CODEX ALIMENTARIUS COMMISSION E

Food and Agriculture Organization of the United Nations

World Health Organization

Viale delle Terme di Caracalla, 00153 Rome, Italy - Tel: (+39) 06 57051 - E-mail: codex@fao.org - www.codexalimentarius.org

Agenda Item 7 **CX/NFSDU 16/38/8-Add.1**

JOINT FAO/WHO FOOD STANDARDS PROGRAMME
CODEX COMMITTEE ON NUTRITION AND FOODS FOR SPECIAL DIETARY USES

Thirty-eighth Session

Hamburg, Germany

5 – 9 December 2016

PROPOSED DRAFT NRV-NCD FOR EPA AND DHA LONG CHAIN OMEGA-3 FATTY ACIDS

COMMENTS AT STEP 3

Comments of Canada, Colombia, Cuba, Ghana, Mexico, New Zealand, Paraguay, Philippines, CRN, ELC, GOED, IADSA, ICGMA and ISDI

CANADA

GENERAL COMMENTS

At this time, Canada is not in a position to support the NRV-NCD proposed for EPA and DHA. Canada is of the opinion that there has not been sufficient opportunity for discussion between the members of the eWG and the co-chairs with regard to the rationale for the proposed NRV-NCD for EPA and DHA of 250 mg/day and that further discussion is needed before a final recommendation can be made.

SPECIFIC COMMENTS

Paragraph 8: "In 2015, eWG members provided an extensive list of references and texts of scientific reports related to the association of the EPA/DHA intake with cardiovascular health outcomes (see the list of references in CX/NFSDU 15/37/7). Based on the PICO question formulated, co-chairs had identified systematic reviews and meta-analyses published since 2009 and reviewed results related to the target health outcome. The strength of evidence was assessed with the GRADEpro tool as described in CX/NFSDU 15/37/7. Table 2 summarizes the systematic reviews and meta-analyses included in the review."

The assessment of the strength of evidence other than that included in the reports of the selected RASBs is outside the scope of work of this eWG. Any proposed NRV-NCD for EPA and DHA Long Chain Omega-3 Fatty Acids should be based primarily on recommendations from RASBs' publications as stipulated in the *Annex: General Principles for Establishing Nutrient Reference Values for the General Population* in the *Guidelines on Nutrition Labelling (CAC/GL 2-1985)*.

Other scientific reports could be used as supporting evidence.

Paragraphs 9 to 17: Systematic reviews

Canada does not support using the meta-analyses described in the report to establish a NRV-NCD for EPA-DHA because these meta-analyses have not been commissioned by a RASB for the purposes of providing advice on daily intake values as per GP 3.1.2.

Paragraphs 18 to 29: "Fish or EPA/DHA"

Canada is of the opinion that members of the eWG should have an opportunity to comment on the analysis of the evidence made by the co-chairs with regard to the source of EPA and DHA in support of an NRV-NCD prior to reporting back to the committee.

Paragraph 33: "The following RASBs proposed by eWG members appeared to meet all of the criteria included in the RASB definition (please see Appendix II for a detailed information):"

Canada would like to clarify that Item No. 5 in Table 3 should refer to the Authority as the U.S. Department of Health and Human Services and the U.S. Department of Agriculture which jointly issued the RASB publication, the "2015-2020 Dietary Guidelines for Americans". This policy was based on the scientific reports of the Dietary Guidelines Advisory Committee (2010, 2015). Canada supports the conclusion that with this correction, the 10 RASBs proposed by eWG members as listed in Table 3, meet all of the criteria included in the RASB definition and should be considered for further discussion on establishing NRV-NCD for EPA and DHA Long Chain Omega-3 Fatty Acids.

Paragraph 35: "Organisations 3, 8, 9 and 10 provided intake recommendations for minimising the risk of CVD/CHD events, however, their recommendations did not mention the CVD/CHD-related mortality."

Canada strongly recommends that all 10 RASB reports be taken into consideration for further discussion on establishing NRV-NCD for EPA and DHA Long Chain Omega-3 Fatty Acids.

Canada is of the opinion that members of the eWG should have an opportunity to comment on the analysis of the evidence made by the co-chairs.

Canada notes that the review of the evidence included in the reports of RASBs 3, 8, 9 and 10 covered studies that examined the association between the intake of EPA and DHA or fish consumption and mortality due to coronary heart disease. Furthermore, the recommendation for EPA and DHA of the 2003 WHO/FAO report entitled *Joint WHO/FAO Expert Consultation on Diet, Nutrition and the Prevention of Chronic Disease Technical Report Series 916,* was based on convincing evidence for the reduction of risk of coronary heart disease and ischaemic stroke and not CVD/CHD-related mortality. The recommendation from the report is "Regular fish consumption (1-2 servings per week) is protective against coronary heart disease and ischaemic stroke and is recommended. The serving should provide an equivalent of 200-500 mg of eicosapentaenoic and docosahexaenoic acid".

Therefore, the recommendations from RASB 3, 8, 9 and 10 should be included as part of the totality of the evidence for further discussion on establishing NRV-NCD for EPA and DHA Long Chain Omega-3 Fatty Acids.

Paragraph 36: "Finally, the authorities 4 and 6 have not provided quantitative recommendations for EPA and DHA intake. Australia's NHMRC (4) has reviewed the evidence on the EPA/DHA intake-health outcome relationship and found it inconclusive. Out of 11 systematic reviews studied, 7 focused on surrogate markers of cardiovascular disease such as lipid profiles. Three studies have not established relationship with CVD risks, and one was not relevant to EPA/DHA. It has been also noted that the major component of the NHMRC review, study by Hooper et al 2006, was subject of extensive criticism [35]."

