CODEX ALIMENTARIUS COMMISSION E

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Agenda Item 6 **CX/NFSDU 17/39/6**

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

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REPORT OF ELECTRONIC WORKING GROUP ON ESTABLISHING NRV-NCD FOR EPA AND DHA (DRAFT)

(Prepared by the Russian Federation)

BACKGROUND

1. The new work on an NRV-NCD for omega-3 fatty acids based on EPA and DHA was agreed at the 36th session of the CCNFSDU and approved by CAC38 in 2015. An electronic working group, co-chaired by Chile and the Russian Federation, was tasked to:

- Assess the most current scientific evidence in line with the General Principles for Establishing Nutrient Reference Values for the General Population as set out in the Annex to the Guidelines on Nutrition Labelling (CAC/GL 2-1985) [1].
- Make recommendations to set a potential Codex NRV-NCD for the total of Omega-3 fatty acids DHA and EPA.

2. At CCNFSDU's 37th session, under agenda item 7, Chile and the Russian Federation voiced the eWG 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 (see CX/NFSDU 15/37/7 for details).

3. 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.

4. 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 General Principles, section 3.2.2.1 had been met, in particular with regard to the GRADE classification; and
- Not all RASBs had been considered.

5. Based on the difference of opinion, the Committee has decided to re-establish the eWG, led by Chile and Russia, to further develop the NRV-NCD for EPA and DHA long chain omega-3 fatty acids in accordance with the General Principles, taking into account also the work of NUGAG[2] as was done when establishing the NRV-NCD for sodium and potassium.

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[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] WHO Nutrition Guidance Expert Advisory Group.

6. In 2016-17, the co-chairs established working 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 the CHD mortality, and summarizing data of randomized clinical studies of fish and EPA/DHA consumption and their effect on the CHD mortality, as described in CX/NFSDU 16/38/8.

7. CCNFSDU's 37th session considered the need to obtain additional scientific advice through JEMNU[3] or NUGAG, and it was noted that NUGAG was already in the process of scoping a review on PUFAs associations with human health. It was agreed that the committee continued to work on the NRV once NUGAG report would be available[4].

8. Following the 11th meeting of NUGAG in July 2017, two abridged versions of NUGAG reports on health effects of polyunsaturated fatty acids (PUFAs) were shared with the eWG for review and commenting. In line with the eWG terms of reference, the co-chairs initiated eWG discussion of the documents and collected members' opinions[5].

EVIDENCE

9. The eWG proposal of 250 mg/day for EPA/DHA was based on two FAO/WHO expert consultations and one FAO expert consultation:

i. **Report of the JOINT FAO/WHO EXPERT CONSULTATION ON THE RISKS AND BENEFITS OF FISH CONSUMPTION, Rome, 25–29 January 2010, FAO Fisheries and Aquaculture Report No. 978.** This report concluded (section 3.2 page 32): "There is **convincing** evidence that:

- fish consumption and EPA plus DHA intake lower the risk of coronary heart disease mortality". On page 30 of the report (footnote to table 6 of section 2.6.3) it was noted: "The maximum positive effect from EPA + DHA was estimated to occur at 250 mg/day".

ii. **Fats and fatty acids in human nutrition, Report of an expert consultation, Geneva, 10 − 14 November 2008, FAO, Food and Nutrition Paper 91.** Page 16 of this report reads: "There is evidence that the n-3 LCPUFA may contribute to the prevention of CHD and possibly other degenerative diseases of aging. 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".

iii. **Diet, nutrition and the prevention of chronic diseases, Report of a Joint WHO/FAO Expert Consultation, Geneva, 28 January–1 February 2002, WHO Technical Report Series 916.** Section 5.4.4 on page 81 reads that "…convincing associations for reduced risk of CVD include consumption of fruits (including berries) and vegetables, fish and fish oils (eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA))". Recommendations on page 89 in section 5.4.5 add: "…Diets should provide an adequate intake of PUFAs, i.e. in the range 6–10% of daily energy intake. There should also be an optimal balance between intake of n-6 PUFAs and n-3 PUFAs, i.e. 5–8% and 1–2% of daily energy intake, respectively."

