1st CONSULTATION DOCUMENT ON NRV’s-NCD FOR EPA AND DHA

CODEX ALIMENTARIUS COMMISSION

Joint FAO/WHO Food Standards Program

Codex Committee on Nutrition and Foods for Special Dietary Uses (CCNFSDU)

Electronic Working Group to establish a Codex NRV-NCD

for DHA and EPA

(Co-chaired by The Russian Federation and Chile)

FIRST CONSULTATION PAPER, APRIL 2015

The 36th Session 2014 of the Codex Committee on Nutrition and Foods for Special Dietary Uses (CCNFSDU) agreed to recommend new work to develop and add a potential new Codex nutrient reference value (NRV) to docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) intended for the general population for labelling purposes in relation to the risk of Non-Communicable Diseases (NCDs).

The project document for the new work will be considered for approval by the Codex Alimentarius Commission in the 38th session, in July 2015.

The reference aspects of this work for CCNFSDU are to:

- Assess the most current scientific evidence in line with the General Principles.
- Make recommendations to set a potential Codex NRV-NCD for the total of Omega-3 fatty acids DHA and EPA, in accordance with the general principles for NRV-NCD as set out in the Annex to the Guidelines on Nutrition Labelling (CAC/GL 2-1985).

The document reviews the main scientific evidence available on the beneficial effects of DHA and EPA intake for health, in order to assess it according to the general principles to establish NRV-NCD.
When reviewing, observing and analyzing the data supporting a positive effect on health in many ways (thrombosis risk, arrhythmia risk, post heart attack, better cardiovascular rate including sudden death from arrhythmias) it may be considered that the omega 3 fatty acid of 18 carbon atoms 18:3 n-3 (alpha-linolenic acid) is precursor to form EPA and DHA. Similarly, EPA 20:5 n-3 serves as precursor in DHA 22:6 n-3 formation. Nevertheless, this conversion is limited and variable. Therefore, the effects of diet or supplement contributions rich in omega 3 fatty acids will depend on how each individual is able to form more or less amount of active compounds (EPA and DHA). This makes the data combination of diverse studies difficult, and weakens the evidence, which must be judged in a global way. For this reason, this review will be focused on the evidence available for health effects of EPA and DHA specifically.

2. GENERAL PRINCIPLES FOR ESTABLISHING NRV-NCD (REP 13/NFSDU Appendix IV)

“Potential Attachment to guidelines of Codex on Nutritional Labelling, consolidated version: general principles to establish the reference values of nutrients for general population (for adoption).”

3. GENERAL PRINCIPLES FOR ESTABLISHING NRVs

3.1 Selection of Suitable Data Sources to Establish NRVs

3.1.1 Relevant daily intake reference values provided by FAO/WHO that are based on a recent review of the science should be taken into consideration as primary sources in establishing NRVs.

3.1.2 Relevant daily intake reference values that reflect recent independent review of the science, from recognized authoritative scientific bodies other than FAO/WHO could also be taken into consideration. Higher priority should be given to values in which the evidence has been evaluated through a systematic review.

3.1.3 The daily intake reference values should reflect intake recommendations for the general population.
3.2 Selection of Nutrients and Appropriate Basis for NRVs

3.2.1 Selection of Nutrients and Appropriate Basis for NRVs-R

3.2.1.1 The NRVs-R should be based on Individual Nutrient Level 98 (INL98). In cases where there is an absence of an established INL98 for a nutrient for a specific sub-group(s), it may be appropriate to consider the use of other reference values or ranges that have been established by recognized authoritative scientific bodies. The derivation of these values should be reviewed on a case-by-case basis.

3.2.1.2 The general population NRVs-R should be determined by calculating the mean values for a chosen reference population group older than 36 months. NRVs-R derived by the CCNFSDU are based on the widest applicable age range for each of adult males and females.

