CODEX ALIMENTARIUS COMMISSION E

Food and Agriculture Organization of the United Nations

World Health Organization

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Agenda Item 7 **CX/NFSDU 15/37/7**
September 2015

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

Bad Soden am Taunus, Germany, 23 – 27 November 2015

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

(At Step 3)

Governments and interested international organizations are invited to submit comments on the proposed draft NRV-NCD as presented in Appendix I at Step 3, and should do so in writing in conformity with the Uniform Procedure for the Elaboration of Codex Standards and Related Texts (see *Procedural Manual of the Codex Alimentarius Commission*) **to**: German Secretariat of CCNFSDU, email ccnfsdu@bmel.bund.de with copy to Secretariat, Codex Alimentarius Commission, Joint WHO/FAO Food Standards Programme, FAO, Rome, Italy, email codex@fao.org **by 30 October 2015.**

Format for submitting comments: In order to facilitate the compilation of comments and prepare a more useful comments document, Members and Observers, which are not yet doing so, are requested to provide their comments in the format outlined in the Annex to this document.

1. BACKGROUND

Main Aspects, Importance, and Timeline for this Work

1. In July 2015, the 38th session of the Codex Alimentarius Commission (CAC38) approved new work on a Nutrient Reference Value (NRV) for omega-3 fatty acids based on docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) intended for the general population for labelling purposes in relation to the risk of Non-Communicable Diseases (NCDs) for inclusion to Section 3.4.4.2 of the *Guidelines on Nutrition Labelling* (CAC/GL 2-1985), as proposed by the 36th session of the CCNFSDU (CCNFDSU36).

2. This work will make an important contribution to the implementation of the WHO Global Strategy on Diet, Physical Activity and Health (WHA Resolution 57.17) in addressing the global burden of diet-related NCDs. It responds to the following Codex Strategic Objectives in the Codex Strategic Plan 2014–2019:

Strategic Goal 1: Establish international food standards that address current and emerging food issues.

Strategic Goal 2: Ensure consistent use of risk analysis principles and scientific advice.

3. The establishment of an NRV-NCD for EPA and DHA will complement the existing NRV-NCD for intake levels not to exceed 20 g for saturated fatty acids and 2,000 mg for sodium, and an intake level of 3,500 mg to achieve for potassium.

Conduct of the Electronic Working Group

4. At CCNFSDU36 it was agreed to establish an electronic working group (eWG), co-chaired by the Russian Federation and Chile and working in English and Spanish with the following terms of reference:

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

5. In February 2015, an invitation to participate in this eWG was extended to Codex member countries (CMCs) and observers (COs). Thirty-three (33) participating eWG members are acknowledged in footnote[1].

[1] CMCs: Argentina, Australia, Canada, Chile, China, Ecuador, the European Union, Germany, Greece, Ireland, Japan, Luxemburg, Mexico, the Netherlands, New Zealand, Norway, Peru, Russian Federation, Singapore, Sweden, Thailand, United States of America.
COs: Council for Responsible Nutrition (CRN) USA, ELC Federation of European Speciality Food Ingredients Industries, Food Drink Europe, International Alliance of Dietary/Food Supplements Associations (IADSA), International Special Dietary Foods Industries (ISDI), Global Organisation for EPA and DHA Omega-3 (GOED), IFFO - The Marine Ingredients

In April 2015, the Co-Chairs circulated a consultation paper to the eWG members. Twelve CMCs and 6 COs responded to the consultation with comments. In July 2015, a second consultation paper was circulated. Ten CMCs and 4 COs responded to the second consultation.

6. The Russian Federation and Chile would like to express their thanks to the eWG participants who submitted comments and participated in discussions. These comments were considered in preparing this report and they raised important issues for discussion by the Committee.

PROPOSED NRV-NCD FOR EPA AND DHA

Application of the General Principles (GP) for Establishing NRVs for the General Population

3.1Selection of Suitable Data Sources to Establish NRVs

GP 3.1.1

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

7. The eWG was asked to consider three joint FAO/WHO expert consultations:

- World Health Organisation (2003) Joint WHO/FAO Expert Consultation on Diet, Nutrition and the Prevention of Chronic Disease (Geneva, Switzerland). Technical Report Series 916.
- World Health Organisation (2010) Fats and fatty acids in human nutrition. Report of an expert consultation, (Geneva, Switzerland). Technical Report Series 91.
- Joint FAO/WHO Expert Consultation on the risks and benefits of fish consumption, 25–29 January 2010, Rome. FAO Fisheries and Aquaculture Report No. 978. FIPM/R978 (En), ISSN 2070-6987.

All the respondents from CMCs and COs agreed on the inclusion of these expert consultations. (See Appendix II for summaries).

GP 3.1.2

GP 3.1.2 states 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. Higher priority should be given to values in which the evidence has been evaluated through a systematic review*."

8. For the purposes of establishing an NRV-NCD, the working definition for a Recognized Authoritative Scientific Body (RASB) other than the FAO and/or WHO is an organization supported by a competent national and/or regional authority that provides independent, transparent[2], scientific and authoritative advice on daily intake values through primary evaluation[3] of the scientific evidence upon request and for which such advice is recognized through its use in the development of policies in one or more countries.

9. The eWG was asked to identify which accepted RASBs meet all the components of the RASB definition. The list of accepted RASBs is:

- European Food Safety Authority (EFSA)
- National Institute of Health and Nutrition, Japan
- Nordic Council of Ministers/Norwegian Scientific Committee

The summary of nominated RASBs proposed and highlights of their work in regards to the intake of EPA and DHA are given in the Appendix III.

Several CMCs and Cos identified other sources of scientific information. A detailed review of the meta-analyses published since 2012 are presented in paragraphs 30-39. Despite some convincing evidence emerging in support of a positive role of omega-3 fatty acids in reducing the risk of CVD, Co-Chairs proposed to focus their attention to RASBs already accepted by CCNFSDU and nominated by the eWG.