Canada notes that the report of the National Health and Medical Research Council (NHMRC)[1] concluded that the evidence suggests that consumption of at least two servings a week of fish is associated with reduced risk of mortality from cardiovascular disease, and with reduced incidence of cardiovascular disease. This brings us back to the question of fish vs. EPA and DHA and the appropriateness of extrapolation from the recommended servings of fish to a daily intake of EPA and DHA, which should be discussed through an eWG.

Paragraph 37: "The US IOM 2007 report has also come short of yielding an intake recommendation for EPA/DHA intake. The authors concluded that "while it is uncertain how much these omega-3s contribute to improving health and reducing risk for certain conditions such as heart disease, there is evidence for benefits both to the general population and to some groups of people. For those with existing heart disease there may be benefits from consuming EPA and DHA in seafood, although more research is needed in this area". At the same time, no strong scientific evidence was established to suggest a threshold of consumption, such as two servings per week, below which seafood consumption provides no benefit and above which increasing consumption provides additional benefits."

Although the US IOM report[2] did not recommend a specific value for EPA and DHA, several findings have been reported with regards to the strength of the evidence. These findings should be used as part of the body of evidence for establishing an NRV-NCD for EPA and DHA Long Chain Omega-3 Fatty Acids.

Paragraph 45: "Based on the data of systematic reviews and most recent scientific publications reviewed as described in this report in addressing the critical points identified at the CCNFSDU37, and the recommendations from the FAO/WHO Expert Consultations and other nominated RASBs, it is recommended that CCNFSDU considers an NRV-NCD for EPA and DHA of 250 mg/day, for inclusion in paragraph 3.4.4.2 NRV-NCD of the Guidelines on Nutrition Labelling (CAC/GL 2-1985) as presented in Appendix I."

Canada notes that there has not been sufficient opportunity for discussion between the members of the eWG and the co-chairs with regard to the rationale for the proposed NRV-NCD for EPA and DHA of 250 mg/day. In particular, this value is not consistent with some of the RASBs' recommendations, such as the recommendation for EPA and DHA intake made by the "Agence nationale de sécurité sanitaire de

[1] A review of the evidence to address targeted questions to inform the revision of the Australian Dietary Guidelines (https://www.nhmrc.gov.au/_files_nhmrc/file/publications/n55d_australian_dietary_guidelines_evidence_report.pdf)

[2] Committee on Nutrient Relationships in Seafood: Selections to Balance Benefits and Risks, Food and Nutrition Board (2007). Benefits for prevention of adult chronic disease. Seafood choices: balancing benefits and risks. http://www.nap.edu/catalog/11762.html

l'alimentation, de l'environnement et du travail" (ANSES) in their report, "Actualisation des apports nutritionnels conseillés pour les acides gras"

(https://www.anses.fr/fr/system/files/NUT2006sa0359Ra.pdf). ANESES recommended an intake of 500 mg/day of EPA and DHA for the reduction of the risk of cardiovascular mortality.

At this time, Canada is not in a position to support the NRV-NCD proposed for EPA and DHA. Considering the differing conclusions from the various RASB reports included, Canada is of the opinion that further discussion is needed before a final recommendation can be made. The discussion should include various aspects such as dietary vs. supplementary EPA and DHA vs. fish, the health outcome (s), secondary vs. primary prevention and the quality of the evidence.

Canada does not support using the data from systematic reviews and meta-analyses described in the report to establish an NRV-NCD for EPA-DHA. Any proposed NRV-NCD for EPA and DHA Long Chain Omega-3 Fatty Acids should be primarily based on recommendations from RASBs reports as stipulated in the *Annex: General Principles for Establishing Nutrient Reference Values for the General Population* in the *Guidelines on Nutrition Labelling*. Scientific reports other than RASBs reports could be used as supporting evidence.

Appendix I: "The establishment of an NRV was based on convincing/generally accepted evidence for a relationship with NCD risk as reported in the Diet, Nutrition and the Prevention of Chronic diseases. WHO Technical Report Series 916, WHO, 2003; and in the FAO/WHO Expert Consultations. Technical report Series 91 and 978, WHO 2010."

It is unclear to Canada why only the three WHO reports are cited as the basis for the NRV-NCD when other reports from other RASBs could also be part of the evidence in support of the proposal.

As mentioned in our previous comment under paragraph 35, the recommendation for EPA and DHA of the 2003 WHO/FAO report entitled *Joint WHO/FAO Expert Consultation on Diet, Nutrition and the Prevention of Chronic Disease, Technical Report Series 916,* was based on convincing evidence for the reduction of risk of coronary heart disease and ischaemic stroke and not CVD/CHD-related mortality. The recommendation from the report is "Regular fish consumption (1-2 servings per week) is protective against coronary heart disease and ischaemic stroke and is recommended. The serving should provide an equivalent of 200-500 mg of eicosapentaenoic and docosahexaenoic acid".

COLOMBIA

In the Proposed Draft NRV-NCD for EPA and DHA long chain omega-3 fatty acids, where:

Colombia thanks Chile and Russia for the work they have done on the draft and it maintains its position from 2015 in support of the value of 250 mg for EPA and DHA, as well as the proposed footnote. However, it is important to be cautious and examine the proposal by the Codex Commission slowly, as:

1. In Colombia, cardiovascular disease is the leading cause of mortality among adults aged 18 to 65, i.e. the increased ingestion of DHA and EPA is important and relevant for our population.
2. However, attaining the recommended levels would require the recommendation that supplements be taken, as the habitual consumption of fatty fish (one or two portions weekly) does not exist in our population.
3. Countries that produce fatty fish, such as Chile, the Nordic countries, Japan, have dietary habits that allow them to achieve the proposed targets; in Colombia, this is not possible with food alone.
4. Colombia supports the value of 250 mg of EPA and DHA, as well as the proposed footnote.

