, M.B., Lewis, R.A., Newsome, D.A., and Fishman, G.A. 1987. Abnormal plasma levels of polyunsaturated fatty acids in autosomal dominant retinitis pigmentosa. *Exp. Eye Res.* **44:** 155-158.

[207] Gong, J., Rosner, B., Rees, D.G., Berson, E.L., Weigel-DiFranco, C.A., and Schaefer, E.J. 1992. Plasma docosahexaenoic acid levels in various genetic form of retinitis pigmentosa. *Invest. Ophtalmol. Vis. Sci.* **33:**2596-2602.

[208] Uauy, R.D., Birch, D.G., Birch, E.E., Tyson, J.E., and Hoffman, D.R. 1990. Effects of dietary omega-3 fatty acids on retinal function of very-low-birth-weight neonates. *Pediatr. Res.* **28:** 485-492.

[209] Birch, D.G., Birch, E.E., Hoffman, D.R., and Uauy, R.D. 1992. Retinal development in very-low-birth-weight infants fed diets differing in omega-3 fatty acids. *Invest. Ophtalmol. Vis. Sci.* **33:** 2365-2376.

[210] Smith W, Mitchell P & Leeder SR (2000) Dietary fat and fish intake and age-related maculopathy. *Archives of Ophthalmology* **118**, 401-404.

[211] Putnam, J.C., Carlson, S.E., DeVoe, P.W., and Barness, L.A. 1982. The effect of variations in dietary fatty acids on the fatty acid composition of erythrocytes phosphatidylcholine and phosphatidylethanolamine in human infants. *Am. J. Clin. Nutr.* **36:** 106-114.

[212] Carlson SE (2001) Docosahexaenoic acids and arachidonic acids in infant development. *Semin Neonatol* **6**, 437-449.

[213] Lapillonne A & Carlson SE (2001) Polyunsaturated fatty acids and infant growth. *Lipids* **36**, 901-911.

[214] Olsen SF & Secher NJ (2002) Low consumption of seafood in early pregnancy as a risk factor for preterm delivery: prospective cohort study. *British Medical Journal* **324**, 1-5.

[215] Helland IB, Saugstad OD, Smith L, Saarem K, Solvoll K, Ganes T & Drevon CA (2001) Similar effects on infants on n-3 and n-6 fatty acids supplementation to pregnant and lactating women. *Pediatrics* **108**, e82-e91.

[216] Helland IB, Smith L, Saarem K, Saugstad OD & Drevon CA (2003) Maternal supplementation with very-long-chain n-3 fatty acids during pregnancy and lactation augments children's IQ at 4 years of age. *Pediatrics* **111**, e39-e44.

[217] Heird WC (2001) The role of polyunsaturated fatty acids in term and preterm infants and breastfeeding mothers. *Pediatr Clin North Am* **48**, 173-188.

[218] Koletzko B, Agostoni C, Carlson SE, Clandinin T, Hornstra G, Neuringer M, Uauy R, Yamashiro Y & Willatts P (2001) Long chain polyunsaturated fatty acids (LC-PUFA) and perinatal development. *Acta Paediatr* **90**, 460-464.

[219] Miller, M.E., Anagnostou, A.A., Ley, B., Marshall, P., and Steiner, M. 1987. Effect of fish oil concentrates on hemorheological and hemostatic aspects of diabetes mellitus: A prelimnary study. *Thromb. Res.* **47:** 201-214.

[220] Rillaerts, E.G., Englemann, G.J., Van Camp, K.M., and DeLeeuw, I. 1989. Effect of omega-3 fatty acids in diet of type I diabetic subjects on lipid values and hemorheological parameters. *Diabetes* **38:** 1412-1416.

[221] Friedberg, C.E., Janssen, M.J.F.M., Heine, R.J., and Grobbe, D.E. 1998. Fish oil and glycemic control in diabetes – A meta-analysis. *Diab. Care* **21:** 494-500.

[222] Malasanos, T.H. and Stacpoole, P.W. 1991. Biological effects of n-3 fatty acids in diabetes mellitus. *Diab. Care* **14:** 1160-1179.