Organisation, The Early Nutrition Academy, The International Council of Grocery Manufacturers Association (ICGMA), FEDOIL

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

[3] Primary evaluation involves a review and interpretation of the scientific evidence to develop daily intake reference values, rather than the adoption of advice from another RASB.

GP 3.1.3

"*The daily intake reference values should reflect intake recommendations for the general population.*"

10. The Joint FAO/WHO Expert Consultations 2010 found convincing evidence that moderate consumption of oily fish lowers mortality from coronary heart disease (CHD) in the general population. These reports did not make a distinction between the strength of the evidence for primary and secondary prevention, and it was concluded that the totality of the evidence is convincing for a risk-reducing effect of EPA and DHA on CHD. The clear distinction between primary prevention in healthy adults and primary prevention in high-risk groups, as well as for mixtures of subjects qualifying for primary and secondary CHD/cardiovascular disease (CVD) prevention are difficult to resolve and are dependent on the authors' definition in the particular study (Nestel *et al.* 2015). With regard to the consideration of reduction of risk of CHD and sudden cardiac death, it was noted that the pathophysiology of CVD is the same, whether for a first heart attack or a second. (Nestel P, et al. 2015) . In relation to primary and secondary prevention, one CMC noted that the NRV-NCD for potassium was accepted by the CCNFSDU on the basis of its positive effect only in those individuals with pre-existing hypertension, and that this disease was sufficiently prevalent to affect public health adversely. Therefore, consistent with this precedent, the Co-Chairs consider evidence of both primary and secondary prevention to be acceptable in the establishment of an NRV-NCD for EPA + DHA for the general population.

11. The intake recommendations by WHO/FAO and nominated RASBs are summarised in the table:

Table. Dietary intakes recommended by WHO/FAO and nominated RASBs for omega-3 fatty acids in connection with reducing risk of CVD outcomes

RASB	Recommendation	Note
World Health Organisation (2010) Fats and fatty acids in human nutrition Report of an expert consultation, (Geneva, Switzerland). Technical Report Series 91 http://www.who.int/nutrition/publications/nutrientrequirements/fatsandfattyacids_humannutrition/en/	250 mg/day of EPA plus DHA	For adult males and non-pregnant/non-lactating adult females, based on convincing evidence of reduced risk of fatal CHD events
European Food Safety Authority, 2010 *EFSA J* 2010; 8 (3): 1461.	250 mg/day of EPA plus DHA	Adequate intake in adults considering cardiovascular benefits, sufficient for primary CVD prevention in health subjects
National Institute of Health and Nutrition, Japan/Ministry of Health and Welfare, 2010 Dietary Reference Intakes for Japanese 2010: Fat, J.Nutr. Sci Vitaminol, **59, S44-S52, 2013** https://www.jstage.jst.go.jp/article/jnsv/59/Supplement/59_S44/_article	900 mg/day of EPA plus DHA (without considering basal intake of ALA)	For adults over 18 y.o. lower boundary dietary goal for preventing life-threatening disease (DG) based on findings that high EPA and DHA intake reduce the incidence of coronary artery disease
Norwegian Scientific Committee for Food Safety/Nordic Council of Ministers, 2011 Evaluation of negative and positive health effects of n-3 fatty acids as constituents of food supplements and fortified foods, Opinion of the Steering Committee of the Norwegian Scientific Committee for Food Safety, 2011 http://www.vkm.no/dav/c7a41adb79.pdf	0.25 g to 0.5 g of EPA and DHA daily decreases the risk of mortality from coronary heart disease and sudden cardiac death	The evidence show that it is possible to obtain positive health effects in the Norwegian population from intake of EPA and DHA, including from food supplements, without any appreciable risk of negative or adverse health effects.

GP 3.2.2.1

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

Relevant convincing[4]/generally accepted[5] scientific evidence or the comparable level of evidence under the GRADE classification[6] 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).

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

12. The eWG was asked if the first criterion in GP 3.2.2.1 was met for the long-chain PUFAs EPA + DHA.

13. The terms of reference of the new work project document state that strong scientific data has supported a primary prevention benefit for omega-3 fatty acids based on EPA + DHA relating to cardiovascular health for the general population. The first consultation paper asked the eWG to consider the following benefits: primary reduction of death risk from coronary heart disease (CHD), sudden cardiac death and other cardiovascular benefits. All of the respondents agreed that the focus should only be on cardiovascular benefits of combined EPA + DHA intended for the general population. However, several CMCs commented that the term cardiovascular benefits is too vague and, based on the FAO/WHO 2010 reports and the EFSA 2010 scientific opinion, the following outcome is proposed for this new work:

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

14. Members of the eWG were asked to consider that the totality of evidence available is convincing/generally accepted for the benefit described in bold in paragraph 14. The Co-Chairs also requested members of the eWG to send any additional information or additional evidence to that already provided with the consultation document. Sources considered by eWG as relevant to this work are listed in the closing section of the report.

15. In the first consultation, 11 CMCs and 6 COs concluded that the totality of the available scientific data and weight of evidence is convincing and generally accepted. These evaluations were based mostly on the conclusions of the 2008 and particularly the 2010 FAO/WHO expert consultations, as well as the 2010 EFSA scientific opinion and 2010 Dietary Reference Intakes for Japanese.

16. The majority of responses to the two consultation papers from CMCs and COs demonstrated general agreement that the totality of the evidence is convincing or generally accepted. However, five CMCs do not consider that the evidence is sufficient to meet the criterion in General Principles 3.2.2.1.