CUBA

With respect to document CX/NFSDU 16/38/8 Proposed Draft NRV-NCD for EPA and DHA long chain omega-3 fatty acids, Cuba agrees in principle and it has no comments to add.

GHANA

Ghana supports the establishment of an NRV-NCD of 250mg for EPA and DHA.

Rationale

The establishment of NRV-NCD of 250mg for EPA and DHA was based on strong evidence from approved by scientific bodies that meet the criteria on RASBs. Studies have also shown that, consumption of 250 mg of EPA and DHA is associated with primary and secondary prevention of cardiac deaths.

MEXICO

Mexico appreciates the opportunity to comment on document **CX/NFSDU 16/38/8** on the **Proposed Draft NRV-NCD for EPA and DHA long chain omega-3 fatty acids** produced by an electronic working group led by Chile and the Russian Federation, corresponding to **Item 7** of the agenda for the next meeting of the CCNFSDU.

Mexico agrees that the consumption of food that contains EPA and DHA long chain omega-3 fatty acids should be promoted, as according to the 2006 Mexican National Health and Nutrition Survey (ENSANUT), the dietary intake of saturated fatty acids among the population is high and the intake of polyunsaturated fatty acids (PUFA) and in particular n-3 and n-6 is lower than the recommendations of the OMS, which represents a predisposition to risk factors for chronic non-communicable diseases in the Mexican population[3].

Therefore, we consider it important to establish the NRV-NCD for omega-3 long chain EPA and DHA proposed by the eWG of **250 mg**, in line with the recommended intake levels in section 3.4.4.2 of the *Guidelines on Nutritional Labelling* (CAC/GL 2-1985), as this NRV-NCD may contribute to an increase in the consumption of these fatty acids in the population.

However, we do not think that the scientific evidence that has been presented is sufficiently conclusive for the establishment at present of an NRV-NCD value, as the indicated benefit ("the reduction of risk of coronary heart disease mortality/fatal CHD events") does not correspond to the proposal to establish an NRV-NCD because it does not clearly meet the criterion established in the General Principles for Establishing NRVs, which states that "relevant convincing/generally accepted scientific evidence or the comparable level of evidence under the GRADE classification for the relationship between a nutrient and non-communicable disease risk relationship, including validated biomarkers for disease risk, for at least one major segment of the population (e.g. adults)", as result of which it is recommended that we wait for more scientific evidence.

NEW ZEALAND

Significant progress has been made during the 2016 electronic working group to identify suitable recognised authoritative scientific bodies (RASBs). New Zealand considers that the next step required is to evaluate these RASBs against the Codex General Principles for establishing an NRV-NCD (CAC/GL 2-1985, Annex). Specifically the level of evidence underpinning the relationship between EPA and DHA against the risk of mortality from coronary heart disease. Once this has been completed the Committee will be in a position to evaluate the suitability of establishing an NRV-NCD for EPA and DHA.

General Principles for establishing an NRV-NCD

As specified in the General Principles for Establishing Nutrient Reference Values for the General Population (CAC/GL 2-1985, Annex), there are several steps involved in the derivation of an NRV-NCD:

1. Selection of suitable data source to establish NRVs;
2. Selection of nutrients and an appropriate basis for NRV-NCD;
    a. Assessment of the level of evidence for the relationship between the nutrient and non-communicable disease risk in accordance with WHO or WHO/FAO definitions;
    b. Public health importance of the relationship among Codex Member Countries;
3. Consideration of Daily Intake Reference Values for Upper Levels.

It is acknowledged that steps 1 and 2b have been completed by the eWG; but further work is required to review the level of evidence underpinning the RASB relationships to ensure that the relevant scientific evidence is convincing/generally accepted (or comparable level of evidence under the GRADE classification).

The definition contained within the FAO/WHO report cited in the General Principles is as follows:

> Convincing evidence. Evidence based on epidemiological studies showing consistent associations between exposure and disease, with little or no evidence to the contrary. The available evidence is based on a substantial number of studies including prospective observational studies and where relevant, randomized controlled trials of sufficient size, duration and quality showing consistent effects. The association should be biologically plausible.

[3] Ramírez-Silva et al. Fatty acids intake in the Mexican population. Results of the National Nutrition Survey 2006. Nutrition & Metabolism 2011, 8:33
http://www.nutritionandmetabolism.com/content/8/1/33

New Zealand has some concerns that a consistent association between the exposure and the primary outcome has not been fully demonstrated. This is reflected in the differing levels of evidence ascribed by various RASBs regarding EPA and DHA.

WHO Nutrition Guidance Expert Advisory Group

At CCNFSDU37 the Representative of WHO highlighted the ongoing work of the Nutrition Guidance Expert Advisory Group (NUGAG) Subgroup on Diet and Health which was in the process of initiating work on review of polyunsaturated fatty acids (PUFAs) which could be used to inform this Agenda item (REP16/NFSDU, para 76).

At the ninth NUGAG subgroup on diet and health meeting, the group reviewed and finalised the PICO questions, priority outcomes and effects on health and other issues related to the consumption of polyunsaturated fatty-acids[4]. The methods for the systematic review related to polyunsaturated fatty acids and the outcome of interest, prevention of cardiovascular disease (including mortality from coronary heart disease), are now published on the Cochrane Database of Systematic Reviews[5]. The systematic review will include all eligible trials which compare higher with lower total polyunsaturated fat intake, either through dietary supplementation, dietary interventions, or advice on diet. Subgroup analyses will be conducted on a variety of factors including omega-3: omega-6 ratios; replacement of saturated or monounsaturated fats with polyunsaturated fats, and dose response trials. As such this work will inform the questions raised by some eWG members regarding the level of scientific evidence and need to consider the omega-3: omega-6 ratio.