[223] Lou, J., Rizkalla, S.W., Vidal, H., Oppert, J.M., Colas, C., Boussairi, A., GuerreMillo, M., Chapuis, A.S., Chevalier, A., Durand, G., and Slama, G. 1998. Moderate intake of n-3 fatty acids for 2 months has no detrimental effect on glucose metabolism and could ameliorate the lipid profile in type-2 diabetic men. Results of a controlled study. *Diab. Care* **21:** 717-724.

[224] Sirtori, C.R., Crepaldi, G., Manzato, E., Mancini, M., Rivellese, A., Paoletti, R., Pazzucconi, F., Pamparana, F., and Stragliotto, E. 1998. One-year treatment with ethyl esters of n-3 fatty acids in patients with hypertriglyceridemia and glucose intolerance. Reduced triglyceridemia, total cholesterol and increased HDL-C without glycemic alterations. *Atherosclerosis* **137:** 419-427.

[225] Sirtori CR & Galli C (2002) N-3 fatty acids and diabetes. *Biomed Pharmacother* **56**, 397-406.

[226] Gallai, V., Sarchielli, P., Trequattrini, A., Franceschini, M., Floridi, A., Firenze, C., Alberti, A., Dibenedetto, D., and Stragliotto, E. 1995. Cytokine secretion and eicosanoid production in the peripheral-cells of MS patients undergoing dietary supplementation with n-3 polyunsaturated fatty acids. *J. Neuroimmunol.* **56:** 143-153.

[227] Calder, P.C. 1997. N-3 polyunsaturated fatty acids and cytokine production in health and disease. *Ann. Nutr. Metab.* **41:** 203-234.

[228] Zhang SM, Willett WC, Hernan MA, Olek MJ & Ascherio A (2000) Dietary fat in relation to risk of multiple sclerosis among two large cohorts of women. *Am J Epidemiol* **152**, 1056-1064.

[229] Adams PB, Lawson S, Sanigorski A & Sinclair AJ (1996) Arachidonic acid to eicosapentaenoic acid ratio in blood correlates positively with clinical symptoms of depression. *Lipids* **31**, (Suppl) S157-S161.

[230] Edwards R, Peet M, Shay J & Horrobin D (1998) Omega-3 polyunsaturated fatty acid levels in the diet and in red blood cell membranes of depressed patients. *J Affect Disord* **48**, 149-155.

[231] Hibbeln JR (1998) Fish consumption and major depression. *Lancet **351**, 1213.*

[232] Peet M, Murphy B, Shay J & Horrobin D (1998) Depletion of omega-*3* fatty acid levels in rede blood cell membranes of depressive patients. *Biol Psychatry* **43**, 315-319.

[233] Stoll AL, Severus WE, Freeman MP, Rueter S, Zboyan HA, Diamond E, Cress KK & Marangell LB (1999) Omega-3 fatty acids in bipolar disorder: a prelimnary double-blind, placebo controlled trial. *Arch Gen Psychiat* **56**, 407-412.

[234] Severus WE, Littman AB & Stoll AL (2001) Omega-3 fatty acids, homocysteine, and the increased risk of cardiovascular mortality in major depressive disorder. *Harv Rev Psychiatry* **9**, 280-293.

[235] Tanskanen A, Hibbeln JR, Tuomiletho J, Uutela A, Haukkala A, Viinamäki, Lehtonen J & Vartiainen E (2001) Fish consumption and depressive symptoms in the general population in Finland. *Psykiatric Services* **52**, 529-531.

[236] Maes M, Smith R, Christophe A, Cosyns P, Desnyder R & Meltzer H (1996) Fatty acid composition in major depression: decreased n3 fractions in cholesteryl esters and increased C20:4n6/C20:5n3 ratio in cholesteryl esters and phospholipids. *J Affect Disord* **38**, 35-46.

[237] Maes M, Christophe A, Delanghe J, Altamura C, Neels H & Meltzer H (1999) Lowered n3 polyunsaturated fatty acids in serum phospholipids and cholerstreyl esters of depressed patients. *Psychiatr Res* **85**, 275-291.