17. Three CMCs suggested that the evidence that is currently available from prospective cohort studies is largely based on the consumption of fish, not EPA + DHA in isolation. As such, a guideline supporting consumption of fish rich in omega-3 PUFAs as reported by WHO/FAO in 2010 is consistent with the evidence. The extrapolation of this evidence base to solely EPA + DHA was considered as not being consistent with the available evidence.

18. Co-chairs would like to note that the Joint FAO/WHO 2010 Expert Consultation found that fish consumption lowers mortality from CHD in the general population. The conclusion states that moderate consumption of oily fish (one or two servings per week) would provide maximum benefit (two servings provide about 250 mg EPA + DHA, but risks are lowered by any level of fish consumption evaluated (up to seven 100 g servings per week).

19. Dietary intakes of fish and oily fish are not sufficient to obtain the quantities of EPA + DHA needed for the beneficial effects. Worldwide, typical intakes of marine omega-3 long-chain PUFAs are low. There is an abundance of evidence that people should be eating oily fish at least twice a week to obtain adequate amounts of EPA + DHA for the benefits for reduction of risk of CHD mortality. The 2006 Australian NHMRC Report on NRVs comments that there has been an exponential rise in publications on the health benefits of omega-3 PUFAs, particularly the longer chain omega-3s, EPA, DPA and DHA, and the evidence is strongest for reduction of CVD risk by EPA and DHA. The report also notes that it is increasingly common to relate the outcomes of epidemiological studies to estimates of EPA and DHA intakes or to plasma or erythrocyte EPA and DHA levels in each sector of the population. The NHMRC 2006 report includes references confirming

[4] At the time these guiding principles were drafted the definition and criteria for "convincing evidence" were taken from the FAO/WHO Report "Diet, Nutrition and the Prevention of Chronic Diseases" (WHO Technical Report Series 96, WHO, 2003).
[5] For these General Principles the terms convincing/generally accepted evidence are considered synonymous.
[6] WHO Guidelines Review Committee, WHO Handbook for Guideline Development. Geneva: WHO, 2012.

the observations that there is a tight inverse relationship between sudden death and blood EPA and DHA levels associated with the consumption of fish at least once weekly (90–160 mg EPA + DHA/day). A reference was also included showing that fish consumption counteracts cardiovascular mortality in quintiles of a healthy ageing population consuming at least 267 mg/day of EPA + DHA, whereas eating fish low in EPA + DHA gave no benefit. The NHMRC Report concludes that, given the body of evidence and the modest intakes currently consumed in Australia and New Zealand, it would seem prudent to encourage increased consumption of LC n-3 fatty acids (DHA, EPA and DPA).

20. One CMC commented that the EFSA scientific opinion (*EFSA 2010*) concluded that there was insufficient evidence to derive a population reference intake for EPA + DHA, and consequently an Adequate Intake (AI) was set. The Co-Chairs thought it appropriate to include the complete paragraph from the report, which confirms that EFSA does recognize the cardiovascular benefits of EPA + DHA, having established an amount of 250 mg/day, which appears to be sufficient for primary prevention of CHD in healthy subjects.

21. The complete paragraph from the EFSA scientific opinion (EFSA Journal 2010; 8(3):1461) is as follows:

The human body can synthesise eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) from alpha-linolenic acid. Intervention studies have demonstrated beneficial effects of preformed n-3 long-chain polyunsaturated fatty acids on recognised cardiovascular risk factors, such as a reduction of plasma triacylglycerol concentrations, platelet aggregation, and blood pressure. These effects were observed at intakes 1g per day, well above levels that were associated with lower cardiovascular disease (CVD) risk in epidemiological studies. With respect to cardiovascular diseases, prospective epidemiological and dietary intervention studies indicate that oily fish consumption or dietary n-3 long-chain polyunsaturated fatty acids supplements (equivalent to a range of 250 to 500 mg of eicosapentaenoic acid plus docosahexaenoic acid daily) decrease the risk of mortality from coronary heart disease (CHD) and sudden cardiac death. An intake of 250 mg per day of eicosapentaenoic acid plus docosahexaenoic acid appears to be sufficient for primary prevention in healthy subjects. Therefore, and taking into account that available data are insufficient to derive an Average Requirement, the Panel proposes to set an Adequate Intake of 250 mg for eicosapentaenoic acid plus docosahexaenoic acid for adults based on cardiovascular considerations.

22. Co-chairs also would like to refer to the EFSA Scientific Opinion on principles for deriving and applying Dietary Reference Values (EFSA 2010, 1458) which define the Adequate Intake (AI) as the average (median) daily level of intake based on observed, or experimentally determined approximations or estimates of nutrient intake, by a group (or groups) of apparently healthy people that is assumed to be adequate. The AI is different from the Average Requirement (AR) with the latter being a level of intake estimated to satisfy the physiological requirement or metabolic demand in half of healthy individuals. In the context of the NRV discussion, the AI based on cardiovascular considerations is closely related to the NRV-NCD while the AR value is clearly more relevant to NRV-R.

23. One CMC has noted that in recent years, intervention trials with omega-3 LC PUFAs have started a trend towards no effect with respect to secondary prevention of CHD. These outcomes have been perplexing based on the established and convincing epidemiological evidence of the benefits and on the research on mechanistic cardiovascular pathways, not to mention earlier investigations (Burr *et al* 1989; GISSI-Prevenzione 1999; Yokoyama *et al* 2007; GISSI-HF 2008).

24. The key question today is whether the reported consumption of omega-3 LC PUFAs from fish, or dietary patterns high in omega-3 LC PUFAs (measured through plasma or red blood cell LC PUFAs) are associated with lower incidence of CHD events in primary prevention. Nestel *et al.* (August 2015) reviewed the evidence published since 2007 and concluded that dietary intake of fish was found to be mostly consistent with respect to protection from heart disease and stroke. Higher fish intake was associated with lower incident rates of heart failure in addition to lower sudden cardiac death, stroke and myocardial infarction. In relation to omega-3 LC PUFA supplementation, neither a beneficial nor an adverse effect was demonstrated in primary or secondary prevention of CHD.