Noting the divergence of opinions of RASBs and authors of recent systematic reviews, New Zealand considers it appropriate to await the results of the WHO NUGAG work. This approach is consistent with the conclusions at CCNFSDU37, which acknowledged that this work should progress taking into account the work of NUGAG, as was done when establishing the NRV-NCD for sodium and potassium (REP16/NFSDU, para 79). Based on the update of the Representative of the WHO regarding the progress of the WHO NUGAG group, the Committee may need to consider whether the best approach is to await the results of the systematic reviews, or continue work on the Agenda item to evaluate the scientific evidence which underpins the assessment of the RASBs until the NUGAG review is available.

PARAGUAY

General Comments

Given that Paraguay is a landlocked country, the consumption of seafood is practically impossible, as a result of which supplements are a valid option for ingesting fatty acids in view of their preventive ability to reduce the risk of mortality from coronary heart disease.

Therefore, Paraguay supports the inclusion of the NRV-NCD for EPA and DHA in the Guidelines on Nutritional Labelling (CAC/GL 2-1985).

Specific comments

3.4.4.2 NRV-NCD EPA1 and DHA2 250 mg 1 Eicosapentaenoic acid 2 Docosahexaenoic acid

Paraguay agrees with the value proposed by the eWG.

PHILIPPINES

General Comments:

The Philippines supports the proposed Draft Nutrient Reference Value for diet-related non-communicable diseases (NRV-NCD for Eicosapentanoic acids (EPA) and docosahexanoic acids (DHA) Long Chain Omega-3 Fatty Acids at 250 mg based on convincing/generally accepted evidence showing the beneficial relationship between the long chain omega-3 fatty acids EPA plus DHA in the diet as well as the reduction ofrisk of coronary heart disease (CHD) mortality/fatal CHD events. It was concluded that the totality of the evidence is convincing for a risk-reducing effect of EPA +DHA on CHD.

[4] http://www.who.int/nutrition/events/2016_9th_NUGAG_meeting_15to18March/en/
[5] http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD012345/full

Rationale

Specific Comments:

Wesupport the proposed NRV-NCD for EPA and DHA Long Chain Omega-3 Fatty Acids at 250 mg based on consistent and recent scientific evidence. The Joint FAO WHO Expert Consultations in 2010 found convincing evidence that moderate consumption of oily fish lowers mortality from coronary heart disease (CHD) in general population. Epidemiologic studies and trials showed the benefits of polyunsaturated fatty acids (PUFA), specifically EPA and DHA, in cardio vascular disease (CVD) prevention and in stroke risk reduction**(**Asif, 2014, Arkesteijn et al, 2013;Mozaffarian& Wu, 2011; Kris-Ehterton et al, 2003; Harris et al, 2008).

The beneficial effect in increasing the dietary intake of EPA and DHA Long Chain Omega 3 Fatty acids will have substantial global benefits in particular taking into account the gap between current consumption and recommendations.

a. It is recommended that the level of NRV-NCD for EPA & DHA be 250mg/day;

i. The World Health Organization (2010) recommended a daily EPA and DHA intake of 0.3-0.5 grams and a daily ALA intake of 0.8-1.1 grams.

- The overall efficiency of conversion from αLNA is 0.2% to EPA, 0.13% to DPA & 0.05% to DHA (Burdge and Calder, 2005);
- Newer findings using tracer isotope showed that the rate of conversion by humans of ALA to EPA is low, with estimates ranging from 0.2% to 8%, as is the conversion of EPA to DHA (Goyens et al, 2006, AJCN);
- The rate of conversion by humans of ALA to EPA is low, with estimates ranging from 0.2% to 15%, as is the conversion of EPA to DHA. Thus, both n-3 & n-6 PUFA are entirely derived from the diet and are necessary for human health (Andiz&Ünlüsayın, 2015, Rubio-Rodríguez et al., 2010)

The meta-analysis evidence from several RCTs indicated that provision of EPA+DHA at 2g or more per day may reduce both systolic blood pressure and diastolic blood pressure. The strongest benefits were noted in hypertensive individuals without antihypertensive medication. Randomized control trials (RCTs) in the context of secondary prevention also indicated that the consumption of EPA plus DHA is protective at doses <1 g/d. The therapeutic effect appears to be due to suppression of fatal arrhythmias rather than stabilization of atherosclerotic plaques. From a clinical and public health perspective, provision of EPA+DHA may lower blood pressureand other risk factors which could ultimately reduce the incidence of CVD (Miller et al 2014; Flock et al, 2013, Breslow, 2006). Several scientific studies showed the beneficial effects of EPA and DHA on reducing the risks of cardiovascular diseases (;Burr et al, 1989;; Kris-Etherton et al 2003; Leaf, 2009; Mozzafarian, 2006; Mozzafarian and Hu, 2006;Chowdury et al, 2014)particulary coronary heart disease (Breslow, 2006; De Goede et al, 2010; Harris et al, 2006) and cardiac death (Mozaffarian, et al 2011). Hence, the proposed draft NRV-NCD for EPA and DHA is acceptable since it is based on scientific judgement and consensus.

We are of the opinion that the evidence of both primary and secondary prevention is acceptable in the establishment of an NRV-NCD for EPA+DHA for the general population.

Thus, it is recommended that CCNFSDU consider a harmonized NRV-NCD for EPA and DHA of 250 mg/day, for inclusion in paragraph 3.4.4.2 NRV-NCD of the Guidelines on Nutrition Labelling (CAC/GL 2-1985).