[238] Schins A, Honig A & Maes M (2001) Polyunsaturated fatty acids: the missing link between cardiac events and depression. *Acta Neurophysica* **13**, 38-45.

[239] Zalcman S, Green-Johnson JM, Murray L, Nance DM, Dyck D, Anisman H & Greenberg AH (1994) Cytokine-specific central monoamine alterations induced by interleukin-1, -2, and –6. *Brain Res* **643**, 40-49.

[240] Block ER & Edwards D (1987) Effect of plasma membrane fluidity on serotonin transport by endothelial cells. *Am J Physiol* **253**, C672-C678.

[241] Yehuda S, Rabinovitz S & Mostofsky DI (1999) Essential fatty acids are mediators of brain biochemistry and cognitive functions. *J Neurosci Res* **56**, 565-570.

242] Yokogoshi H, Kimiko O & Okitsu M (1993) Accumulation of brain tryptophan in rats after administration of various fats or fatty acids. *Biosci Biotech Biochem* **57**, 181-184.

[243] Hibbeln JR, Linnoila M, Umhau JC, Rawlings R, George DT & Salem N Jr. (1998) Essential fatty acids predict metabolites of serotonin and dopamine in cerebrospinal fluid among healthy control subjects, and early- and late-onset alcoholics. *Biological Psychiatry* **44**, 235-242.

[244] Lombard CB (2000) What is the role of food in preventing depression and improving mood, performance and cognitive function? *Med J Aust* **173**, (Suppl) S104-S105.

[245] Silvers KM & Scott KM (2002) Fish consumption and self-reported physical and mental health status. *Public Health Nutrition* **5**, 427-431.

[246] Jumpsen J, Lien EL,Goh YK & Clandinin MT (1997) Small changes of dietary (n-6) and (n-3) polyunsaturated fatty acids in brain phosphatidylethanolamine and phosphatidylcholine fatty acid composition during development of neuronaland glial cells in rats. *J Nutr* **127**, 724-731.

[247] Jensen MM; Skarsfeldt T & Hoy CE (1996) Correlation between level of (n-3) polyunsaturated fatty acids in brain phospholipids and learning ability in rats. A multiple generation study. *BiochimBiophys Acta* **1300**, 203-209.

[248] de Wilde MC, Farkas E, Gerrits M, Kiliaan AJ & Luiten PGM (2002) The effect of n-3 polyunsaturated fatty acid-rich diets on cognitive and cerebrovascular parameters in chronic cerebral hypoperfusion. *Brain Research* **947**, 166-173.

[249] Gamoh S, Hashimoto M, Sugioka K, Shahdat HM, Hata N, Misawa Y & Masumura S (1999) Chronic administration of docosahexaenoic acid improves reference memory-related learning ability in young rats. *Neuroscience* **93**, 237-241.

[250] Kalmijn S, Feskens EJ, Launer LJ & Kromhout D (1997) Polyunsaturated fatty acids, antioxidants, and cognitive function in very old men. *Am J Epidemiol* **145**, 33-41.

[251] Kalmijn S, Launer LJ, Ott A, Witterman JC, Hofman A & Breteler MM (1997) Dietary fat intake and the risk of incident dementia in the Rotterdam Study. *Ann Neurol* **42**, 776-782.

[252] Yamada T, Kadekaru H, Matsumoto S, Inada H, Tanabe M, Moriguchi EH, Moriguchi Y, Ishikawa P, Ishikawa AG,Taira K & Yamori Y (2002) Prevalence of dementia in the older Japanese-Brazilian population. *Psychiatry Clin Neurosci* **56**, 71-75.

[253] Fenton WS, Dickerson F, Boronow J, Hibbln JR & Knable M (2001) A placebo-controlled trial of omega-3 fatty acid (ethyleicosapentaenoic acid) supplementation for residual symptoms and cognitive impairment in schizophrenia. *Am J Physiol* **158**, 2071-2074.