10. In addition to the three WHO/FAO reports, members and observers have identified ten RASBs whose opinion was recommended to be taken into account when discussing NRV-NCD for EPA and DHA.

11. At the same time, there were conflicting views on the RASB selection. While the co-chairs and several CMCs believed that only those RASBs that set a reference intake value for EPA/DHA should be considered in line with 3.1.2 of the General Principles[6] several CMCs insisted that opinions of RASBs which did not find convincing evidence for setting a DIRV should also be considered.

[3] Joint FAO/WHO Expert Meetings on Nutrition

[4] In 2017, 31 Codex member countries and observers have participated in the eWG: Australia, Brazil, Canada, Chile, Colombia, Cuba, Estonia, the European Union, France, Indonesia, Japan, Republic of Korea, New Zealand, the Russian Federation, Switzerland, Singapore, the United Kingdom, the United States, Uruguay, International Alliance of Dietary Supplement Associations, Institute of Food Technologists, FoodDrinkEurope, International Food Policy Research Institute, International Special Dietary Foods Industries, International Council of Grocery Manufacturers Associations, Global Organization for EPA and DHA Omega-3, Food Industry Asia, Food and Agriculture Organization of the United Nations, Council of Responsible Nutrition, EU Specialty Food Ingredients.

[5] Twelve responses have been received.

[6] 3.1.2: "…relevant daily intake reference values (DIRV) that reflect recent independent review of the science, from recognized authoritative scientific bodies other than FAO/WHO could also be taken into consideration…"

12. Finally, on request of several CMCs, co-chairs undertook a review of recently published meta-analyses and systematic reviews that studied associations of EPA and DHA intake on cardiovascular health outcomes. Thirteen systematic reviews and meta-analyses that covered randomized clinical trials were identified and reviewed. In assessing the strength of evidence, co-chairs applied approach used for setting population nutrient intake goals for preventing diet-related chronic diseases[7].

NUGAG REPORTS

13. Two NUGAG documents (abridged versions) were shared with co-chairs on 16 August 2017:

1. Set of systematic reviews of RCTs on the health effects of omega 3 and polyunsaturated fats in adults (Document 1)
2. 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).

Members of the eWG have expressed their appreciation for the work undertaken by NUGAG and for providing abridged reports on PUFA health effects in such a short time facilitating eWG discussion.

DOCUMENT 1: SYSTEMATIC REVIEW OF RCTS

14. Document 1 was an abridged version of the original NUGAG systematic review which excluded six health outcomes not relevant to the eWG discussion. Most importantly, Document 1 contained a separate section (pages 48-54 of the abridged version) dedicated to the CHD mortality.

15. The review concluded that random effects meta-analysis suggested no effect of long chain n-3 PUFAs on the CHD mortality. The sensitivity analysis, excluding studies only reporting cardiac deaths, suggested 17-per-cent reduction of CHD mortality with elevated intake of long chain n-3 acids. However, this reduction was not confirmed when studies at moderate to high risk of bias were excluded.

16. In their comments, CMCs were unanimous that evidence presented in Document 1 did not allow for establishing NRV-NCD as criterion set in 3.2.2.1 of the General Principles[8] was not met and the evidence did not support association of EPA and DHA with the CHD mortality.

17. At the same time, the scientific evidence was found to be relevant and convincing and the quality assessment of the body of evidence by GRADE[9] classification [2] has been conducted appropriately by the authors.

18. It was also noted that the GRADE assessment for quality of evidence for the relationship between EPA and DHA and CHD deaths was moderate (Table p.112 of the report) which could not be accepted as meeting 3.2.2.1 criterion of the General Principles.

19. One CMC has commented that Document 1 did not present evidence which satisfied 3.2.2.1 for the relationship between EPA/DHA and non-communicable disease risk, however, if study selection would have been done differently, this outcome may have changed.

20. One observer commented that in relation to the CHD mortality Document 1 reviewed RCTs which were conducted before 2010 while most recent ones were disregarded due to the high risk of bias. Thus, the evidence could not be viewed as most recent and should be looked at as complimentary to more recent observational studies.