3.2.1.3 For the purpose of establishing these NRVs-R, the values for pregnant and lactating women should be excluded.

3.2.2 Selection of Nutrients and Appropriate Basis for NRVs-NCD

3.2.2.1 The following criteria should be considered in the selection of nutrients for the establishment of NRVs-NCD:

- Relevant convincing³/ generally accepted⁴ scientific evidence or the comparable level of evidence under the GRADE classification⁵ for the relationship between a nutrient and noncommunicable disease risk relationship, including validated biomarkers for the disease risk, for at least one major segment of the population (e.g., adults).

- Public health importance of the nutrient-noncommunicable disease risk relationship(s) among Codex member countries.

3.2.2.2 Relevant and peer-reviewed scientific evidence for quantitative reference values for daily intake should be available in order to determine an NRV-NCD that is applicable to the general population.

3.2.2.3 Daily intake reference values from FAO/WHO or other recognized authoritative scientific bodies that may be considered for NRVs-NCD include values expressed in absolute amounts or as a percentage of energy intake.

3.2.2.4 For practical application in nutrition labelling, a single NRV-NCD for the general population should be established for each nutrient that meets the principles and criteria in this Annex.

3.2.2.5 An NRV-NCD for the general population should be determined from the daily intake reference value for the general population or adults, or if given by sex, the mean of adult males and adult females.
3.2.2.6 Where a daily intake reference value is based on a percentage energy intake, the single NRV-NCD should be expressed in grams or milligrams based on a reference intake for the general population of 8370 kilojoules/2000 kilocalories.

Governments may use a Codex NRV-NCD based on the reference energy intake of 8370 kilojoules/2000 kilocalories, or may derive their own reference values for nutrition labelling based on another reference energy intake that considers factors specific to their country or region.

3.3 Consideration of Daily Intake Reference Values for Upper Levels

The establishment of general population NRVs should also take into account daily intake reference values for upper levels established by FAO/WHO or other recognized authoritative scientific bodies where applicable (e.g., Upper Level of Intake, Acceptable Macronutrient Distribution Range).

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3 At the time these guiding principles were drafted, the definition and criteria for "convincing evidence" from the following FAO/WHO report were used: Diet, Nutrition and the Prevention of Chronic Diseases. WHO Technical Report Series 916. WHO, 2003.

4 For these General Principles the terms convincing/generally accepted evidence are considered synonymous.


3. REVIEW OF SCIENTIFIC EVIDENCE FROM FAO/WHO AND RASB*

*RASB: Recognized Authoritative Scientific Body. (REP14/CNFSU, paragraph 31 and REP15/CNFSU, paragraph 56 ;80)

The Committee agreed with the following working definition for RASBs. For the purposes of establishing Codex Nutrient Reference Values, a recognized, authoritative, scientific body other than FAO and/or WHO is an organization supported by a competent national and/or regional authority(ies) that provides independent, transparent*, authoritative and scientific advice on daily intake reference values through primary evaluation** of the scientific evidence upon request and for which such advice is recognized through its use in the development of policies in one or more countries.

* In receiving transparent scientific advice, the Committee would have access to what was considered by a RASB in establishing a daily intake reference value in order to understand the derivation of the value.

** Primary evaluation involves a review and interpretation of the scientific evidence to develop daily intake reference values, rather than the adoption of advice from another RASB.
The Committee accepted the six listed scientific bodies as RASB

- European Food Safety Authority (EFSA);
- United States Institute of Medicine (IOM);
- Australian National Health and Medical Research Council & New Zealand Ministry of Health (NHMRC/MOH);
- Japanese National Institute of Health and Nutrition (NIHN);
- International Zinc Nutrition Consultative Group (IZiNCG);
- Nordic Council of Ministers (Nordic countries).