25. Several major early studies using fish or fish oils to reduce CHD events were favourable. These included DART, JELIS and two GISSI studies. It was on the basis of DART and GISSI-Prevenzione that most recommendations in the late 1990s and early 2000s for the use of EPA + DHA in secondary prevention were founded. However, at least six trials published between 2010 and 2014 did not find a benefit for EPA + DHA in patients with known CHD or with risk factors for heart disease. It is not surprising that these findings have been replicated in several systematic reviews, given the inclusion of the most recent neutral reviews.

26. As noted by the authors of the studies themselves, the lack of effect of EPA + DHA on subjects with cardiac disease (i.e. secondary prevention) is likely due to a combination of the low doses administered, short follow up, high background n-3 LC PUFA intake and different n6: n3 ratios, frequent use of modern pharmacotherapy, relatively low-risk patient populations, and/or small sample sizes. These differences in study designs, population characteristics, types and amounts of omega-3 LC PUFAs account for some of the

inconsistencies in research findings. Authors also noted that the beneficial effects of EPA + DHA could be masked by current effective drug therapies that may override or obscure additional benefits of EPA + DHA supplementation. Researchers found it increasingly difficult to recruit subjects with low baseline n-3 intake from marine sources and to maintain low n-3 intake from marine sources in the control group. The contradictions in research findings may well be explained by the fact that trial participants were recruited irrespective of their baseline status in EPA + DHA—an important predictor of cardiovascular events (Schacky, 2015). The overlap in EPA + DHA levels between the test and control arms has important implications for the final statistical comparisons. The pitfalls in the design, execution and statistical analysis of randomised controlled trials for fish oil studies and flaws in subsequent meta-analyses have been highlighted in several scientific publications including those by James *et al.* (2014), DiNicolantonio *et al.* (2012), von Schacky (2015), Harris (2013) and Hu and Manson (2012).

27. Co-chairs also would like to point at dose-response effect observed in several studies. In particular, the plot of the relative risk of CHD deaths against EPA + DHA intake demonstrates a dose response from a very low intake up to 250 mg/day of EPA + DHA and then little further reduction with higher intakes. The relative change in the risk of CHD mortality and sudden cardiac death with omega-3 LC PUFA consumption is greatest when the comparator has consumed little or no n-3 (Mozaffarian D and Rimm EB (2006) *JAMA* **296**, 1885-1889).

28. Another difficulty in interpretation of the results is concerned with the fact that most studies have used composite outcomes (fatal and non-fatal myocardial infarction, sudden death, mortality from heart failure, non-fatal stroke and fatal stroke, percutaneous intervention and coronary artery bypass grafting (CABG). Their use greatly increases the chance of a null finding and detecting an effect on the primary outcome measure, which is the main aim of a randomised clinical trial (RCT).

29. As several CMCs suggested, the co-chairs reviewed meta-analyses of randomised clinical trials that studied relation between the supplementation with PUFAs and risk of cardiac death.

30. There have been several meta-analyses published over the last 5 years that focused on n-3 fatty acids and various CVD outcomes. Some have reported overall benefit; some mixed benefit and others no benefit. Co-chairs would like to point out that none scientific bodies represented by the authors of the meta-analyses identified in the literature search were qualified as RASB and their scientific opinions need to be treated with care.

31. The Appendix IV summarises five large meta-analyses performed in the last three years and their parameters in studying EPA/DHA effect on the risk of cardio and CVD-related mortality. The table shows that the five analyses covered mostly the same list of RCTs with the work by Chowdhury et al. (Chowdhury, 2014) also covering two most recent RCTs conducted in 2012 and 2013. The total number of patients was in the range of 10,000s. The largest coverage was provided in meta-analyses by Chowdhury et al. and Rizos et al. (over 60,000 patients) (Rizos 2012) and the smallest – by the study of Kwak (ca. 17,000 patients) (Kwak 2012).

32. The number of clinical studies covered was between 11 and 14. In our evaluation of risk of bias we have taken into account only information provided by the authors of meta-analysis. The percentage of RCTs that were reported to have no significant risks was the highest in the analysis by Trikalinos et al. (58%) and the lowest in the work by Kwak et al. (28%)

33. We first would like to highlight the limitations of the analyses. The evidence accumulated in the RCTs analyzed is mostly limited to secondary prevention with studies on healthy populations being largely excluded in all analyses. Only four RCTs out of 23 listed considered primary prevention and only one study reported results for the healthy population group separately. In addition, in all meta-analyses authors pointed out that in the RCTs studied patients were likely to be under intensive medication treatment. One RCT (Kromhout et al. 2010, 4837 patients) included only patients who had a myocardial infarction and who were receiving state-of-the-art antihypertensive, antithrombotic, and lipid-modifying therapy at the time of the trial. Authors in another trial (Rauch et al. 2010, 3851 patients) reported that 85 per cent of patients were receiving five different medications per day. Unfortunately, these intensive therapies were not accounted for in the RCT baselines hindering acceptance of the results for the general population.

34. There were certain flaws in the RCT design. The three largest RCTs in the list were open-label having high risk of bias due to the lack of blinding both for participants and personnel. Another limitation was indirectness, e.g. patients differed from those of interest. One of the largest RCTs in the meta-analysis by Rizos et al. that contributed 30% of the data weight, the ORIGIN study, covered exclusively patients with diabetes or impaired fasting glucose or impaired glucose tolerance thereby making it nearly impossible to use the trial results in the context of the NRV-NCD.