References

Andizand Ünlüsayın*, J Food Health*Sc; 2015

Asif, D.A. 2014. The Role of Omega-3 Fatty Acids in Heart Disease Prevention. *J Pharma Care* 16 (7):323-326.

Arkesteijn et al, 2013, Rev Unilever R & D

Breslow, JL. N-3 Fatty acids and cardiovascular disease.https"//www.ncbi.nlm.nih.gov/pubmed/16841857.*American Journal of Clinical Nutrition. 2*006. 83 (6 Suppl):14775-14825.

Burdge, GC and Calder, PC. Conversion of α-Linolenic acid to longer-chain polyunsaturated fatty acids in human adults. *Reprod. Nutr. Dev*. 2005; 45: 581-597.

Burr ML, Fehily AM, Gilbert JF, et al. Effect of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: Diet AndReinfarction Trial (DART). *Lancet* 1989;**2**:757–61

Chowdhury R, Warnakula S, Kunutsor S, Crowe F, Ward HA, Johnson L,Franco OH, Butterworth AS, Forouhi NG, Thom pson SG, et al Association of dietary, circulating, and supplement fatty acids with coronary risk: a systematic review and meta-analysis. *Ann Intern Med* 2014;**160**:398–406.

De Goede J et al. Marine (n-3) fatty acids, fish consumption, and the 10-year risk of fatal and non-fatal coronary heart disease in a large population of Dutch adults with low fish intake. https://www.ncbi.nlm.nih.gov/pubmed/20335635. Journal of Nutrition. 14-(5);1023-8.

Flock MR, Skulas-Ray AC, Harris WS, Etherton TD, Fleming JA and Kris-Ehterton PM. Determinants of Erythrocyte Omega-3 Fatty Acid Content in Response to Fish Oil Supplementation: A Dose-Response Randomized Controlled Trial. *Journal of the American Heart Association.* 10 (1161):1-12.

Goyens PL, Spilker ME, Zcok PL, Katan MB and Mensink RP. Conversion of α-linolenic acid in human is influenced by the absolute amouts of α-linolenc acid and linoleic acid in the diet and not by their ration. *Am J ClinNutr*. 2006;(84): 44-53.

Harris WS, Chung M, Lichtenstein AH, Balk EM, Kupelnick B. N-3 fatty acids from fish or fish-oil supplements, but not α-linolenic acid, benefit cardiovascular disease outcome in primary- and secondary- prevention studies: a systematic review. *Am J ClinNutr* 2006;**84**:5–17.

Harris, W.L. et al. Of long chain omega-3 fatty acid associated with reduced risk for death from coronary heart disease in healthy adults. https://blm.nih.gov/pubmed. d/18937898; 2008 Dec; 10(6):503-9.

Kris-Etherton PM, Harris WS, Appel LJ. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease: New Recommendations from the American Heart Association. *AretriosclerThrombBascBiol*2003; 23:151-152.

Kris-Etherton PM, Harris WS, Appel LJ. Omega-3 fatty acids, and cardiovascular disease*. Circulation* 2002;**106**:2747–57.

Leaf, DA. The Role of Omega-3 Fatty Acids n Heart Disease Prevention. *JCOM*. 2009; 16 (7); 323-326.

Mozaffarian, F and Wu, JH. 2011. Omega 3 Fatty Acids and Cardiovascular Disease. *J Am CollCardiol*. 58 (30):3047-3060.

Miller PE, Elswyk MV, Alexander DD. (2014).Long Chain Omega-3 Fatty Acids Eicosapentanoic and Docosahexanoic Acid and Blood Pressure: A Meta-Analysis of Randomized Controlled Trial. *American Journal of Hypertension* 27 (7): 885-893.

Mozaffarian D, Rimm EB. (2006). Fish intake, contaminants, and human health: evaluating the risks and the benefits. *JAMA*;**296**:1885–99.

Mozaffarian D, Ascherio A, Hu FB, et al. Interplay between different polyunsaturated fatty acids and risk of coronary heart disease in men.*Circulation* 2005;**111**:157–64.

WHO Technical Report Series 916, WHO, 2003; and in the FAO/WHO Expert Consultations. Technical report Series 91 and 978, WHO, 2010.

CRN

Previous CRN Comments – Written, June, 2015

CRN respectfully submitted comments to the chairs of the electronic Working Group (eWG) regarding a series of ten questions, related specifically to the development of a NRV-NCD for Omega 3 (DHA/EPA). We remain committed to this process and our response to Question 4 remains relevant and has not been dismissed.

Justification of NRV-NCD Do you agree that DHA and EPA intake is sufficiently important for public health, and that all information reviewed so far justifies the establishment of an NRV-NCD for food labelling purposes? If you disagree, please justify your answer supported by scientific references.	CRN and CRN Members agree that the intake of DHA and EPA is sufficiently important for public health, and that all information reviewed so far does justify the establishment of an NRV-NCD for food labelling purposes. Further, several robust and adequately controlled "health care cost analyses" have reported that intake of DHA and EPA can lead to demonstrable public health and personal health benefits, and the reduction of significant hospitalization events. Shanahan C.J & deLorimier, R. (2014) From Science to Finance-A Tool for Deriving Economic Implications from the Results of Dietary Supplement Clinical Studies. *Jrnl. Diet. Suppl.* DOI:10.3109/19390211.2014.952866.

Previous CRN Comments – Written, August, 2015

After the Codex Alimentarius Commission (CAC) meeting in Geneva, CRN and CRN Members submitted a response to the second consultation and again applauded the

scientifically-relevant process and conclusion by the chairs of the electronic Working Group. The CRN statement in support of the conclusion by the chairs of the electronic Working group is below.

