



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

Fortieth Session

**Berlin, Germany
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PROPOSED DRAFT NRV-NCD for EPA and DHA long chain omega-3 fatty acids

(Prepared by the electronic working group led by Chile and the Russian Federation)

Codex members and Observers wishing to submit comments on the recommendations 1 - 4 should do so as instructed in CL 2018/66-NFSDU available on the Codex webpage/Circular Letters 2018: <http://www.fao.org/fao-who-codexalimentarius/circular-letters/en/>

1. BACKGROUND

The new work on NRV-NCD for omega-3 fatty acids (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 the Republic of Chile and the Russian Federation, was tasked to:

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

At CCNFSDU's 37th session, the co-chairs presented 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) events¹, based on information and data of three WHO and/or FAO/WHO consultation reports; three RASBs' opinions, and a summary of meta-analyses and systematic reviews of randomised clinical trials (RCT) published since 2012, prepared by the co-chairs.

The Committee considered the recommendations as presented in CX/NFSDU 15/37/7 and noted that there were divergent views on the proposal.

Based on the difference of opinions, the Committee had re-established the eWG 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 NUGAG² as was done when establishing the NRV-NCD for sodium and potassium [2].

CCNFSDU's 38th session in 2016 considered the need to obtain additional scientific advice through JEMNU³ 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.

Following the 11th meeting of NUGAG in 2017, two abridged versions of NUGAG reports on polyunsaturated fatty acids were shared with the eWG, and the co-chairs initiated eWG discussion of the documents and collected members' opinions.

No consensus was reached at the following 39th CCNFSDU as delegations were of the view that:

- the systematic reviews conducted by NUGAG for the PUFA guideline development by NUGAG were: very comprehensive, but had been presented late to the EWG and more time would be needed to consider them;

¹The 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.

²WHO Nutrition Guidance Expert Advisory Group

³JEMNU - Joint FAO/WHO Expert Meetings on Nutrition

- risk assessors should consider the systematic NUGAG reviews rather than CCNFSDU delegates who were mostly risk managers.

Subsequently, the terms of reference of the re-established electronic working group on NRV-NCD for EPA/DHA were agreed as follows [3]:

1. complete the assessment of the most current scientific evidence as presented in the NUGAG systematic reviews taking into consideration further advice from FAO/WHO;
2. to clarify under Section 3.1 of the General Principles if opinions from RASBs that did not set nutrient intake values could also be taken into account when establishing NRV-NCDs;
3. to discuss the first bullet of Section 3.2.2 of the General Principles and clarify what level of evidence quality under the GRADE classification shall be considered as the "relevant convincing/generally accepted scientific evidence";
4. to discuss if the definition of convincing evidence given in "Diet, Nutrition and the Prevention of Chronic Diseases: Report of a Joint FAO/WHO Expert Consultation, 2002" [6] is applicable for the purpose of establishing an NRV-NCD; and
5. to make proposals to CCNFSDU40.

2. WHO/FAO INQUIRY

In accordance with the latest eWG terms of reference, co-chairs addressed both WHO and FAO seeking further advice on the following:

- How findings in NUGAG draft reviews 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 [4] and FAO expert consultation on fats and fatty acids [8];
- NUGAG's systematic review of RCTs suggested that LCn3 fats reduce serum triglycerides, one of the biomarkers of coronary heart disease. The WHO/FAO advice was sought if this outcome was of public health importance;
- What further advice could FAO and WHO provide to the committee in establishing NRV-NCD for EPA and DHA.

The full text of the letters to WHO and FAO can be found in Annex 1.

As of October 2018 there was no response received from both organisations.

3. 2018 DISCUSSIONS

The eWG discussion of the items included in the 2018 terms of reference was based on the questionnaire distributed to eWG members in early 2018 (Annex 2).⁴ The following sections summarize opinions and comments received from 14 eWG members.

3.1. NUGAG systematic reviews and meta-analyses of PUFAs

The eWG was tasked to complete discussion of the two systematic reviews provided by NUGAG in 2017:

- Set of systematic reviews of RCTs on the health effects of omega-3 polyunsaturated fats in adults;
- 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.

It should be noted that the systematic review of RCTs was published in Cochrane library in 2018 [5].

The eWG members have expressed their view that the evidence studied in the NUGAG systematic reviews for the relationship between EPA and DHA and CHD mortality could not be considered as the relevant convincing/generally accepted scientific evidence or as the evidence of comparable level under the GRADE classification, as required to establish an NRV-NCD. While the RCT review provided no convincing evidence that the relationship existed, the evidence presented in the review of prospective cohort studies (19% of

⁴ In 2018, 27 Codex members and 12 observers have participated in the eWG: WHO, FAO, Argentina, Australia, Austria, Brazil, Canada, China, Colombia, The European Union, France, India, Iran, Ireland, Japan, The Republic of Korea, Mexico, New Zealand, Norway, Peru, Singapore, Sudan, Thailand, Uruguay, Tanzania, the United Kingdom, the United States of America, American Oil Chemists' Society, Council for Responsible Nutrition (CRN), EU Specialty Food Ingredients, FoodDrinkEurope, The Food Industry Asia (FIA), GOED, IADSA, IFFO, Institute of Food Technologists, ISDI, ICGMA, and Early Nutrition Academy ESPGHAN.

reduced risk of fatal CHD) was rated as LOW to MODERATE under the GRADE classification, which most eWG members regarded as not convincing.