3.1 Food and Agriculture Organisation and World Health Organisation (FAO/WHO)


This WHO report made recommendations for preventing cardiovascular diseases (CVDs), which are the major contributor to the global burden of disease among the non-communicable diseases. A number of key points arose from the expert consultation, which related to diet, physical activity and disease, including, for example, (a) the “lag time” effect of risk factors for CVD means that present mortality rates are the effects of previous long-term exposure to behavioral risk factors such as inappropriate nutrition and insufficient physical activity; and (b) provision of a summary of the strength of evidence on lifestyle factors and risk of developing CVDs.

The report concludes that there are convincing associations for reduced risk of CVDs including consumption of fruits and vegetables, fish and fish oils (EPA and DHA), foods high in linoleic acid and potassium, as well as physical activity and low to moderate alcohol intake. With respect to the relationship between fats and CVD, especially coronary heart disease, the report states that there have been extensive investigations, with strong and consistent associations emerging from a wide body of evidence accrued from animal experiments, as well as from observational studies, clinical trials and metabolic studies conducted in diverse human populations.
With respect to the nutritionally important fatty acids, the report states that the most important Omega-3 (PUFAs) are EPA and DHA found in fatty fish.

The text states, "The biological effects of Omega-3 PUFAs are wide-ranging, involving lipids and lipoproteins, blood pressure, cardiac function, arterial compliance, endothelial function, vascular reactivity and cardiac electrophysiology, as well as potent anti-platelet-aggregation and anti-inflammatory effects. The very long chain Omega-3 PUFAs (EPA and DHA) powerfully lower serum triglycerides but they raise serum LDL cholesterol. Therefore, their effect on CHDs is probably mediated through pathways other than serum cholesterol". The same text indicates: "Most of the epidemiological evidence related to Omega-3 PUFAs is derived from studies of fish consumption in populations or interventions involving fish diets in clinical trials."

From these observations, it was considered likely that dietary EPA + DHA are beneficial for secondary prevention, i.e. for those with previous CHD.


From this expert consultation it was recognised that individual fatty acids may have unique biological properties and health effects, and that for the purposes of food labelling, it would be necessary to specify fully these fatty acids and their amounts.

For EPA and DHA combined, the recommended acceptable macronutrient distribution range (AMDR) is 0.250–2 g/day. The intake of 2 g/day is for secondary prevention of CHD. The experts agreed the criteria to judge the levels and strength of evidence required to conclude that the fatty acids affect major health and disease outcomes (i.e. convincing, probably, possible, insufficient). It was concluded that there is “convincing” evidence of reduced risk of fatal CHD events for EPA and DHA and a level of evidence of “possible” for reduction of risk of CHD events and stroke. For adult males and non-pregnant/non-lactating adult females, 0.250 g/day of EPA plus DHA is recommended, with insufficient evidence to set a specific minimum intake of either EPA or DHA alone; both should be consumed.

From this expert consultation the evidence was found convincing that fish consumption lowers mortality from coronary heart disease in the general population. The report recommends that Member States should emphasise the benefits of fish consumption in reducing coronary heart disease mortality (and the risks of mortality from coronary heart disease associated with not eating fish) for the general adult population. The conclusions also stated that moderate consumption of fatty fish (one or two 100 g servings per week) would provide maximum benefit (two servings provide about 250 mg EPA + DHA), but risks are lowered by any level of fish consumption evaluated (up to seven 100 g servings per week) unless very high dioxin levels are present.

In addition, this expert consultation did not make a distinction between the strength of the evidence for primary and secondary prevention, and it was concluded that the totality of the evidence is convincing for a risk-reducing effect of EPA +DHA on CHD, as is described in the document, based on large numbers of prospective cohort studies, it is evident that there is consistent and convincing evidence for a beneficial effect of EPA and DHA for primary prevention of heart disease.