"CRN is wholly in agreement with the text of the Second Consultation Document on an NRV-NCD for EPA+DHA and supports its submission for discussion at the 37th session (November 2015) of the Codex Committee on Nutrition and Foods for Special Dietary Uses (CCNFSDU).

New Information; Omega-3 Acid Ethyl Esters and Post-Myocardial Infarction

A prospective multicenter, double-blind, placebo-controlled clinical trial (RCT) funded by the National institutes of Health was conducted as the OMEGA-REMODEL (Omega-3 Acid Ethyl Esters on Left Ventricular Remodeling After Acute Myocardial Infarction) trial to evaluate the hypothesis that 4 g/day of omega-3 fatty acids for 6 months post-acute myocardial infarction would provide cardia remodeling benefits, as determined by the primary study endpoint, change in left ventricular systolic volume index and secondary endpoints of change in noninfarct myocardial fibrosis, left ventricular ejection volume and infarct size (Heydari, et al., 2016[6]). The results published indicate that patients randomly assigned to the Omega-3 fatty acids treatment group had a significantly reduced left ventricular systolic volume index (-5.8%, P=0.17) and noninfarct myocardial fibrosis (-5.6%, P=0.026) in comparison to the placebo control. Further, patients treated with Omega-3 fatty acids also had a reduction in serum biomarkers of systemic and vascular inflammation and myocardial fibrosis. There were no adverse effects associate with the 4 g/day dose. This recent study provides important context to the importance of omega-3 fatty acids and a marker for cardiovascular disease.

Conclusion

Nothing has been proposed in the scientific literature and/or amongst national regulatory bodies that in any way changes the conclusion of CRN and CRN Members, as echoed by the chairs of the electronic Working Group. In fact the current recommendations set by the European Food Safety Authority (EFSA) identify a 250 mg intake of EPA and DHA per day for the general adult population with a maximum tolerated dose of 5 g per day. CRN and CRN Members are in agreement with EFSA on their analysis, conclusion and recommendation!

Q10	**Proposed NRV-NCD value** If you replied affirmatively to question 9, what Reference Value amount for EPA and DHA would you propose, expecting the mentioned health benefits? Please justify your answer.	CRN and CRN Members support the establishment of a single internationally harmonized NRV-NCD for EPA and DHA combined for the general population for labeling purposes in an amount between 250-500 mg/day.

ELC

We agree with the analysis of systematic reviews and meta-analysis compiled by the e-WG and using the GRADE classification as explained in CX/NFSDU 16/38/8. Most RASBs selected provide quantitative recommendation for intake of EPA and DHA either for reduction of risk of coronary heart disease or for CVD/CHD events.

In addition, as indicated in CX/NSFDU 16/38/8, three reports from WHO and/or FAO underline the **convincing level of evidence for EPA and DHA in the field of coronary heart disease**:

- "Convincing evidence for reduced risk of CVD for fish and fish oils (EPA and DHA)" in Diet, nutrition and the prevention of chronic diseases, Report of the joint WHO/FAO expert consultation WHO Technical Report Series, No. 916 (TRS 916)
- "Convincing evidence that fish consumption and EPA plus DHA intake lower the risk of coronary heart disease mortality" in FAO/WHO (2011). Report of the Joint FAO/WHO Expert Consultation on the Risks and Benefits of Fish Consumption. Rome, Food and Agriculture Organization of the United Nations; Geneva, World Health Organization, 50 pp.
- "Convincing decrease risk for CHD events and probable decrease risk for fatal CHD" in FAO Fats and fatty acids in human nutrition - Report of an expert consultation. Technical report 91, 2008.

Recalling that CVD/CHD is globally a critical NCD, and recalling that the work on NRV-NCD is based on a WHO mandate to CCNFSDU for contributing to the Global Strategy on Diet, Physical Activity and Health, and that this work of CCNFSDU on NCDs was deemed an important contribution to achieving the goals of this strategy, **ELC supports the proposed NRV-NCD for EPA and DHA at 250 mg/d** and its timely inclusion in the guidelines on nutrition labelling.

[6] Heydari B, Abdullah S, Pottala JV, Shah R, Abbasi S, Mandry D, Francis SA, Lumish H, Ghoshhajra BB, Hoffmann U, Appelbaum E, Feng JH, Blankstein R, Steigner M, McConnell JP, Harris W, Antman EM, Jerosch-Herold M, Kwong RY. (2016).Effect of Omega-3 Acid Ethyl Esters on Left Ventricular Remodeling After Acute Myocardial Infarction: The OMEGA-REMODEL Randomized Clinical Trial. Circulation;134(5):378-91. doi: 10.1161/CIRCULATIONAHA.115.019949.

GOED

General Comments

GOED applauds the continued diligence of Chile and Russia as the co-chairs of the electronic working group (e-WG). They have done a fantastic job soliciting feedback and turning it into an extremely coherent, not to mention well-supported, discussion document. **GOED continues to support the proposed draft NRV-NCD of 250 mg/day for EPA+DHA for inclusion in the *Guidelines on Nutrition Labelling* (CAC/GL2-1985).** Discussions to adopt an NRV-NCD for EPA+DHA remain timely. A recently published global survey of EPA and DHA in the bloodstream of healthy adults indicates that the majority of the world has low to very low blood levels of these fatty acids resulting in an increased risk of chronic diseases (i.e. heart).[7]