One CMC also argued that prospective studies reveal associations only and therefore cannot provide causal evidence of an effect of PUFAs on the reduction of risk of CHD mortality/fatal CHD events.

At the same time, the eWG did not have a consensus view whether the evidence for EPA and DHA cardiovascular benefits for the general population, collected and reviewed by the eWG since its initiation in 2015, was sufficient to meet the requirements set out in the first item of 3.2.2 of the General Principles.

The definition of CHD mortality

Two CMCs and two observers commented that the definition of CHD mortality used by NUGAG in their systematic reviews was not consistent with generally accepted definitions of CHD mortality used by RASBs and conflicted with that used previously in relevant and peer-reviewed scientific publications regarding the association between EPA and DHA and CHD mortality. It was argued that a CHD mortality definition should not prioritise one element of CHD death over another, as NUGAG did in their assessment of RCT data, but rather sum all relevant and related deaths to determine the collective outcome of CHD mortality.

It was recommended to obtain clarification from NUGAG on their definition of CHD death and cardiac death in the systematic review of RCTs. Once CMC has noted that it was unclear if sudden cardiac death was included in cardiac death. In addition, there was no rationale included in NUGAG RCT systematic review to explain the way outcome data was chosen from relevant studies.

3.2. Opinions from RASBs that did not set recommended intake values

The second objective of the eWG in 2018 was to clarify if opinions from RASBs that did not set recommended intakes could also be taken into account when establishing NRVs.

In 2016 ([CX/NFSDU 16/38/8](#)), the eWG members agreed that opinions of the ten RASBs on EPA/DHA intake should supplement the WHO/FAO expert consultations chosen in support of the NRV-NCD. Several CMCs suggested that despite the second paragraph of section 3.1 of the General Principles which stated that:

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...

the EPA/DHA NRV-NCD discussion should not be restricted only to those authorities that established reference intake values. It was further suggested that those RASBs that did not find sufficient evidence to establish a recommended daily intake for EPA and DHA had rational argumentation which could not be disregarded in the NRV-NCD discussion.

There was a consensus in the eWG that opinions of RASBs that did not establish reference intake values for EPA/DHA should also be taken into consideration for the purpose of establishing the NRV-NCD.

Most members agreed that a relevant change was required in the text of the General Principles to allow for the consideration of all RASBs' opinions regardless if they have established a reference intake value or not. One member disagreed that such change was needed.

It was also suggested that the change should not be made in section 3.1 of the General Principles as this section was applicable to both NRV-R and NRV-NCD. Instead, an additional text may be added to the first criterion as listed in 3.2.2 Selection of Nutrients and Appropriate Basis for NRVs-NCD.

Several members commented that the work on amendments of the General Principles fell out of the scope of this eWG and should be discussed by the Committee as new work.

3.3. Convincing evidence and GRADE classification

The first item of the 3.2.2 of the General Principles implies that selection of nutrients for establishing an NRV-NCD requires

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.

CCNFSDU39 noted that since the implementation of the organisation-wide change in the guideline development process in WHO in 2010, the criteria for evaluating the strength of evidence using "convincing, probably, possible and insufficient" applied by the joint WHO/FAO Expert Consultation on Diet, Nutrition and the Prevention of Chronic Disease [6] were no longer in use by WHO, having been replaced by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) [7]. Therefore, the use of *convincing* as a descriptor of the scientific evidence required in support of the NRV-NCD nutrient selection may no longer be relevant.

At the same time, it was also noted that reference to the GRADE classification in 3.2.2 has left certain ambiguity over what level of evidence under the GRADE classification would be considered as acceptable: *very low, low, moderate or high*.

eWG members agreed that the CCNFSDU should continue to use the terms *convincing, generally acceptable, probable, possible and insufficient* as defined in [6] when establishing an NRV and evaluating the evidence strength. All members but one have strongly disagreed with proposal to use the GRADE classification only as limiting to GRADE may exclude several current and future high-quality reviews prepared by certain RASBs from being considered.

Members expressed their agreement that the current wording *Relevant convincing/generally accepted scientific evidence or the comparable level of evidence under the GRADE classification* of the first criterion in 3.2.2 of the General Principles allows for the use of both convincing-insufficient approach as well as the GRADE classification, and both should be used where appropriate.

Several eWG members suggested that further discussion may be required to specify which level of evidence in the GRADE classification is comparable to *convincing*. Though, it has been commented, such a discussion was out of the EPA/DHA NRV-NCD eWG terms of reference and would need to be agreed by the Committee separately.

At the same time, others objected that by specifying a level of evidence quality under the GRADE classification for the purpose of establishing the NRV-NCD, one effectively eliminates the ability to consider reviews that are not based on GRADE. This way, the totality of the available scientific evidence is compromised.