3.2 European Food Safety Authority (EFSA)


EFSA concluded that intervention studies have demonstrated beneficial effects of EPA and DHA on recognised cardiovascular risk factors, such as a reduction of plasma triacylglycerol concentrations, platelet aggregation and blood pressure. These effects were mainly observed at intakes ≥ 1 g/day, well above levels that were associated with lower CVD risk in epidemiological studies. With respect to cardiovascular diseases, prospective epidemiological and dietary intervention studies indicate that oily fish consumption or Omega-3 LCPUFA dietary supplements (equivalent to a range of 250–500 mg of EPA plus DHA daily) decrease the risk of mortality from CHD and sudden cardiac death. An intake of 250 mg per day of EPA plus DHA appears to be sufficient for primary prevention in healthy subjects. Therefore, and because available data are insufficient to derive an Average Requirement (AR), the EFSA Panel set an Adequate Intake (AI) of 250 mg for EPA plus DHA in adults considering cardiovascular health.
3.3 Norwegian Scientific Committee for Food Safety/ Nordic Council of Ministers


The VKM scientific opinion makes important observations on the positive health effects of DHA and EPA in relation to cardiovascular diseases:

- Considerations on adequate intakes of omega 3 fatty acids should be specific to EPA and DHA on the positive health effects.

- From the reviewed literature it is not possible to distinguish the health effects of EPA and DHA consumed as triacylglycerol (TAG) or as ethyl esters.

- The strongest evidence for possible beneficial effects of supplementation with Omega-3 fatty acid in humans is provided by randomised controlled trials involving more than 43,000 study participants with cardiovascular disease (secondary prevention). In patients given either 0.8 g EPA and DHA or 1.8 g of EPA as ethyl ester daily, the risk of cardiovascular events and mortality was reduced.

- Primary prevention from EPA and DHA supplementation has been less studied. However, VKM endorsed EFSA’s recommendation for adults based on the scientific evidence indicating that oily fish consumption (1–2 servings per week or dietary supplements containing EPA and DHA and equivalent to a range of 0.25 to 0.5 g of EPA and DHA daily) decrease the risk of mortality from coronary heart disease and sudden cardiac death.

The VKM scientific opinion also considers evaluations of cardiovascular functions of EPA and DHA made by WHO/FAO 2008, WHO/FAO 2010, EFSA 2009 and FDA. In the EFSA scientific opinion in 2009, the EFSA NDA Panel concluded that a cause and effect relationship had been established between consumption of 3 g/day EPA and DHA and a reduction in blood pressure. This relates to both hypertensive and normotensive persons. Similarly, the Panel concluded that a cause and effect relationship has been established between consumption of 2–4 g/day of EPA and DHA and a reduction in normal fasting TAG. Both maintenance of normal blood pressure and a reduction in fasting plasma TAGs are considered to be positive cardiovascular health effects.
The VKM scientific opinion provides an extensive literature search, including studies with fish oils and marine ethyl esters and studies with plant oils. The mechanisms of actions are not fully understood and there is less evidence for primary prevention than secondary prevention, the conclusions suggest that increased consumption of Omega-3 fatty acids from fish or fish oil supplements reduce the rates of CVD-related deaths, cardiac and sudden death, and possibly stroke, and that a sufficient intake of EPA and DHA is important for good health.

VKM also states that the optimal dose is not known, and that the amount may vary in different populations depending on the basal dietary intakes of Omega-3 fatty acids and Omega-6 fatty acids.

In 2013 the Nordic Council of Ministers recommended that Omega-3 fatty acids should contribute at least 1% energy. Taking into account GP 3.2.2.6, 1% energy equates to 1% of 2000 kcal/day, which is 20 kcal. Assuming 9 kcal/g of fat, the equivalent amount of Omega-3 fatty acids is 2.2 g/day.

3.4 Australian and New Zealand Health Authorities (2006): National Health and Medical Research Council and New Zealand Ministry of Health (NHMRC/MOH)


For men and women (19+ years) a recommendation of 160 mg and 90 mg, respectively, of total-Omega-3 (DHA + EPA + DPA) was made for an adequate intake. The suggested dietary target to reduce chronic disease risk was 610 mg and 430 mg, respectively, for DHA + EPA + DPA per day.

