Electronic working group on establishing NRV-NCD for EPA and DHA long chain OMEGA-3 fatty acids

Call for comments

5 September 2017

Please respond to codex@ion.ru and cristian.cofre@minsal.cl by 5 October 2017

1 BACKGROUND

At the 37th session of the CCNFSDU in November 2015, under agenda item 7, the Russian Federation and Chile, as co-chairs of the electronic working group on establishing NRV-NCD for EPA and DHA long chain OMEGA-3 fatty acids, voiced a proposal to establish an NRV-NCD of 250 mg/day for EPA/DHA combined intake associated with risk reduction of fatal coronary heart disease (CHD) events[1], based on information and data from three WHO and/or FAO/WHO consultation reports; three RASBs' opinions, and a summary of RCT meta-analyses and systematic reviews published since 2012.

The Committee considered the recommendations as presented in CX/NFSDU 15/37/7 and noted that there were divergent views on the proposal. Those delegations and observers who supported the recommendation of 250 mg/day pointed out that there was sufficient evidence to support the association between EPA/DHA intake and reduction in risk of CHD mortality.

Those delegations of the opinion that it was premature to establish an NRV-NCD expressed the following views:

- The relationship between DHA and EPA and CHD mortality had not been sufficiently characterized to establish an NRV-NCD;
- The evidence was largely based on the consumption of fish and it was not clear whether it was possible to extrapolate this to individual DHA and EPA;
- Not all criteria as per the GP 3.2.2.1 had been met, in particular with regard to the GRADE classification; and
- Not all RASBs had been considered.

Based on the difference of opinion, the Committee has decided to re-establish the eWG, led by Chile and Russia, working in English and Spanish, 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[2], taking into account also the work of NUGAG[3] as was done when establishing the NRV-NCD for sodium and potassium.

In 2016, the co-chairs established contacts with NUGAG and participated in three meetings of the group discussing health effects of polyunsaturated fatty acids (PUFAs). In the eWG, the work was concentrated on finalizing the list of RASBs, reviewing the evidence of EPA and DHA association with CHD mortality, and summarizing data of randomized clinical studies of fish and EPA/DHA consumption and their effect on the target health outcome.

At the time of the 38th CCNFSDU session in December 2016 in Hamburg, the NUGAG systematic review of

[1] The eWG agreed that there was sufficient amount of scientific data available to select CHD mortality/fatal CHD events as a health outcome for the NRV-NCD under discussion.

[2] Annex to the Guidelines on Nutrition Labelling (CAC/GL 2-1985)

[3] WHO Nutrition Guidance Expert Advisory Group

PUFAs was not yet available. In view of the previous decision of CCNFSDU37 for the need to take into account the work of NUGAG, the CCNFSDU agreed to defer discussion until the next session. The Committee agreed to re-establish the eWG, hosted by Russia and Chile, working in English to take into account the final report of NUGAG and to make recommendations for an NRV-NCD for consideration by CCNFSDU at the next session.

2 NUGAG reports

Most recently, the 11th meeting of NUGAG in July 2017 looked at draft systematic reviews of RCTs and cohort studies dedicated to PUFAs and their role in reducing risk of NCDs. Following the meeting, two documents have been shared with the eWG co-chairs:

- Set of systematic reviews of RCTs on the health effects of omega 3 and polyunsaturated fats in adults (Document 1)
- Effects of polyunsaturated fatty acids intake and risk of all-cause mortality, cardiovascular disease, breast cancer, mental health, and type 2 diabetes: a systematic review and meta-analysis of prospective cohort studies (Document 2)

In line with the eWG terms of reference, the co-chairs are now distributing the documents and request eWG members to review them and provide answers to the questions listed below. We also welcome any additional comments or suggestions and would be grateful if your responses could reach us **by 5 October 2017** at the latest.

Document 1: Systematic review of RCTs

Document 1 entitled *Set of systematic reviews of RCTs on the health effects of omega 3 polyunsaturated fats in adults* is an abridged version of the original NUGAG systematic review which excludes six health outcomes not relevant to this eWG discussion. Document 1 presents results of the systematic review for the following health outcomes:

- effects of omega 3 fats on all-cause mortality
- effects of omega 3 fats on cardiovascular outcomes, including cardiovascular mortality, cardiovascular events, coronary heart disease and stroke
- effects of omega 3 fats on lipids and other CVD risk factors
- effects of omega 3 fats on atrial fibrillation.

Most importantly for the eWG discussion, Document 1 contains a separate section (pages 48-54) dedicated to the CHD mortality. It concludes that random effects meta-analysis suggested no effect of long chain n-3 PUFAs (RR 0.93, 95% CI 0.79 to 1.09, I2 35%). At the same time, in the sensitivity analysis, excluding studies only reporting cardiac deaths suggested 17-per-cent reduction of CHD mortality with long chain n-3 acids (RR 0.83, 95% CI 0.74 to 0.94, I2 05, Figure 4.16).

