



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

**Thirty-eighth Session**

**Hamburg, Germany**

**5 – 9 December 2016**

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

*(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 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](mailto:ccnfsdu@bmel.bund.de) with copy to Secretariat, Codex Alimentarius Commission, Joint WHO/FAO Food Standards Programme, FAO, Rome, Italy, email [codex@fao.org](mailto:codex@fao.org) by **15 October 2016**.

**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

1. At the 37th session of the Committee (CCNFSDU37) (November 2015), the Russian Federation, as the co-chair of the eWG, introduced the eWG report ([CX/NFSDU15/37/7](#)) and a proposal to establish an NRV-NCD of 250 mg/day for EPA/DHA intake combined based on information and data from three WHO and/or FAO/WHO consultation reports; three RASBs (which had met the definition of an RASB), and a review of meta-analyses published since 2012.

2. CCNFSDU37 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 the NRV-NCD and reduction in risk of coronary heart disease mortality.

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

4. Based on the differences of opinion, the Committee has decided to re-establish the eWG<sup>1</sup>, led by Chile and the Russian Federation, working in English and Spanish, to further develop the NRV-NCD for EPA and DHA long chain omega-3 fatty acids in accordance with the General Principles for Establishing Nutrient Reference Values for the General Population (Annex to the [Guidelines on Nutrition Labelling \(CAC/GL 2-1985\)](#) [1], taking into account also the work of NUGAG as was done when establishing the NRV-NCD for sodium and potassium.

5. In 2015, the eWG members agreed that the following health outcome needed to be chosen for a potential EPA and DHA NRV-NCD:

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

in line with the General Principles.

6. In selecting sources of evidence that can be used to supplement opinions of RASBs, the co-chairs followed GP 3.1.2, which 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.*

7. In formulating the selection criteria, the co-chairs were also advised to utilize the WHO PICO format<sup>2</sup>, commonly used in framing a healthcare research question. The following PICO question has been proposed:

Table 1: PICO question

<b>Population</b>	Adults (≥16 years of age) with or without hypertension, or a population of adults not acutely ill with or without history of coronary heart disease, other cardiovascular diseases, type 2 diabetes, cancer etc.
<b>Intervention</b>	Increased EPA and DHA intake via dietary advice, specific foods, supplements or whole diet provided and unconfined by other dietary, weight, lifestyle or pharmaceutical interventions
<b>Comparison</b>	Diet with an EPA and DHA level lower than in the intervention
<b>Outcome</b>	The health outcome should be focused on coronary heart disease mortality/fatal events

## 2 EPA AND DHA ASSOCIATION WITH CVD MORTALITY AND EVIDENCE AVAILABLE

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

<sup>1</sup> As of March 2016 the following countries and organizations expressed their willingness to participate in the eWG: Argentina, Australia, Brazil, Canada, Costa Rica, the European Union, Ghana, Greece, India, Ireland, Japan, Mexico, New Zealand, Norway, Paraguay, The Republic of Korea, Rwanda, Singapore, Sweden, Thailand, the United States of America, Council for Responsible nutrition (CRN), Early Nutrition Academy ESPGHAN, FoodDrinkEurope, Federation of European Specialty Food Ingredients Industries (ELC), Food and Agriculture Organization of the United Nations (FAO), Global Organization for EPA and DHA Omega-3s (GOED), The Alliance of Supplement Associations (IADSA), International Food Policy Research Institute (IFPRI), International Council of Grocery Manufacturer Associations (ICGMA), The Marine Ingredients Organisation (IFFO).

<sup>2</sup> P- Patient, I - Intervention, C - Comparison, O - Outcome

Table 2: Systematic reviews and meta-analyses that studied association of EPA/DHA intake with risk of CVD mortality including sudden cardiac death (in chronological order)

Author and Year	Reference	Study design	Number of studies	Participants	Source of EPA/DHA	Prevention	RR (95% CI) for cardiac mortality	Impact	GRADE <sup>a</sup>
Del Gobbo, 2016	[2]	PC <sup>b</sup>	19	45,637	All	Primary	0.9 (0.84–0.96) <sup>c</sup>	Conclusive	⊕⊕⊕⊕ low
Chowdhury, 2014	[3]	PC (dietary intake)	16	422,786	Diet	Primary, secondary	0.87 (0.78-0.97) <sup>d</sup>	Conclusive	⊕⊕⊕⊕ low
		PC (biomarkers)	13	23,065	Diet	Primary, secondary	0.75 (0.62-0.89)	Conclusive	⊕⊕⊕⊕ low
		RCT <sup>e</sup>	17	76,580	Supplements		0.94 (0.86 - 1.03)	Inconclusive	⊕⊕⊕⊕ moderate
Wen, 2014	[4]	RCT	14	16,338	Supplements	Secondary	0.88 (0.80-0.96) <sup>f</sup>	Conclusive	⊕⊕⊕⊕ moderate
Casula, 2013	[5]	RCT	11	15,348	Supplements	Secondary	0.68 (0.56–0.83)	Conclusive	⊕⊕⊕⊕ high
Rizos, 2012	[6]	RCT	13	56,407	Supplements	Primary, Secondary	0.91 (0.85–0.98)	Conclusive	⊕⊕⊕⊕ low
Kwak, 2012	[7]	RCT	14	20,485	Supplements	Primary, Secondary	0.91 (0.84–0.99)	Conclusive	⊕⊕⊕⊕ low