The recommendation to lower the risk of CHD is that all adult Australians should consume about 500 mg/day of combined DHA and EPA through a combination of the following:

- 2 or 3 servings/ per week (150 g servings) of oily fish
- Fish oil capsules or liquid

Consuming fish at least once a week is associated with a lower risk of total stroke and CHD mortality in the general population and in post-myocardial infarction patients. Level of evidence is III-2 of NHMRC, obtained from comparative studies with concurrent controls and non-randomised allocation, cohort studies, case-control studies, or interrupted time series with a control group.
3.5 United States Institute of Medicine (2005)


The United States Institute of Medicine made DHA and EPA intake recommendations for adult men and women (+19 years old) of 10% of total omega-3 intake (1.6 g and 1.1 g/day, respectively). i.e. 160 mg/day and 110 mg/day.

4. ADDITIONAL BACKGROUND ABOUT THE SCIENTIFIC EVIDENCE REVIEW REGARDING GENERAL PRINCIPLES FOR ESTABLISHING NRVS

Attached are 4 reviews made by The Russian Federation, Chile and IADSA, of scientific evidence on the beneficial health effects of EPA and DHA (Attachment 2, 3, 4 and 5). On these reviews, quality of the available evidence is analysed with the GRADE approach and recommendations from RASBs.

Attachment 2
Document on “International Alliance of Dietary/Food Supplement Associations (IADSA) Proposal to CCNFSDU of new work to establish a Codex NRV for omega 3 fatty acids based on eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). November 2014.

Attachment 3
Review of scientific and regulatory approaches in establishing a Codex NRV values for ω-3-fatty acids based on eicosapentaenoic (EPA) and docosahexaenoic acid (DHA) acids. By the Russian Federation.

Attachment 4
Ministry of Health of Chile. Summary of the available evidence on the benefits of EPA and DHA fatty acids to determine a reference value recommended for intake. March 2015.
In addition to the recommendations from the RASBs, several global, regional and expert scientific organisations have set out recommendations for intakes of fish, fish oils and DHA + EPA per day. These recommendations have been summarised and tabulated by the Global Organisation for EPA and DHA Omega-3 (GOED), included on attachment 6 for additional information.

Attachment 6

5. POTENTIAL MECHANISMS THAT COULD CONTRIBUTE TO EFFECTS OF EPA + DHA ON REDUCED RISK OF CARDIOVASCULAR DISEASE IN RELATION TO CAC/GL 2-1985

The studies on risk markers and the potential underlying mechanisms are beyond the scope of this review. However, in almost all the human studies investigating the biological mechanisms of the beneficial effects, the amounts of EPA + DHA have been large (i.e. intakes of ≥ 3000 mg/day). It is therefore difficult to translate the findings from these mechanistic studies to realistic everyday situations of the general population where EPA + DHA are consumed. However, the following mechanisms that could explain the main cardiovascular benefits have been proposed:

• Reduction of cardiac arrhythmias
• Lowering of plasma triglycerides
• Anti-atherosclerotic potential
• Reductions in both systolic and diastolic blood pressure
• Reduction in arterial stiffness
• Effects on platelet aggregation and haemostasis
• Effects on endothelial function and inflammation
6. PUBLIC HEALTH IMPORTANCE

6.1 Dietary intake assessment and Omega-3 (DHA and EPA) nutritional status

The bulk of the scientific evidence is now pointing towards not so much optimal ratios of dietary Omega-3 and n-6 fatty acids, but rather towards the absolute intakes of specific Omega-3 and n-6 PUFAs that are associated with many different endpoints and health outcomes, such as CHD, mental health or immune/inflammatory responses (Deckelbaum and Calder, 2010). As previously shown, the evidence related to intake amounts for Omega-3 PUFAs are best defined for CVD. What is abundantly clear is the total disconnect regarding the amounts of seafood and EPA and DHA and what is actually consumed (Grieger et al., 2013). Most populations are not meeting current recommendations for DHA and EPA intakes.