[254] Armstrong B & Doll R (1975) Environmental factors and cancer incidence and mortality in different countries. *Int J Cancer* **15**, 617-631.

[255] Decarli A & La Vecchia C (1986) Environmental factors and cancer mortality in Italy. *Oncology* **43**, 116-126.

[256] Kaizer L, Boyd NF, Kruikov V & Tritchler D (1989) Fish consumption and breast cancer risk: an ecological study. *Nutr Cancer* **12**, 61-68.

[257] Willett WC, Stampfer MJ, Colditz GA, Rosner BA & Speizer FE (1990) Relation of meat, fat,and fiber intake to the risk of colon cancer in a prospective study among women. *New Englan Journal of Medicine* **323**, 1664-1672.

[258] Caygill CP & Hill MJ (1995) Fish, n-3 fatty acids and human colorectal and breast cancer risk: an ecological study. *European Journal of Cancer Prevention* **4**, 329-332.

[259] Caygill CP, Charlett A & Hill MJ (1996) Fat, fish oil and cancer. *Br J Cancer* **74**, 159-164.

[260] Kim Y & Mason JB (1996) Nutrition, chemoprevention of gastrointestinal cancers: a critical review. *Nutrition Reviews* **54**, 259-279.

[261] Fernandez E, Chatenoud L, La Vecchia C, Negri E & Franceschi S (1999) Fish consumption and cancer risk. *American Journal of Clinical Nutrition* **70**, 85-90.

[262] La Vecchia C, Chatenoud L, Altieri A & Tavani A (2001) Nutrition and health: epidemiology of diet, cancer and cardiovascular diseases in Italy. *Nutr Metab Cardiovasc Dis* **11** (suppl 4) 10-15.

[263] Notani PN & Jayant K (1987) Role of diet in upper aerodigestive tract cancers. *Nutr Cancer* **10**, 103-113.

[264] Ziegler RG,Morris LE, Blot WJ, Pottern LM, Hoover R & Fraumeni JF Jr (1981) Esophageal cancer among blackmen in Washington, D.C.II. Role of nutrition. *J Natl Cancer Inst* **67**, 1199-1206.

[265] Launoy G, Milan C, Day NE, Pienkowski MP, Gignoux M & Faivre J (1998) Diet and squamous-cell cancer of the oesophagus: a French multicentre case-control study. *Int J Cancer* **76**, 7-12.

[266] Hansson LE, Nyren O, Bergstrom R, Wolk A, Lindgren A, Baron J & Adami HO (1993) Diet and the risk of gastric cancer. A population-based case-control study in Sweden. *Int J Cancer* **55**, 181-189.

[267] Nogan LT, Mizoue T, Fujino V, Tokui N & Yoshimura T (2002) Dietary factors and stomach cancer mortality. *British Journal of Cancer* **87**, 37-42.

[268] Kato I, Akhmedkhanov A, Koenig K, Toniolo PG, Shore RE & Riboli E (1997) Prospective study of diet and female colorectal cancer. The New York University Womens`Health Study. *Nutr Cancer* **28**, 276-281.

[269] Bostick RM, Potter JD, Kushi LH, Sellers TA, Steinmetz KA, McKenzie DR, Gapstur SM & Folsom AR (1994) Sugar, meat, and fat intake and non-dietary risk factors for colon cancer incidence in Iowa women (United States). *Cancer Causes and Control* **5**, 38-52.

[270] Deckere EAM (1999) Possible beneficial effects of fish and fish n-3 polyunsaturated fatty acids in breast and colorectal cancer. *European Journal of Cancer Prevention* **8**, 213-221.

[271] Tiemersma EW, Kampman E, Bueno de Mesquita HB, Bunschoten A, van Schothorst EM,Kok FJ & Kromhout D (2002) Meat consumption, cigarette smoking, and genetic susceptibility in the etiology of colorectal cancer: results froma Dutch prospective study. *Cancer Causes Control* **13**, 383-393.

[272] Zhang J, Temme EHM & Kesteloot H (2000) Fish consumption is inversely associated with male lung cancer mortality in countries with high levels of cigarette smoking or animal fat consumption. *International Journal of Epidemiology* **29**, 615-621.