<sup>a</sup>For selected outcome only

<sup>b</sup>Prospective cohort studies

<sup>c</sup>for DHA only

<sup>d</sup>average for all outcomes studied including all-cause mortality, cardiac mortality, sudden cardiac death, MI, CHD

<sup>e</sup>randomized clinical trials

<sup>f</sup>Odds ratio

Author and Year	Reference	Study design	Number of studies	Participants	Source of EPA/DHA	Prevention	RR (95% CI) for cardiac mortality	Impact	GRADE <sup>a</sup>
Trikalinos, 2012	[8]	RCT	14	48,500	Supplements	Primary, secondary	0.89 (0.83-0.96)	Conclusive	⊕⊕⊕⊕
		PC	7	123,122	Fish or fish oil		0.64 (0.46-0.89)	Conclusive	⊕⊕⊕⊕ low
Delgado-Lista, 2012	[9]	RCT	13	46,737	Supplements or diet	Primary, secondary	0.91 (0.83–0.99)	Conclusive	⊕⊕⊕⊕ high
Kotwal, 2012	[10]	RCT	20	63,030	Supplements or diet	Primary, secondary	0.86 (0.75–0.99)	Conclusive	⊕⊕⊕⊕ high
Chen, 2011	[11]	RCT	10	33,429	Supplements	Secondary	0.81 (0.69–0.95)	Conclusive	⊕⊕⊕⊕ high
Filion, 2010 <sup>b</sup>	[12]	RCT	25	34,501	Supplements	Secondary	0.89 (0.72–1.06) <sup>c</sup>	Inconclusive	⊕⊕⊕⊕ low
Marik, 2009	[13]	RCT	11	39,044	Supplements	Secondary	0.87 (0.79–0.95) <sup>d</sup>	Conclusive	⊕⊕⊕⊕ high
Zhao, 2009	[14]	RCT	8	20,997	Supplements	Secondary	0.71 (0.5–1.0)	Inconclusive	⊕⊕⊕⊕ low

<sup>a</sup>For selected outcome only

<sup>b</sup>The study did not look at the target outcome but analyzed all-cause mortality in CVD patients

<sup>c</sup>All-cause mortality in high CVD risk group

<sup>d</sup>Odds ratio, sudden cardiac death

9. Thirteen (13) systematic reviews and meta-analyses were identified that covered randomised clinical trials and prospective cohort studies being relevant to the PICO question. The lowest number of participants included in the RCTs reviewed was 16,338 people and the largest was 76,580 participants. Typically, prospective cohort studies included hundred thousand people.

10. In evaluating the impact of the reviews, the approach taken in the WHO's Guideline was utilized: Potassium intake for adults and children [15]. Evidence was considered conclusive of either a benefit or a harm from increased EPA/DHA intake if the relative risk (RR) point estimate suggested a benefit or harm and the 95% confidence interval (CI) did not overlap a threshold of relevance. If the point estimate was near the null value and the 95% CI did not overlap a threshold of relevance, the evidence was considered conclusive of no effect.

11. Conversely, evidence was considered inconclusive if the point estimate suggested a benefit or a harm but the 95% CI crossed a threshold of relevance.

12. RRs below 1 were considered (in favour of the association of EPA/DHA intake) with the CI not overlapping a threshold of relevance as *conclusive* evidence. The results with RR being below 1 but the 95% confidence interval overlapping the threshold of reference were regarded as inconclusive.

13. Based on this approach, the impact of all but three studies were ranked as *conclusive* with at least minor association between the EPA/DHA intake and cardiac mortality revealed in the statistical analysis. It has to be noted that no RRs above 1 have been reported for the cardiac mortality outcome in any of the systematic reviews.