35. The Appendix V summarises GRADE evidence profiles for the five meta-analyses reviewed in the aspect of cardiac and CVD fatal events constructed with the GRADEpro guideline development tool[7] using the series of GRADE guidelines in quality assessment published by the GRADE working group[8] (Guyatt 2011). The Appendix also shows the quantitative findings for each analysis, e.g. a relative effect of EPA and DHA on CVD and cardiac mortality. The scoring was interpreted in accordance with the WHO Handbook for Guideline Development (WHO 2014).

36. Our most conservative approach in the assessment yielded LOW quality level for meta analyses by Rizos et al. and by Kwak et al. rating them as having low confidence in the effect estimate: the true effect may be substantially different from the estimate of effect. In particular, the risk of bias and indirectness of the meta-analyses by Rizos et al. undermined the published conclusion regarding secondary prevention in cardiac patients that read: "*Our findings are to not justify the use of n-3 as a structural intervention in everyday clinical practice or guidelines supporting dietary n-3 PUFA administration*". The more accurate conclusion that would reflect study design and findings should have been, "*In patients of average age 63, with a wide variety of types of CVD, with large part of those suffering from diabetes, and under intensive drug therapy, the administration of about 1 g of EPA + DHA for about two years did not significantly reduce risk for major clinical outcomes*".

37. Analyses by Trikalinos et al. (Trikalinos 2012) and by Chowdhury et al. scored MEDIUM. There was moderate confidence in the effect estimate. The HIGH score was awarded to the work by Delgado-Lista et al. (Delgado-Lista 2012) enabling high confidence that the true effect lies close the effect estimate.

38. The scorings were generally consistent with the GRADE quality assessment performed in the EVIPnet report on evidence of the EPA and DHA health benefits (EVIPnet 2015).

39. Co-chairs took extra time and care in studying findings of the meta-analyses. Two out of five (Rizos et al. 2012 and Chowdhury et al. 2014) reported no statistically significant effects of EPA plus DHA supplementation on either cardiovascular mortality or major cardiovascular outcomes. In the analysis by Kwak et al. which established insufficient evidence of a secondary preventive effect of omega-3 fatty acid supplements, authors at the same time clearly indicated that "omega-3 fatty acid supplementation significantly reduced cardiovascular death (RR 0.91; 95% CI)". Even after exclusion of one doubtful RCT, the analysis still yielded a statistically significant value of RR of 0.92 (95% CI).

40. Two other analyses by Trikalinos et al. 2012 and Delgado-Lista et al. 2012 concluded that omega-3 fatty acids were effective in preventing cardiovascular events, including cardiac death. The former analysis also established that the mean EPA and DHA intake up to 200 mg daily was associated with decreased risk of cardiac, cardiovascular or sudden cardiac deaths.

41. Co-chairs would like to emphasise that, as shown in Appendix V, all five meta-analyses independently estimated the relative risk (RR) of EPA plus DHA intake in reducing risk of fatal CVD outcomes in the RR range of 0.89 - 0.92 (CI 95%) averaging at 0.91 or 9% absolute decrease in the CVD mortality rate. While different studies arrived at different conclusions, the consistency of these quantitative outcomes of the five analyses is striking and should not be ignored. Despite the drawbacks of the meta-analyses as described above, co-chairs recommend to take into account the quantitative results of the analyses as a strong evidence in support of the proposal to establish NRV-NCD for EPA and DHA in reducing risks of coronary heart disease mortality/fatal CHD events.

42. Systematic reviews and meta-analyses have been instrumental in advancing scientific research and informing policy. Because they synthesize aggregate data, they are regarded by some to be the most authoritative form of the available evidence. Overall, a meta-analysis is only as good as the studies it pools together. They are useful tools for summarising a large body of evidence, but it is important to recognize their limitations, give adequate consideration to sources of heterogeneity or bias, and consider their conclusions in the context of other relevant scientific literature (Satija A, 2015).

43. Therefore, results from meta-analyses need to be considered carefully. Overall, omega-3 LC PUFAs are among the most extensively studied nutrients for their potential cardiovascular benefits. There are few other nutritional factors that have the strength and consistency of evidence, and the biological plausibility for reduction of risk of CHD mortality and fatal CHD events. Further discussion by CCNFSDU is warranted, including the 2010 FAO/WHO conclusion that the evidence is convincing, in order to gain further clarification of the relationship between EPA + DHA and CHD mortality.

44. We would like to conclude this part on the evidence provided by meta-analysis by stating that neither of the meta-analyses studied added any evidence to the contrary or demonstrated inconsistency in the effect, as was suggested by several CMCs. On the contrary, the meta-analyses were rather consistent arriving at

[7] http://www.guidelinedevelopment.org
[8] http://www.gradeworkinggroup.org/publications/jce_series.htm

the same quantitative result. It remains to be discussed by this committee if 9% in cardiac mortality rate reduction detected in meta-analyses represents a significant difference to be considered as a favourable effect of EPA and DHA intake.

45. Co-chairs would like to note that the shortcomings of individual RCTs of fish or fish oil intervention inevitably affect the conclusions of meta-analyses performed in the recent years. The neutral results of the more recent intervention trials are in sharp contrast to the consistent results of epidemiological studies, animal studies and proposed plausible mechanisms of action. Walter Willett's team at the Harvard School of Public Health has pointed out the role of nutritional epidemiology in inferring causality and the appropriateness and limitations of RCTs in determining diet and disease relationships. Evidence from several types of studies, in particular prospective cohort studies of hard clinical endpoints and intervention trials of intermediate outcomes, in totality can be used to infer causality and inform nutrition policy. Well-conducted observational studies have played a major role in shaping policies. Research is an evolving process and consensus is often hard to achieve. A paper in the American Society for Nutrition journal (Satija A 2015), helps to clarify common misunderstandings of nutritional epidemiology, and challenges the drug trial paradigm in nutrition research for disease outcomes that can take years or decades to show in the general population

46. To address the second criterion for GP 3.2.2.1, the eWG was asked if it agreed that EPA + DHA intake is sufficiently important for public health among Codex member countries.