21. It was also noted that conclusions of Document 1 related to the CHD mortality contradicted conclusions of 13 systematic reviews of RCT studies conducted worldwide since 2005. Two most recent systematic reviews published in 2017 [3, 4] were also brought to the eWG attention.

[7] Evidence was considered convincing if it was based on epidemiological studies showing consistent associations between exposure and disease, with little or no evidence to the contrary. The available evidence should be 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.

[8] 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, including validated biomarkers for the disease risk, for at least one major segment of the population (e.g. adults).

[9] Grades of Recommendation, Assessment, Development, and Evaluation.

22. eWG members shared an opinion that Document 1 did not represent/summarize 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[10] for Establishing NRVs.

23. An CMC noted that questions remained in relation to a clear explanation of the inclusion/exclusion criteria of studies, therefore, relevant studies that could have influenced the outcome may not have been included in the analysis.

24. The co-chairs have contacted authors of Document 1 and they confirmed that only two RCTs included in the analysis looked at EPA and DHA intake level at the range of 250-400 mg per day. Those RCTs have arrived at the opposite conclusions.

25. In their comments, CMCs and observers have noticed the results of the sensitivity analysis which excluded cardiac deaths and yielded 17 per cent reduction of CHD mortality with elevated intake of EPA and DHA. Nevertheless, it was not clear why cardiac deaths were excluded from the main analysis. The clarification from NUGAG on their definition of CHD death and cardiac death was also requested.

26. In addition, there was no explanation provided for the way outcome data was chosen from relevant studies and why all the various outcomes relevant to coronary heart disease death were not summed as was done for the outcome of cardiovascular death.

27. Co-chairs have contacted authors of Document 1, and they explained that the reason for excluding cardiac death in sensitivity analysis was that cardiac deaths went "slightly outside" of the CHD mortality outcome as they included other causes of death in addition to CHD, such as cardiomyopathies, congenital and valvular heart diseases.

28. The authors attributed such a significant association between EPA and DHA intake and CHD mortality to reporting bias and partly to studies at moderate to high risk of bias. At the same time, they informed us that there were missing components in their summary risk of bias analysis for several RCTs, and they could not yet confirm them with RCT authors whom they have already contacted.

29. One CMC noted that the risk of bias assessment was based primarily on blinding, which meant that likely studies at "low risk of bias" differ from the others on other characteristics (such as single item vs whole diet intervention, dose, type of population studied). It was also remarked that risk of bias assessment based on blinding can be done for studies in pills but less for studies based on dietary intake or advice, for example DART-Burr 1989.

30. It was also noticed that Document 1 has reported a sizable effect of EPA and DHA on lowering serum triglycerides or triacylglycerols (TG), which has been shown to be an independent cardiovascular risk factor [5].The effect was confirmed in the sensitivity analysis by grouping studies with low summary risk of bias.

31. It should be mentioned that similar findings have been recently reported by a study prepared for Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services [6]. Based on randomized controlled trials (RCTs), in both healthy people and those at increased risk for cardiovascular disease, marine oil supplementation raises HDL-c and LDL-c to a small degree (≤2 mg/dL), while lowering triglycerides. People with high triglyceride levels have larger decreases in triglyceride levels than people with lower levels.

DOCUMENT 2 - SYSTEMATIC REVIEW AND META-ANALYSIS OF PROSPECTIVE COHORT STUDIES

32. Document 2 was an abridged version of NUGAG systematic review and meta-analysis of prospective cohort studies for n-3 polyunsaturated fatty acids (PUFAs). The purpose of the document was to systematically review prospective cohort studies and quantify associations between PUFAs and all-cause mortality, cardiovascular disease, breast cancer, mental health, inflammatory bowel disease and type 2 diabetes.

33. For fatal CHD events, assuming linearity, a 0.5-per-cent increase in long chain n-3 PUFAs were associated with a 26-per-cent reduced risk of CHD mortality. The GRADE assessment of the confidence in the estimates of the association was moderate.

34. In their comments, the majority of eWG members shared the opinion that Document 2 summarised current relevant scientific evidence from prospective cohort studies, however it did not on its own fulfil the requirement for providing the convincing level of evidence required for establishing NRVs. One CMC noted that observational studies could not provide causal evidence of an effect of PUFAs on the development of the health outcomes addressed; they can only describe associations.