In the further sensitivity analysis, this remarkable association has been removed by omitting studies at moderate to high risk of bias (RR 0.99, 95% CI 0.70 to 1.41, I2 27%, Figure 4.18).

Questions to the eWG

Q1.1 Do you believe that Document 1 represents/summarizes relevant convincing/generally accepted scientific evidence or the comparable level of evidence under the GRADE classification for the relationship between EPA/DHA and noncommunicable disease risk, as required for the selection of nutrients by 3.2.2.1 of General Principles for Establishing NRVs?

Q1.2 Do you believe that Document 1 represents/summarizes relevant and peer-reviewed scientific evidence *for quantitative reference values* for daily intake that is required in order to determine an NRV-NCD that is applicable to the general population, according to 3.2.2.2 of General Principles for Establishing NRVs?

Q1.3 Do you believe that Document 1 (section Coronary Heart Disease deaths, pages 48-54) presents evidence that sufficiently characterizes the relationship between EPA/DHA intake and the reduction of risk of CHD mortality/fatal CHD events, the health outcome selected for establishing the NRV-NCD?

Q1.4 Authors of Document 1 have run sensitivity analysis excluding certain RCTs from the scope of the review.

Do you find results of the sensitivity analysis which excluded RCTs reporting cardiac deaths only (figure 4.16 on page 50) relevant to establishing the NRV-NCD for EPA/DHA associated with CHD mortality?

Q1.5 Figure 4.18 on page 52 depicts results of the sensitivity analysis which grouped studies based on the summary risk of bias.

Do you find results of the sensitivity analysis which grouped RCT studies according to their summary risk of bias relevant to establishing the NRV-NCD for EPA/DHA associated with CHD mortality?

Q1.6 Several RCT studies selected for review in the CHD mortality section of Document 1 were based on a comparison of EPA/DHA intake with intake of monounsaturated fatty acids (MUFA). Considering that there was convincing evidence that MUFA lowered levels of heart health biomarkers[4], comparing effects of EPA/DHA with MUFA intakes might not be entirely suitable for establishing an NRV-NCD.

Do you agree that for the purpose of establishing the NRV-NCD the sensitivity analysis may require exclusion of all studies that compared EPA/DHA intake with MUFA intake?

Document 2 - Systematic review and meta-analysis of prospective cohort studies

Document 2 entitled *Effects of polyunsaturated fatty acids intake and risk of all-cause mortality, cardiovascular disease, breast cancer, mental health, and type 2 diabetes: a systematic review and meta-analysis of prospective cohort studies* is an abridged version which contains results for n-3 polyunsaturated fatty acids (PUFAs) only. The purpose of the document was to systematically review prospective cohort studies and quantify associations between polyunsaturated fatty acids, and all-cause mortality, cardiovascular disease, breast cancer, mental health, inflammatory bowel disease and type 2 diabetes.

For fatal CHD events, the following association has been established for long-chain n-3 polyunsaturated fatty acids (EPA, DHA and DPA):

> The fixed-effect estimate was 0.87 (95% CI: 0.79 to 0.96; P=0.004). Assuming linearity, a 0.5-g increase in long chain n-3 PUFA was associated with a 14-per-cent reduced risk of CHD mortality (mvRR: 0.86, 95% CI: 0.78 to 0.95). Assuming linearity, a 0.5-per-cent increase in long chain n-3 PUFA was associated with a 26-per-cent reduced risk of CHD mortality (mvRR: 0.74, 95% CI: 0.60 to 0.90). The GRADE assessment of the confidence in the estimates of the association was moderate.

Questions to the eWG

Q2.1 Do you believe that Document 2 represents/summarizes relevant convincing/generally accepted scientific evidence or the comparable level of evidence under the GRADE classification for the relationship between EPA/DHA and noncommunicable disease risk relationship, as required for the selection of nutrients by 3.2.2.1 of General Principles for Establishing NRVs?

Q2.2 Do you believe that Document 2 represents/summarizes relevant and peer-reviewed scientific evidence *for quantitative reference values* for daily intake that is required in order to determine an NRV-NCD that is applicable to the general population, according to 3.2.2.2 of General Principles for Establishing NRVs?

Q2.3 Do you believe that Document 2 presents evidence that sufficiently characterizes the relationship between long chain n-3 PUFA intake and the reduction of risk of CHD mortality/fatal CHD events, the health outcome selected for establishing the NRV-NCD?

[4] See for example the FAO report of 2008 expert consultation: Fats and fatty acids in human nutrition

Q2.4 Do you agree that results reviewed in Document 2 for total long chain n-3 PUFAs could be accepted as representative for associations of EPA/DHA with various health outcomes studied including the CHD mortality?