4. RECOMMENDATIONS⁵

4.1. Recommendation 1

Taking into consideration that no consensus has been reached on quality of evidence collected in support of the EPA and DHA effect on CHD mortality, to postpone further discussion of the NRV-NCD for EPA and DHA until new convincing/generally accepted evidence becomes available.

The Committee might also want to seek clarification from NUGAG on their definition of CHD death and cardiac death in the systematic review of RCTs

4.2. Recommendation 2

To initiate new work on revision of the General Principles addressing the following:

- Amending item 3.2.2 to account opinions of RASBs that considered not to set intake reference values for nutrients reviewed for establishing an NRV-NCD.

4.3. Recommendation 3

To continue using the terms *convincing, generally acceptable, probable, possible and insufficient* as defined in the Joint FAO/WHO Expert Consultation [6] for the purpose of establishing NRV-NCD according to the General Principles.

4.4. Recommendation 4

To consider if discussion needs to be initiated on reviewing criteria of the evidence that meets definition of convincing/generally accepted.

⁵ Comments are requested on these recommendations through CL 2018/66-NFSDU

ANNEX 1 - LETTER TO WHO AND FAO REQUESTING ADVICE ON ESTABLISHING NRV-NCD FOR EPA AND DHA

Codex Alimentarius Committee on Nutrition and Foods for Special Dietary Purpose (CCNFSDU) has been recently engaged in the process of establishing a Nutrient Reference Value – Non-communicable Disease (NRVs-NCD) for two polyunsaturated fatty acids - EPA and DHA in accordance with Codex *Guidelines on Nutrition Labelling* (CXG 2-1985 1). In 2015, the electronic working group chaired by the Russian Federation and co-chaired by Republic of Chile formulated a proposal to establish the NRV-NCD at 250 mg/day in association with coronary heart disease (CHD) mortality.

The proposal was based primarily on recommendations of three WHO/FAO expert consultations:

1. 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. 4. 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*".
2. Fats and fatty acids in human nutrition, Report of an expert consultation, Geneva, 10 – 14 November 2008, FAO, Food and Nutrition Paper 91. 8. 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*".
3. 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. 6. 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 "*...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*".

In 2015-16 discussions, the committee failed to reach consensus as there was a considerable difference of opinion if the scientific evidence available was sufficient to support EPA/DHA intake association with the risk of CHD mortality.

CCNFSDU's 37th session considered the need to obtain additional scientific advice through Joint FAO/WHO Expert Meetings on Nutrition (JEMNU) or WHO Nutrition Guidance Expert Advisory Group (NUGAG), and it was noted that NUGAG was already in the process of scoping a review on associations of polyunsaturated fatty acids (PUFAs) with human health.

Following the 11th meeting of NUGAG in July 2017, two abridged draft versions of NUGAG systematic reviews on PUFAs were shared with the eWG for review and commenting. Both reviews have not supported recommendations of the WHO/FAO expert consultations (1-3) arriving at considerably different conclusions. In particular, for EPA and DHA no associations were found for CHD mortality.

The 39th session of CCNFSDU entrusted us to seek further advice from the WHO and FAO in regards to the following questions:

- How findings in NUGAG draft reviews 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 [4] and FAO expert consultation on fats and fatty acids [8].
- NUGAG's systematic review of RCTs suggested that LCn3 fats reduce serum triglycerides, one of the biomarkers of coronary heart disease. We would greatly appreciate your opinion if this outcome is of any public health importance.
- What further advice could FAO and WHO provide to the committee in establishing NRV-NCD for EPA and DHA.

ANNEX 2 - QUESTIONS FOR 2018 DISCUSSION

PLEASE ANSWER QUESTIONS BELOW AND PROVIDE COMMENTS WHERE APPROPRIATE

- 1.1 **Q1: Do you agree that NUGAG systematic reviews of RCT and prospective cohort studies present relevant convincing/generally accepted scientific evidence characterising the relationship between EPA and DHA and CHD mortality, as required by the first item of section 3.2.2 of the Annex to CAC/GL 2-1985?**
- 1.2 **Q2: Do you agree that for the purpose of establishing NRV-NCD for EPA/DHA opinions of RASBs that did not establish reference intake values for EPA/DHA should also be taken into consideration?**
- 1.3 **Q3: Do you agree that a change may be required in the text of the second paragraph of Section 3.1 of the Annex in CAC/GL 2-1985 to account for opinions of RASBs that did not establish reference intake values for EPA/DHA?**
- 1.4 **Q4: Do you agree that the criteria *convincing, probable, possible and insufficient* should no longer be used in describing the level of scientific evidence required for establishing the NRV-NCD for EPA/DHA?**
- 1.5 **Q5: Do you agree that a level of evidence quality under the GRADE classification accepted for the purpose of establishing the NRV-NCD for EPA/DHA should be specified?**
- 1.6 **Q6: Do you agree that a new revision of the first item of Section 3.2.2 of the Annex to CAC/GL 2-1985 may need to be agreed to facilitate further discussion of the NRV-NCD for EPA/DHA?**

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