[273] Takezaki T, Hirose K, Hamajima N, Yatabe Y, Mitsudomi T, Suglura T, Kuroishi T & Tajima K (2001) Dietary factors and lung cancer risk in Japanese: with special reference to fish consumption and adenocarcinomas. *British Journal of Cancer* **84**, 1199-1206.

[274] Baghurst PA, McMichael AJ, Slavotinek AH, Baghurst KI, Boyle P & Walker AM (1991) A case-control study of diet and cancer of the pancreas. *Am J Epidemiol* **134**, 167-179.

[275] Kato K, Akai S Tominaga S & Kato I (1989) A case-control study of biliary tract cancer in Niigata Prefecture, Japan. *Jpn J Cancer Res* **80**, 932-938.

[276] Vatten LJ, Solvoll K & Løken EB (1990) Frequency of meat and fish intake and risk of breast cancer in a prospective study of 14,500 Norwegian women. *Int J Cancer* **46**, 12-15.

[277] Landa MC, Fargo N & Tres A (1994) Diet and the risk of breast cancer in Spain. *Eur J Cancer Prev* **3**, 313-320.

[278] Simonsen N, vant't Veer P, Strain JJ, Martin-Moreno JM, Huttunen JK,Navajas JF, Martin BC, Thamm M, Kardinaal AFM, Kok FJ & Kohlmeier L (1998) Adipose tissue omega-3 and omega-6 fatty acid content and breast cancer in the EURAMIC Study. *American Journal of Epidemiology* **147**, 342-352.

[279] Terry P, Wolk A, Vainio H & Weiderpass E (2002) Fatty fish consumption lowers the risk of endometrial cancer: A nationwide case-control study in Sweden. *Cancer Epidemiology, Biomarkers & Prevention* **11**, 143-145.

[280] Bosetti C, Negri E, Franceschi S, Pelucchi C, Talamini R, Montella M, Conti E & La Vecchia C (2001) Diet and ovarian cancer risk: a case-control study in Italy. *Int J Cancer* **93**, 911-915.

[281] Willett WC (1997) Specific fatty acids and risks of breast and prostate cancer: dietary intake. *Am J Clin Nutr* **66** (Suppl), 1557-1563.

[282] Mori M, Harabuchi I, Miyake H, Casagrande JT, Henderson BE & Ross RK (1988) Reproductive, genetic, and dietary risk factors for ovarian cancer. *Am J Epidemiol* **128**, 771-777.

[283] Kobayashi M, Sasaki S, Hamada GS & Tsugane S (1999) Serum n-3 fatty acids,fish consumption and cancer mortality in sis Japanese populations in Japan and Brazil. *Jpn J Cancer Res* **90**, 914-921.

[284] Terry P, Lichtenstein P, Feychting M, Ahlbom A & Wolk A (2001) Fatty fish consumption and risk of prostate cancer. *Lancet* **357**, 1764-1766.

[285] Chyou P-H,Nomura AM & Stemmermann GN (1993) A prospective study of diet, smoking, and lower urinary tract cancer. *Ann Epidemiol* **3**, 211-216.

[286] McLaughlin JK, Gao YT, Gao RN, Zheng W, Ji BT, Blot WJ & Fraumeni JF Jr. (1992) Risk factors for renal-cell cancer in Shanghai, China. *Int J Cancer* **52**, 562-565.

[287] Franceschi S, Levi F, Negri E, Fassina A & La Vecchia C (1991) Diet and thyroid cancer: a pooled analysis of four European case-control studies. *Int J Cancer* **48**, 395-398.

[288] Bosetti C, Kolonel L, Negri E, Ron E, Franceschi S, Dal Maso L, Galanti MR, Mark SD, Preston-Martin S, McTiernan A, Land C, Jin F, Wingren G, Hallquist A, Glattre E, Lund E, Levi F, Linos D & La Vecchia C (2001) A pooled analysis of case-control studies of thyroid cancer. VI. Fish and shellfish consumption. *Cancer Causes and Control* **12**, 375-382.