47. The majority of the CMCs (except those five that concluded the evidence was not convincing) and all the COs agreed that substantial global public health benefits would be expected for the general population from greater consumption of EPA + DHA, and that the totality of the available scientific data reviewed justifies the establishment of an NRV-NCD for labelling purposes. Many respondents noted that dietary intake assessments and resultant measures of EPA and DHA nutritional status indicate a total disconnect between what is actually consumed and current recommendations.

48. References and examples for evidence of public health benefit were provided by several respondents and included: the European Union, where CVDs are the first causes of death, accounting for 40% of deaths and where intakes of EPA + DHA are often low and well below recommended levels; and "The preventable causes of death in the United States: comparative risk assessment of dietary, lifestyle and metabolic risk factors" by Danaei G, Ding EL, Mozaffarian D *et al. PLoS Med* (2009) **6**: e 1000058. Although these data are specific to the USA, it was considered that there is no reason to believe that the number of deaths would not be similar in other countries with low EPA + DHA intakes. In the Russian Federation, the CVD remains the primary cause of mortality being one of the highest in the world.

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

50. Based on recommendations from RASBs, the majority of the CMCs (except the five that concluded the evidence was not convincing) and all the COs supported the establishment of a single internationally harmonised NRV-NCD for EPA + DHA for the general population identified as older than 36 months for primary reduction of death from CHD and fatal CHD events, in an amount ranging between 250 and 500 mg/day.

51. GP 3.2.2.3 states, "*Daily intake reference values from FAO/WHO or other RASBs that may be considered for NRVs-NCD include values expressed in absolute amounts or as a percentage of energy intake*".

52. The eWG members supporting the new work for the establishment of an NRV-NCD for EPA + DHA stated an absolute amount to be expressed in mg/day.

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

54. GP 3.2.2.5 states, "*An NRV-NCD for the general population should be determined from the daily intake reference value for the general population or adults, or if given by sex, the mean of adult males and adult females*".

55. Most eWG members supported the values for the general population provided in the FAO/WHO 2010 expert consultation, and RASBs.

56. GP 3.3 Consideration of Daily Intake Reference Values for Upper Levels states, "*The establishment of general population NRVs should also take into account daily intake reference values for upper levels established by FAO/WHO or other RASBs where applicable (e.g. upper level of intake, acceptable macronutrient distribution range)*".

57. Recently, EFSA (2012) concluded that intakes up to about 5 g/day of EPA and DHA combined do not appear to increase the risk of bleeding complications and spontaneous bleeding episodes or affect glucose homeostasis, immune function or lipid peroxidation, provided that the oxidative stability of the EPA and DHA is guaranteed.

58. In Dietary Reference Intakes for Japanese 2010: Fat (O, Ezaki 2013), the upper boundary dietary goal (DG) for preventing lifestyle-related diseases for EPA and DHA was not considered as intake at typical daily levels has not been found to result in increased occurrence of clinically significant adverse effects.

59. The GISSI Prevenzione trial in 1999, the JELIS study (Yokoyama *et al.*, 2007) and the GISSI-HF Investigators (2008) study reported no clinically relevant adverse effects in over 35, 000 individuals. Over 10 years ago, the US Food and Drug Administration (FDA) determined that intakes of EPA and DHA of up to 3 g/day are safe for the general population. In 2011, the Norwegian Scientific Committee for Food Safety conducted a safety review of EPA and DHA and found no adverse effect on bleeding time, with levels as high as 6.9 g/day (Froyland *et al.*, 2011).

60. Other considerations: One CMC proposed that the new work on omega-3 fatty acids should include alpha-linolenic acid (ALA) as well as EPA + DHA and that an assessment of the relative strength of the evidence should be undertaken. It is worth noting that ALA remains outside of the terms of reference of this work as stated in paragraph 5 of this paper. Thus, no fatty acid apart from EPA+DHA should be a matter of discussion in this document.

61. One CMC has suggested that any NRV-NCD established would conform to General Principles 3.2.1.2 and 3.2.1.3 relating to the general population aged from 4 years (older than 4 ears) and excluding pregnant and lactating women.

62. Other considerations: potential mechanisms that could contribute to the effects of EPA + DHA on reduced risk of CVD. The studies on risk markers and the potential underlying mechanisms are beyond the scope of this new work. However, the following biologically plausible mechanism could explain the main CVD benefits that have been proposed: reduction of cardiac arrhythmias, lowering of plasma triglycerides, anti-atherosclerotic potential, reduction in both diastolic and systolic blood pressure, reduction in arterial stiffness, effects on platelet aggregation and haemostasis, and effects on endothelial function and inflammation.

3. CONCLUSION AND RECOMMENDATIONS

63. Based on the totality of the available scientific data and weight of evidence, together with the recommendations from the FAO/WHO Expert Consultations and other nominated RASBs, most of the eWG members considered that there is consistent and convincing/generally accepted evidence to support the beneficial relationship between the long chain omega-3 fatty acids EPA plus DHA in the diet and reduction of risk of CHD mortality/fatal CHD events. In countries with low habitual fish consumption (e.g. fewer than one to two servings per week of oily fish), the majority of the general population does not meet the recommended intakes of at least 250 mg EPA + DHA per day.

64. It is recommended that CCNFSDU consider a harmonised 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.

65. Members are requested to consider the underpinning science and conclusions and to make their scientific judgements on the proposed draft NRV-NCD for EPA and DHA.