Since last year's discussion on this topic at the 37th Session of the CCNFSDU, a very large, extremely relevant study was published.[8] The study is the first output from the Fatty Acids & Outcomes Research Consortium (FORCe), a collaboration of scientists who have conducted 19 different observational studies but have pooled their data to identify the role of fatty acids in a wide variety of diseases. The study correlated status of individual omega-3 fatty acids with, among other things, coronary death. A one-standard deviation increase in DHA was associated with a 10% reduction in coronary death, which is very similar to the risk reductions observed in meta-analyses of randomized, controlled trials. EPA status achieved a similar reduction but was only of borderline statistical significance [RR, 0.91; 95% CI, 0.82-1.00]. Since the risk reductions presented are per one standard deviation of fatty acid status, presumably those with higher status should have greater risk reductions, and this is borne out in the data where the first and fifth quintiles of status are compared. The fifth quintiles seem to coincide with an omega-3 index between 7 and 8, or the levels observed in Japanese populations, and at that level DHA was associated with a 24% reduction in coronary death risk.

Specific Comments

Page 2, Paragraph 8: "Comparison" "Diet with an EPA and DHA level lower than in the intervention"

GOED's Comment: It seems that there needs to be more than one comparison. In observational (i.e. prospective cohort) studies, you typically compare different dietary levels of EPA/DHA. In intervention trials, you may do the same, but if you are referring to dietary/food supplement trials, then you would be comparing different amounts of EPA/DHA intake from dietary/food supplements to a placebo (no EPA/DHA).

Page 4, Table 2: "Filion, 2010"

GOED's Comment: Filion, 2010 should be excluded. The primary outcome was all-cause mortality, not cardiac mortality and the secondary outcome had nothing to do with death. The cardiac death analysis referenced in the paper was an analysis based on the collection of safety data, so it isn't considered an appropriate outcome measurement.

Page 4, Table 2:

GOED's Comment: Casula et al., 2013 [RR, 0.68; 95% CI, 0.56-0.83] should be considered for inclusion.

Page 5, Paragraph 14: "Kwak concluded that supplementation with omega-3 fatty acids had no beneficial effect on CVD events, including sudden cardiac death and CVD-related fatal events…"

GOED's Comment: An important detail is missing. Kwak **did** conclude that omega-3 fatty acid supplementation significantly reduced cardiovascular death (RR, 0.91; 95% CI, 0.84-0.99).

Page 5, Paragraph 17: "Finally, we would like to mention..."

GOED's comment: It's not clear why the paragraph beginning with the above sentence is included. The discussion by the eWG and CCNFSDU should be specific to the efficacy of the nutrients, EPA and DHA, not to the quality of a particular source, fish oil. While the cited papers have serious limitations, GOED has chosen not to address them given that they are irrelevant to the discussion at hand. Any discussion on quality should be directed to the appropriate committee. Specifically, fish oil quality issues are currently being discussed by the CCFO as part of its discussion on establishing a fish oil standard. Even then, the issue raised within this paragraph is not appropriate since the CCFO is discussing limits, not deviations from those limits. GOED proposes to remove this paragraph.

[7] Stark KD, Van Elswyk ME, Higgins MR, Weatherford CA, Salem N Jr (2016). Global survey of the omega-3 fatty acids, docosahexaenoic acid and eicosapentaenoic acid in the blood stream of healthy adults. Prog Lipid Res. 63:132-52.

[8] Del Gobbo LC et al.; Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Fatty Acids and Outcomes Research Consortium (FORCe). ω-3 Polyunsaturated Fatty Acid Biomarkers and Coronary Heart Disease: Pooling Project of 19 Cohort Studies. JAMA Intern Med. 2016;176(8):1155-66.

Page 7, Paragraph 29: “Most recently, Kleber et al. [31] have studied omega-3 index association with CVD and all-cause mortality in 3259 participants of the Ludwigshafen Risk and Cardiovascular Health Study (LURIC) [32].”

GOED’s Comment: Change CVD to cardiovascular.

Page 9: “One member country (CMC) has commented that the selection of RASBs should not be limited to those that established DIRVs but also should consider opinions of those scientific bodies which did not think that the totality of evidence amounted to the establishment of a DIRV as was the case in the work on establishing NRV-R (REP 16/CCNFSDU).”

GOED’s Comment: Is this in reference to chromium? If yes, that should be specified so it directs reviewers of the discussion paper to the correct place in the report. If it’s in reference to another discussion, please specify.

IADSA

General Comments

The International Alliance of Dietary/ Food Supplement Associations (IADSA) welcomes the proposed draft NRV non-communicable disease (NCD) for EPA and DHA long chain omega-3 fatty acids and would like to support the setting of NRV-NCD for EPA and DHA at a level of 250 mg/day.

IADSA is of the view that the new document provides an excellent summary and employs the WHO PICO format (P-Patient; I-Intervention; C-Comparison; O-Outcome) to frame the healthcare research question.

The Co-Chairs and eWG have identified systematic reviews and meta-analyses published since 2009 and reviewed results related to the specific health outcome. The strength of the evidence was assessed with the GRADEpro tool, which had been described in 2015 (CX/NFSDU 15/37/7). IADSA believes the new document provides a thorough and comprehensive review of the available scientific data, and then summarises and tabulates the evidence. Thirteen systematic reviews and meta-analyses were identified that covered randomised clinical trials and prospective cohort studies relevant to the PICO question. Based on statistical assessment of relative risk, the impact of all but three studies were ranked as conclusive, thus demonstrating a strong association between the EPA and DHA intake and cardiac mortality.