[289] World Cancer Research Fund, American Institute for Cancer Research. Food, nutrition, and the prevention of cancer: a global perspective. Washington D.C.: American Institute for Cancer Research 1997, 425-429.

[290] Watkins BA, Lippman HE, Le Bouteiller L, Li Y & Seifert MF (2001) Bioactive fatty acids: role in bone biology and bone cell function. *Progress in Lipid Research* **40**, 125-148.

[291] Vessby B (2003) Dietary fat, fatty acid composition in plasma and the metabolic syndrome. *Curr Opin Lipidol* **14**, 15-19.

[292] Storlien LH, Kriketos AD, Jenkins AB, Baur LA, Pan DA, Tapsell LC & Calvert GD (1997) Does dietary fat influence insulin? *Ann N Y Acad Sci* **827**, 287-301.

[293] Kris-Etherton PM, Etherton TD, Carlson J & Gardner C (2002) Recent discoveries in inclusive food-based approaches and dietary patterns for reduction in risk for cardiovascular disease. *Current Opinion in Lipiology* **13**, 397-407.

[294] Stone NJ & Van Horn L (2002) Therapeutic lifestyle change and adult treatment panel III:evidence then and now. *Curr Atheroscler Rep* **4**, 433-443.

[295] Haveman-Nies A, Tucker KL, de Groot LC, Wilson PW & van Staveren WA (2001) Evaluation of dietary quality in relationship to nutritional and lifestyle factors in elderlypeople of the US Framingham Heart Study and the European SENECA study. *Eur J Clin Invest* **55**, 870-880.

[296] Haveman-Nies A, de Groot LP, Burema J,Cruz JA, Osler M & van Stavern WA; SENECA Investigators (2002) Dietary quality and lifestyle factors in relation to 10-year mortality in older Europeans: the SENECA study. *Am J Epidemiol* **156**,962-968.

[297] Karl H, Ruoff U & Blutgen A (2002) Levels of dioxins in fish and fishery products on the German market. *Chemosphere* **49**, 765-773.

[298] Buck GM, Vena JE, Schisterman EF, Dmochowski J, Mendola P, Sever LE, Fitzgerald E, Kostyniak P, Greizerstein H & Olson J (2000) Parenta consumption of contaminated sport fish from Lake Ontario and predicted fecundability. *Epidemiology* **11**, 388-393.

[299] Furberg AS, Sandanger T, Thune I, Burkow IC & Lund E (2002) Fish consumption and plasma levels of organochlorines in a female population in Northern Norway. *J Environ Monit* **4,** 175-181.*European Journal of Clinical Nutrtion* **55**, 870-880.

[300] Clarkson TW (1997) The toxicology of mercury. *Crit Rev Clin Lab Sci* **34**, 369-403.

[301] World Health Organisation (1990) *Methylmercury. Environmental Health Criteria no. 101. International Programme on Chemical Safety,* Geneva:WHO.

[302] Lucchini R, Cortesi I, Facco P, Benedetti L, Camerini D, Carta P, Urbano ML, Zaccheo A & Alessio L (2002) Neurotoxic effect of exposure to low doses ofmercury. *Med Lav* **93**, 202-214.

[303] Davidson PW, Palumbo D, Myers GJ, Cox C, Shamlaye CF, Sloane-Reeves J, Cernichiari E, Wilding GE & Clarkson TW (2000) Neurodevelopmental outcomes of Seychellois children fromthe pilot cohort at 108 months following prenatal exposure tomethylmercury from a maternal fish diet. *Environmental Research* **84**, 1-11.

[304] Palumbo D, Cox C, Davidson PW, Myers GJ, Choi A, Shamlaye CF, Sloane-Reeves J, Cernichiari E, & Clarkson TW (2000) Association between prenatal exposure to methylmercury and cognitive functioning in Seychellois children: a reanalysis of the McCarthy Scales of children’s ability from the main cohort study. *Environmental Research* **84**, 81-88.