Appendix I

PROPOSED DRAFT NRV-NCD FOR EPA AND DHA FOR INCLUSION IN SECTION 3.4.4.2 OF THE *GUIDELINES ON NUTRITION LABELLING* (CAC/GL 2-1985)

(The proposed draft NRV-NCD for EPA and DHA for comment at Step 3 is presented in **bold and underlined format)**

3.4.4.2	**NRVs-NCD**	
	Intake levels not to exceed	
	Saturated fatty acids	20 g[8,9]
	Sodium	2000 mg[10]
	Intake levels to achieve	
	Potassium	3500 mg[10]
	Eicosapentaenoic acid (EPA) and Docosahexaenoic acid (DHA)	**250 mg[11]**

[8] This value is based on the reference energy intake of 8370 kilojoules/2000 kilocalories.

[9] The selection of this nutrient for the establishment of an NRV was based on "convincing evidence" for a relationship with NCD risk as reported in the report *Diet, Nutrition and the Prevention of Chronic Diseases.* WHO Technical Report Series 916. WHO, 2003.

[10] The section of these nutrients for the establishment of an NRV was based on "high quality" evidence for a relationship with a biomarker for NCD risk in adults as reported in the respective 2012 WHO Guidelines on sodium and potassium intake for adults and children.

[11] 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.

APPENDIX II

Food and Agriculture Organisation and World Health Organisation (FAO/WHO) Expert Consultations

1. World Health Organisation (2003) Joint WHO/FAO Expert Consultation on Diet, Nutrition and the Prevention of Chronic Disease (2002: Geneva, Switzerland) Technical Report Series 916.

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

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

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

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

2. World Health Organisation (2010) Fats and fatty acids in human nutrition Report of an expert consultation, (Geneva, Switzerland). Technical Report Series 91
http://www.who.int/nutrition/publications/nutrientrequirements/fatsandfattyacids_humannutrition/en/

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

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

3. Joint FAO/WHO Expert Consultation on the risks and benefits of fish consumption, 25–29 January 2010, Rome. FAO Fisheries and Aquaculture Report No. 978. FIPM/R978 (En), ISSN 2070-6987.

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

In addition, this expert consultation did not make a distinction between the strength of the evidence for primary and secondary prevention, and it was concluded that the totality of the evidence is convincing for a

risk-reducing effect of EPA +DHA on CHD, as is described in the document, based on large numbers of prospective cohort studies, it is evident that there is consistent and convincing evidence for a beneficial effect of EPA and DHA for primary prevention of heart disease.

APPENDIX III

RASBs nominated by eWG

Nominated RASB	**European Food Safety Authority**	**National Institute of Health and Nutrition – Japan (NIHN)**	**Norwegian Scientific Committee for Food Safety/ Nordic Council of Ministers**
1) Supported by one or more government(s) or competent national or regional authorities.	EU member states and the European Commission	Japan Ministry of Health, Labor and Welfare	Norway, Denmark, Iceland, Sweden and Finland
2) Provides independent and transparent authoritative scientific advice through primary evaluation of the scientific evidence upon request.	EFSA's Panel on Dietetic Products, Nutrition and Allergies has established dietary reference values for the intake of carbohydrates, dietary fibre, fats and water. EFSA's advice on nutrient intakes provides an important evidence base to underpin nutritional policies, the setting of diet-related public health targets and the development of consumer information and educational programmes on healthy diets. The opinions published were adopted by the Panel after consultation with Member States, the scientific community, and other stakeholders. The consultation ensures EFSA has benefited from the widest range of views to finalise the work and provide the most up-to-date, clear and comprehensive advice to EU decision makers.	In order to obtain extensive evidence for the "Dietary Reference Intakes (DRIs) for Japanese" which is revised every 5 years, by the Ministry of Health, Labour and Welfare and to promote more effective application, NIHN work on the following three activities; 1. Nutrition research to generate evidence for the DRIs for Japanese and practical research on its application. 2. Collection of basic data necessary to establish the DRIs for Japanese, and database management for next revision. 3. Dissemination of the DRIs for Japanese domestically and internationally, and promotion of its application.	The VKM scientific opinion provides an extensive literature search, including studies with fish oils and marine ethyl esters and studies with plant oils. Although the mechanisms of actions are not fully understood and there is less evidence for primary prevention than secondary prevention. The conclusions suggest that increased consumption of n-3 fatty acids from fish or fish oil supplements reduces the rates of all-cause mortality from CVD, cardiac and sudden death, and possibly stroke, and that a sufficient intake of EPA and DHA is important for good health. VKM also states that the optimal dose is not known, and that the amount may vary in different populations depending on the basal dietary intakes of n-3 fatty acids and n-6 fatty acids.
3) Is one whose advice on DIRVs is recognized through use in policy development in one or more countries?	Yes, through dietary reference values for the European population	Yes, through dietary reference values for Japanese	Yes, through dietary recommendations given by the authorities in Norway, Denmark, Finland, Iceland, and Sweden are based on the Committee's Recommendations
RASB publication	European Food Safety Authority. Scientific opinion on Dietary Reference Values for fats, including saturated fatty acids, polyunsaturated fatty acids,	Dietary Reference Intakes for Japanese 2010: Fat, J.Nutr. Sci Vitaminol, **59, S44-S52, 2013** https://www.jstage.jst.go.jp/article/jnsv/5	Nordic Council of Ministers (2013). Nordic Nutrition Recommendations 2012 - Part 1 (5th ed). Nord 2013:009. [online] Available at http://www.norden.org/en/publications/publika

	monounsaturated fatty acids, trans-fatty acids and cholesterol. *EFSA J*2010;8(3): 1461.	9/Supplement/59_S44/_article	tioner/nord-2013-009 [accessed 11 October 2013]
Recommendation	250 mg for EPA plus DHA in adults considering cardiovascular health.	DG – 900 mg/day in relation to CAD risk	At least 1 per cent of energy intake, 222 mg/day based on 2,000 kcal diet