With regard to the questions of fish or EPA and DHA, the Co-Chairs and eWG highlighted, and IADSA strongly supports their interpretation, that the principal bioactive components of fish are EPA and DHA, based on the following:

1. A recent scientific report of the US Dietary Guidelines Advisory Committee, which stated that the health benefits of seafood are likely to be associated with EPA and DHA.
2. Most of the RCT studies were based on supplementation of the intervention group with pure EPA and DHA or fish oil supplements.
3. There were no RCT-based studies of fish intake in association with CVD health outcomes—all the fish studies were epidemiological prospective cohort studies.
4. The conclusions from the Joint FAO/WHO expert consultation on the risks and benefits of fish consumption (WHO, 2011) concluded that there was convincing evidence for the benefits of EPA + DHA intake on CHD mortality.
5. As fish and seafood are recognised as primary sources of EPA and DHA, it has become a standard practice to quantify fish intake in amounts of EPA and DHA.
6. The reliance in RCTs on the level of EPA and DHA biomarkers in evaluating intake associations with a particular health outcome
7. The use of the omega-3 index[9] as a powerful risk factor for sudden cardiac death rather than traditional risk factors such as cholesterol, triglycerides and C-reactive protein

The document also includes a 2016 publication by Kleber *et al.*[10] that studies omega-3 index association with CVD and all-cause mortality in 3259 participants. Proportions of EPA and DHA were strongly and inversely associated with all-cause and cardiovascular mortality in models adjusted for conventional CVD risk factors.

With regard to the RASBs selected by the eWG, the new document lists 10 potential RASBs. Of the 10, four produced a quantitative recommendations for the EPA and DHA intake in relation to the target outcome:

[9] Red blood cell omega-3 PUFAs expressed as the percentage of EPA + DHA in red cell lipids

[10] Kleber ME *et al.* Omega-3 fatty acids and mortality in patients referred for coronary angiography. The Ludwigshafen Risk and Cardiovascular Health Study. In *Atherosclerosis*(2016). http://dx.doi.org/10.1016/j.atherosclerosis.2016.06.049

reduction of risk of CHD mortality/fatal CHD events. These RASBs are in addition to the supporting evidence from three reports from the primary sources WHO and FAO/WHO.

Conclusion

IADSA believes that the document CX/NFSDU 16/38/8, will help direct the discussion at the CCNFSDU meeting in December 2016.

IADSA supports the recommendation that, based on the totality of the available data and strength of the evidence from systematic reviews and the most recent scientific publications, the CCNFSDU set an NRV-NCD for EPA and DHA of 250 mg/day.

Specific Comments

Page 5, Paragraph 17

~~17. Finally, we would like to mention recent reports on the quality of the EPA/DHA sources used in the RCT studies, the factor which remains largely beyond researchers' control and hidden in the GRADE evaluation. There are several studies recently published that examined the contents of EPA/DHA supplements in New Zealand [17], the USA [18] and South Africa [19], concluding that a substantial share of products did not meet requirements for oxidative markers or had active contents below values declared in labeling. In the USA out of 173 long-chain PUFA supplements tested, 50% exceeded the voluntary recommended levels for markers of oxidation. The oxidation of PUFAs is a well-known process that imparts quality and gives specific smell to fish oils. The process is impacted by light and temperature conditions and cannot be controlled in RCT and PC that involved hundreds of participants.~~

IADSA would like to propose the removal of the above paragraph 17 page 5. It is to be noted that fish oil quality issues are currently being discussed by the CCFO as part of its discussion on establishing a fish oil standard.

ICGMA

ICGMA supports the proposed draft NRV-NCD for EPA and DHA of at least 250 mg EPA + DHA per day for inclusion to Section 3.4.4.2 of the *Guidelines on Nutrition Labelling* (CAC/GL 2-1985). ICGMA also supports the inclusion of the additional footnote, "The establishment of an NRV was based on convincing/generally accepted evidence for a relationship with NCD risk as reported in the Diet, Nutrition and Prevention of Chronic Diseases. WHO Technical Report Series 916, WHO, 2003; and in the FAO/WHO Expert Consultations. Technical Report Series 91 and 978, WHO, 2010."

- Strong scientific evidence and support from Recognized Authoritative Scientific Bodies (RASBs), including the European Food Safety Authority (EFSA), the National Institute of Health and Nutrition – Japan (NIHN), the Norwegian Scientific Committee for Food Safety/Nordic Council of Ministers, as well as two World Health Organization Technical Report Series (916 and 91) and the Joint FAO/WHO Expert Consultation on the risks and benefits of fish consumption (2010), support the establishment of a NRV for EPA and DHA for the general population (ages 4+).
- There is convincing and generally accepted evidence of the risk-reducing effect of EPA + DHA on Coronary Heart Disease (CHD) in the general population.
- The risk of adverse effects in consuming EPA and DHA have not been seen, with many populations consuming minimal levels. EFSA concluded that intakes up to about 5 g/day do not cause adverse effects (2012).
- The proposal meets the conditions established in the Codex General Principles for Establishing NRVs.

ISDI

General Comments

ISDI appreciates the work of the eWG, led by Chile and the Russian Federation, to further develop the NRV-NCD for EPA and DHA long chain omega-3 fatty acids in accordance with the General Principles for Establishing Nutrient Reference Values for the General Population (Annex to the *Guidelines on Nutrition Labelling* (CAC/GL 2-1985)

ISDI supports the health outcome for the proposed NRV-NCD for EPA and DHA:

REDUCTION OF RISK OF CORONARY HEART DISEASE MORTALITY/FATAL CHD EVENTS

Specific Comments

Paragraph 45

ISDI supports the eWG recommendation that CCNFSDU considers an NRV-NCD for EPA and DHA of **250 mg/day**, for inclusion in paragraph 3.4.4.2 NRV-NCD of the *Guidelines on Nutrition Labelling* (CAC/GL 2-1985).