Reliable and valid dietary intake assessments are crucial in determining DIRVs (Flock et al., 2013). This poses a challenge for all nutrients, including EPA and DHA. The amounts, duration of intake, sources of EPA and DHA, dietary and lifestyle factors, choice of healthy individuals versus patients, inconsistencies in the design, execution and interpretation of studies all contribute to the challenge of establishing DIRVs and NRVs. Much more information is needed about the endogenous production of EPA and DHA in vegans and vegetarians, interindividual variability in responses to EPA and DHA, different responses in relation to age, sex, weight, race, specific genotypes and overall health status. Up-to-date food composition databases are also important for assessing Omega-3 PUFA intake, and the limitations of food intake records have to be taken into account.

For example, EFSA (2012) selected references in order to obtain data on intake distributions in European countries. Mean daily intakes for adults of EPA only ranged between 50 and 150 mg/day and median daily intakes were between 14 and 180 mg. For DHA, the mean amounts ranged between 131 and 273 mg/day and the median daily intakes were between 42.5 and 430 mg/day.

For all these reasons, reliable biomarkers of Omega-3 PUFA status are necessary to validate dietary intake data (Flock et al., 2013). Significant progress has been made over the last decade and several markers of EPA and DHA are now available, including levels in plasma, erythrocytes and adipose tissue. The use of blood markers of fatty acid intake has made it possible to evaluate the outcomes related to disease. Plasma levels of fatty acids reflect intake over the past few days, whereas adipose tissue levels of fatty acids are more reflective of longer-term fatty acid intake. The Omega-3 Index (Sala-Vila et al., 2011; Schacky, 2014), i.e. the erythrocyte content of EPA and DHA is a useful biomarker. This standardised assessment method is important for assessing DHA and EPA status and the biological effects of their intake.
### 6.2 Dietary risk factors associated with global burden of NCD: cardiovascular disease

In view of the fact that current DHA and EPA intakes are low compared with the recommended levels, it is important to emphasise that substantial public health benefits would be expected as long as the general population meet the recommended DHA and EPA intake; therefore it is important to establish a NRV for these nutrients.

As part of a systematic analysis for the Global Burden of Diseases Study 2010, Lim et al. (2012) were able to estimate deaths and disability-adjusted life years (DALYs: sum of years lived with disability (YLD) and years of life lost (YLL)) attributable to the independent effects of 67 risk factors and clusters of risk factors for 21 regions in 1990 and 2010. Dietary risk factors and physical inactivity collectively accounted for 10.0% of global DALYs in 2010. Several dietary factors affect ischaemic heart disease and stroke, including consumption of fruits, vegetables, nuts and seeds, whole grain cereals, processed meat, polyunsaturated fats and EPA + DHA seafood. The researchers updated earlier systematic reviews and meta-analyses for seafood omega-3 fatty acids, which included both observational and intervention studies, and they tested whether a significant difference exists between the results of randomised clinical trials of seafood omega-3 fatty acid supplementation and observational studies of seafood omega-3 fatty acid intake. The effect of seafood omega-3 fatty acids tended to be lower in RCTs than in observational studies; however, this difference was not statistically significant ($P = 0.057$). Hence, the researchers used the effect based on the combination of RCTs and observational studies. Of the individual dietary risk factors assessed in 2010, the global burden of a diet low in seafood (rich source of EPA + DHA) was 1.1% of global DALYs (95% CI 0.8–1.5) compared with fruits (4.2%), followed by diets high in sodium (2.5%), low in nuts and seeds (2.1%), low in whole grains (1.6%) and low in vegetables (1.5%). The proportion of ischaemic heart disease DALYs attributable to individual dietary risk factors worldwide in 2010 included 40% for diets low in nuts and seeds, 30% for diets low in fruits, 22% for diets low in DHA and EPA seafood, 17% for diets low in whole grains, 17% for diets high in sodium and 12% for diets low in vegetables.