APPENDIX IV

Summary of the 23 randomised clinical trials (RCT) studied in meta-analyses that estimated effect of the EPA and DHA on CVD outcomes including cardiac and CVD mortality

#	Year	RCT	Number of people	Risk of bias			Meta-analyses				
				No blinding participants/ personnel	Indirectness	Loss to follow-up above 20%	Chowdhury 2014	Rizos 2012	Kwak 2012	Delgado-Lista 2012	Trikalinos 2012
1	2007	Yokoyama (JELIS) et al	18645	YES			*	*		*	*
2	2008	Tavazzi (GISSI-HF) et al	6975				*	*	*	*	*
3	2010	Einvik et al	563							*	*
4	2012	ORIGIN	12563		YES		*	*			
5	1995	Sacks et al	59			YES	*	*	*	*	*
6	1998	Leng et al	120			YES		*	*		
7	1999	Marchioli (GISSI) et al	11334							*	
8	1999	Von Schasky et al	223			YES	*	*	*	*	
9	2001	Nilsen et al	300				*	*	*	*	*
10	2009	Garbagnati et al	72			YES			*		
11	2010	Kromhout et al	4837			YES	*	*	*		*

12	2010	Rauch (OMEGA) et al	3851	YES			*	*	*	*	*
13	2005	Leaf et al	402				*	*	*	*	*
14	2005	Raitt et al	200				*	*	*	*	*
15	2006	Brouwer et al	546				*	*		*	*
16	1997	Singh et al	240		YES				*		*
17	1999	Johansen et al	500								*
18	2001	Durrington et al	59								*
19	2002	Marchioli (GISSI-P) et al	11323	YES			*	*			*
20	2003	Burr et al	3114								*
21	1994	Leaf et al	551							*	
22	2012	Mozaffarian et al (OPERA)	1516				*				
23	2013	Roncaglioni MC et al. (RPS)	12505				*				
Total number of RCTs covered							14	13	11	13	14
Percentage of studies with zero risk of bias							50	39	28	54	58

Risk of bias is estimated as reported by authors of meta-analyses. Risk due to loss of blinding was evaluated in Chowdhury et al. and Rizos et al. Loss to follow-up reported by Kwak et al.

APPENDIX V

Grade evidence table for selected meta-analyses

EPA/DHA supplementation compared to placebo for lowering risks of CORONARY HEART DISEASE MORTALITY/FATAL CHD EVENTS

Quality assessment							№ of patients		Effect	Quality
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**EPA/DHA supplementation**	**placebo**	**Relative (95% CI)**	
Association between omega-3 fatty acid supplementation and risk of major cardiovascular disease events, Ritzos et al, 2012										
13	randomised trials	serious [1]	not serious	serious [2]	not serious	none	1658/28097 (5.9%)	1822/28070 (6.5%)	**RR 0.91** (0.85 to 0.98)	⊕⊕◯◯ LOW [1 2]
Efficacy of omega-3 fatty acid supplements (EPA and DHA) in the secondary prevention of CVD, Kwak et al, 2012 (follow up: mean 1.2 years)										
11	randomised trials	serious [3 4]	not serious	not serious	serious [5]	none	-/6984	-/6990	**RR 0.91** (0.84 to 0.99)	⊕⊕◯◯ LOW [3 4 5]
Effects of EPA and DHA on mortality across diverse settings: systematic review and meta-analysis of randomised trials and prospective cohorts, Trikalinos et al, 2012										
14	randomised trials	serious [1 6]	not serious	not serious	not serious	none	n/a	n/a	**RR 0.89** (0.83 to 0.96)	⊕⊕⊕◯ MODERATE [1 6]
Long chain omega-3 fatty acids and cardiovascular disease: a systematic review, Delgado-Lista et al, 2012										
13	randomised trials	not serious	not serious	not serious	not serious	none	1108/23409 (4.7%)	1198/23328 (5.1%)	**RR 0.91** (0.83 to 0.99)	⊕⊕⊕⊕ HIGH
Dietary, Circulating, and Supplement Fatty Acids and Coronary Risk, Chowdhury et al, 2014										
17	randomised trials	serious [1]	not serious	not serious	not serious	none	2426/38303 (6.3%)	2548/38277 (6.7%)	**RR 0.94** (0.86 to 1.03)	⊕⊕⊕◯ MODERATE [1]

RR – relative risk

1. Three RCTs of total meta-analysis data weight of 61% had high risk of bias due to lack of blinding
2. ORIGIN 2012 study made up 29% of meta-analysis data weight though studied only patients with diabetes or impaired fasting glucose or impaired glucose tolerance.
3. Loss to follow-up is greater than 20% in 5 RCTs comprising 40% of meta-analysis data weight

4. small sample size of 59-500 participants
5. RCTs analysed had confidence intervals reaching below RR of 0.75, undermining main conclusion of the analysis

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Annex

GENERAL GUIDANCE FOR THE PROVISION OF COMMENTS

In order to facilitate the compilation and prepare a more useful comments' document, Members and Observers, which are not yet doing so, are requested to provide their comments under the following headings:

(i) General Comments

(ii) Specific Comments

Specific comments should include a reference to the relevant section and/or paragraph of the document that the comments refer to.

When changes are proposed to specific paragraphs, Members and Observers are requested to provide their proposal for amendments accompanied by the related rationale. New texts should be presented in **underlined/bold font** and deletion in ~~strikethrough font~~.

In order to facilitate the work of the Secretariats to compile comments, Members and Observers are requested to refrain from using colour font/shading as documents are printed in black and white and from using track change mode, which might be lost when comments are copied / pasted into a consolidated document.

In order to reduce the translation work and save paper, Members and Observers are requested not to reproduce the complete document but only those parts of the texts for which any change and/or amendments is proposed.