[10] 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.

35. It was mentioned, nevertheless, that the GRADE assessment of the confidence in the estimates of associations reported in Document 2 was moderate for all-cause mortality and fatal CHD.

36. Several eWG members expressed an opinion that prospective cohort studies were most relevant for the purpose of establishing an NRV-NCD, and, as defined in the report of a Joint WHO/FAO Expert Consultation DIET, NUTRITION AND THE PREVENTION OF CHRONIC DISEASES [7], in relation to population nutrient intake goals for preventing diet-related chronic diseases convincing evidence should be based on epidemiological studies showing consistent associations between exposure and disease, with little or no evidence to the contrary. The available evidence should be 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.

CONCLUSIONS AND RECOMMENDATIONS

37. The opinions expressed in the eWG could be summarised as follows:

- The commenting period given to the eWG was very short considering the extent of the two systematic reviews and the amount of information which was made available for review.
- The NUGAG systematic review of the RCTs (Document 1) did not provide convincing evidence of EPA and DHA effect on CHD mortality. Any significant effect was eliminated in the sensitivity analysis which excluded RCTs of moderate/high summary risk of bias.
- The rationale in the sensitivity analysis run for RCTs which excluded cardiac death as well as NUGAG definitions of CHD death and cardiac death were not clear. Results of the sensitivity analysis for the summary risk of bias were based on many assumptions as several key components of the summary risk of bias were missing.
- No conclusion on quantitative reference value for EPA and DHA effect on the CHD mortality could be drawn from the evidence presented in Document 1.
- The NUGAG systematic review of prospective cohort studies (Document 2) found an association between higher intakes of LCn3 with a 19% reduced risk of fatal CHD. However, the evidence was assessed under GRADE classification as moderate and as such could not be considered as convincing.
- Results reported in Document 2 showed consistency of association in various risk reduction health outcomes for EPA and DHA. However, the lack of support for their effect on CHD mortality revealed in the systematic review of RCTs (Document 1) was an indication that the beneficial association between omega 3 fatty acids and CHD mortality risk reduction cannot yet be translated into a quantitative NRV-NCD in accordance with the General Principles.

38. To conclude, discussions in the eWG have raised several important questions which need to be addressed before the committee could decide how to proceed. Based on opinions expressed in the eWG and considering the highest public importance of the health outcome chosen for this NRV-NCD work, co-chairs would like to recommend the following:

Recommendation 1: Taking into account that only 12 comments were received in the latest round of discussion, to extend commenting period and to allow Codex members to study evidence presented in Documents 1 and 2 taking into account additional information requested in Recommendations 2 and 3.

Recommendation 2: To seek additional advice on how findings in Document 1 and Document 2 correlate with recommendations for EPA and DHA intake of 250 mg/day outlined in WHO/FAO expert consultation on risks and benefits of fish consumption [8] and FAO expert consultation on fats and fatty acids [9].

Recommendation 3: To seek additional advice on significance of NUGAG findings that studies at low summary risk of bias suggested that LCn3 fats reduce serum triglycerides, one of the biomarkers of coronary heart disease.

39. Co-chairs note that major differences of opinion were also revealed in interpretation of the General Principles for Establishing Nutrient Reference Values, which may require a revision of 3.1.2 and 3.2.2.1 of Annex of CAC/GL 2-1985. In this respect, co-chairs would like to add two more recommendations:

Recommendation 4: To revise 3.1.2 of General Principles for Establishing NRVs set out in the Annex to the Codex Guidelines on Nutrition Labelling (CAC/GL 2-1985) and ensure unambiguous interpretation of the following text: “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”. Clarify if opinions from RASBs that did not set daily intake reference values could also be taken into account when establishing NRVs**.**

Recommendation 5: To review text of 3.2.2.1 of General Principles and clarify what level of evidence quality under the GRADE classification shall be considered as the "relevant convincing/generally accepted scientific evidence or the comparable level of evidence under the GRADE classification".

Recommendation 6: To agree if definition of convincing evidence given in the report of a join WHO/FAO expert consultation [7] is applicable for the purpose of establishing an NRV-NCD.

REFERENCES

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