In Table 1 from Lim et al. (2012), the following data for EPA + DHA included:

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Diet low in seafood omega-3 fatty acids (DHA and EPA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure definition</td>
<td>Dietary intake of EPA + DHA measured in mg/day</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Death caused by ischaemic heart disease</td>
</tr>
<tr>
<td>Subgroup</td>
<td>Age ≥ 25 years</td>
</tr>
<tr>
<td>Main data sources for exposure</td>
<td>Food and health surveys</td>
</tr>
<tr>
<td>Theoretical minimum risk exposure distribution</td>
<td>250 mg/day</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Source of relative risks</td>
<td>Updated published review of Mozaffarian et al. 2010</td>
</tr>
</tbody>
</table>

Although further human intervention studies could unravel some of the inconsistencies observed between the epidemiological evidence and some results from human intervention studies, there is already a large body of convincing evidence that supports CVD benefits related to increased intakes of EPA and DHA, and compelling reasons for establishing an NRV (Kris-Etherton et al., 2009; Harris et al., 2009; Flock et al., 2013; Grieger et al., 2013).

In summary, the available evidence shows that EPA and DHA may have beneficial effects on health, including reduction of blood pressure, improvement of the efficiency of hypertension drugs, and reduction of CVD risk.

7. Safety of increased EPA and DHA intake

The primary concerns with regard to the safety of DHA and EPA are its effects on glycaemic control in diabetes, reduced platelet aggregation/increased bleeding time and adverse immunological effects (EFSA, 2012). Long-term human intervention studies that have investigated diverse health results and the effects of supplemental intakes of EPA and DHA, either alone or in combination, at amounts up to about 1 g/day on a variety of health outcomes (e.g. cardiovascular, neurological, immunological), have generally reported no adverse effects in relation to the consumption of EPA or DHA at these levels of intake.

The GISSI Prevenzione trial in 1999, the JELIS study (Yokoyama et al., 2007) and the GISSI-HF Investigators (2008) study reported no clinically relevant adverse effects in over 35,000 individuals. Over 10 years ago, the US Food and Drug Administration (FDA) determined that intakes of EPA and DHA of up to 3 g/day are safe for the general population. In 2011, the Norwegian Scientific Committee for Food Safety conducted a safety review of EPA and DHA and found no adverse effect on bleeding time, with levels as high as 6.9 g/day (Froylandet et al., 2011). More recently, EFSA (2012) concluded that intakes up to about 5 g/day of EPA and DHA combined do not appear to increase the risk of bleeding complications and spontaneous bleeding episodes or affect glucose homeostasis, immune function or lipid peroxidation, provided that the oxidative stability of the EPA and DHA is guaranteed. EFSA also concluded that supplemental intakes of EPA alone up to 1.8 g/day do not raise safety concerns for adults.
8. OTHER CONSIDERATIONS

Consumption of fish raises the issue of human exposure to methyl mercury, a toxic form of mercury found in long-lived predators and fish at the top of the food chain, such as king mackerel, swordfish, shark, tilefish and albacore tuna. Although public health advice has been given for women who may become pregnant and for pregnant women, nursing mothers and young children to avoid certain types of fish potentially high in mercury, risk-benefit analyses indicate that lowering fish consumption would have serious public health consequences (Cohen et al., 2005; Mozaffarian and Rimm, 2006; Wennberg et al., 2012; Hughner et al., 2012; European Food Safety Authority, 2014). The messages about fish consumption should therefore not discourage individuals from eating fish (FDA EE.UU., 2014).
9. REFERENCES


16. European Food Safety Authority. Scientific opinion on the Tolerable Upper Intake level of eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA) and docosapentaenoic acid (DPA). EFSA J 2012;10(7): 2815.


42. U.S. Food and Drug Administration and Environmental Protection Agency. Fish: what pregnant women and parents should know. June 2014. Available at http://www.fda.gov/Food/FoodborneIllnessContaminants/Metals/ucm393070.htm