[305 Salonen JT, Seppänen K, Nyyssönen K, Korpela H, Kauhanen J, Kantola M, Tuomilehto J, Esterbauer H, Tatzber F & Salonen R (1995) Intake of mercury from fish, lipid peroxidation, and the risk of myocardial infarction and coronary, cardiovascular, and any death in Eastern Finnish men. *Circulation* **91**, 645-655.

[306] Sanzo JM, Dorronsoro M, Amiano P, Amurrio A, Aguinagalde FX & Azpiri MA (2001) Estimation and validation of mercury intake associated with fish consumption in an EPIC cohort of Spain. *Public Health Nutrition* **4**, 981-988.

[307] Marien K & Patrick GM (2001) Exposure analysis of five fish-consuming populations for overexposure to methylmercury. *J Expo Anal Environ Epidemiol* **11**, 193-206.

[308] Yoshizawa K, Rimm EB, Morris JS, Spate VL, Hsieh CC, Spiegelman D, Stampfer MJ & Willett WC (2002) Mercury and the risk of coronary heart disease in men. *New England Journal of Medicine* **347**, 1755-1760.

[309] Guallar E, Sanz-Gallardo MI, vVeer P, Bode P, Aro A, Gómez-Aracena J, Kark JD, Riemersma RA, Martín-Moreno J & Kok FJ (2002) Mercury, fish oils, and the risk of myocardial infarction. *New England Journal of Medicine* **347**, 1747-1754.

[310] Aas K & Elsayed S (1969) Characterisation of a major allergen (cod).Effect of enzymic hydrolysis on the allergen activity. *J Allergy* **44**, 333.

[311] Poulsen LK,Hansen TK, Norgaard A, Vestergaard H, Stahl Skov P& Bindslev-Jensen C (2001) Allergens from fish and egg. *Allergy* **67**, 39-42.

[312] Report from a Nordic seminar, *Fish as Food*. ©Nordic Council of Ministers, Copehagen, TemaNord 2001:532, ISBN 92-893-0622-X, ISSN 0908-6692.

[313] Jeebhay MF, Robins TG, Lehrer SB & Lopata AL (2001) Occupational seafood allergy: a review. *Occup Environ Med* **58**, 553-562.

[314] Burks W (2002) Current understanding of food allergy. *Ann N Y Acad Sci* **964**, 1-12.

[315] Deardorff TL (1991) Epidemiology of marine fish-borne parasitic zoonoses. *Southeast Asian J Trop Med Public Health* **22**, (Suppl) 146-149.

[316] Adams AM, Murrell KD & Cross JH (1997) Parasites of fish and risks to public health. *Rev Sci Tech* **16**, 652-660.

[317] Macphearson CN, Gottstein B & Geerts S (2000) Parasitic food-borne and water-borne zoonoses. *Rev Sci Tech* **19**, 240-258.

[318] Bhatia BB (1991) Current status of food-borne parasitic zoonoses in India. *Southeast Asian J Trop Med Public Health* **22**, (Suppl) 36-41.

[319] Li X (1991) Food-borne parasitic zoonoses in the People's Republic of China. *Southeast Asian J Trop Med Public Health* **22**, (Suppl) 31-35.

[320] Trevino S (1998) Fish and shellfish poisoning. *Clin Lab Sci* **11**, 309-314.

[321] Sumner J & Ross T (2002) A semi-quantitive seafood safety risk assessment. *Int J Food Microbiol* **77**, 55-59.

[322] Jemmi T, Pak SI & Salman MD (2002) Prevalence and risk factors for contamination with Listeria monocytogenes of imported and exported meat and fish products in Switzerland, 1992-2000. *Prev Vet Med* **54**, 25-36.

[323] Gonzalez-Rodriguez MN, Sanz JJ, Santos JA, Otero A & Garcia-Lopez ML (2002) Numbers and types of microorganisms in vacuum-packed cold-smoked freshwater fish at the retail level. *Int J Food Microbiol* **77**, 161-168.

[324] Durborow RM (1999) Health and safety concerns in fisheries and aquaculture. *Occup Med* **14**, 373-406.