14. As already noted in CX/NFSDU 15/37/7, authors of different systematic reviews have drawn different conclusions on the association with cardiac mortality even though their reviews produced identical results of the statistical analysis. Thus, Kwak and Delgado-Lista have calculated the same RR values for cardiac mortality for EPA/DHA intervention (0.91), studying almost the same set of RCTs (see Appendix 4 in [CX/NFSDU 15/37/7](#)).

Kwak concluded that

*supplementation with omega-3 fatty acids had no beneficial effect on CVD events, including sudden cardiac death and CVD-related fatal events*

while Delgado stated that

*a 9% decrease of risk of cardiac death was observed in the intervention groups.*

15. We believe that this difference of opinion should have arisen from different perceptions of the clinical relevance of the RR real value. In Kwak study authors considered 9 per cent reduction in the intervention group as irrelevant while Delgado viewed the same result as a proof of the clinical effect.

16. In order to take into account the requirement of GP 3.2.2.1 that states:

*Relevant convincing/generally accepted scientific evidence or the comparable level of evidence under the GRADE classification for the relationship between a nutrient and non-communicable disease risk relationship, including validated biomarkers for disease risk, for at least one major segment of the population (e.g. adults).*

the GRADE approach was applied to evaluate the strength of the evidence presented in the systematic reviews using the GRADEpro tool. The PC studies were always ranked the lowest, and RCT scores were downgraded or upgraded using criteria described in the GRADE handbook [16]. The GRADE score per systematic review is shown in the column 10 of table 2 (see Appendix for detailed summary of findings tables).

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

### 3 FISH OR EPA/DHA

18. During the CCFSDU37 discussion, it was highlighted that fish and seafood intake were recognized as important sources of key macro- and micronutrients, EPA and DHA in particular. In a recently published scientific report of the US dietary guidelines advisory committee it was stated that the health benefits of seafood are likely to be associated with DHA and EPA, although seafood is also known to be a good source of other nutrients including protein, selenium, iodine, vitamin D, and choline [20].

19. The summary presented in Table 2 shows information on the sources of EPA/DHA used in the RCTs and PCs covered in the systematic reviews. It could be seen that majority of the RCT studies were based on supplementation of the intervention groups with pure EPA/DHA or fish oil supplements while dietary sources were used in prospective cohort studies.

20. In order to facilitate further discussion on fish intake associations with CVD health outcomes, the co-chairs reviewed recent scientific publications, however, could not identify systematic reviews or meta-analyses which included RCT-based studies of the fish intake in association with CVD health outcomes and could be regarded as those matching requirements of the General Principles (i.e. reflecting recent review of science).

21. Zheng et al. [21] ran a meta-analysis of 17 cohort studies (315,812 participants) which looked at the association of the fish consumption and CVD mortality. Authors concluded that either low (1 serving/week) or moderate fish consumption (2–4 servings/week) has a significantly beneficial effect on the prevention of CVD mortality. They also suggested that, considering the synergic effect of many components in fish, such as high-quality protein, amino acid and vitamins, analysis of total fish consumption on CVD is probably more valuable than the sole evaluation of long-chain PUFAs.

22. Cardiovascular health benefits of fish and EPA/DHA intakes were compared in the Joint FAO/WHO Expert Consultation on the Risks and Benefits of Fish Consumption [22]. It was observed that

*...based on the available data, together with additional evidence for the effects of EPA plus DHA and fish consumption on cardiovascular risk factors, the Expert Consultation concluded that there was convincing evidence for the benefits of EPA plus DHA intake on coronary heart disease mortality. The Expert Consultation also concluded that both quantitative analyses provided concordant results, with one analysis evaluating EPA plus DHA intake as the exposure and the other evaluating fish consumption. Thus, the results of the first analysis were considered appropriate for quantifying the coronary heart disease mortality benefits of EPA plus DHA intake, and the results of the second analysis for quantifying the coronary heart disease mortality benefits of fish consumption.*

23. Nestel et al. [23] studied literature published in 2007-2013 and concluded that higher fish intake was associated with lower incident rates of heart failure in addition to lower sudden cardiac death, stroke and myocardial infarction. At the same time, In relation to omega-3 LCPUFA supplementation, neither a beneficial nor adverse effect was demonstrated in primary or secondary prevention of coronary heart disease (CHD). Although the authors concluded that the evidence continues to be convincing for a modest positive benefit of omega-3 LCPUFAs in heart failure and mortality.

24. As fish and seafood have been recognized as primary sources of EPA and DHA, it has become a standard practice to quantify fish intake in EPA and DHA amounts. For example, the 2015 US Dietary Guidelines recommend for the general population to consume about 230 g per week of a variety of seafood, which provides an average consumption of 250 mg per day of EPA and DHA and is associated with primary and secondary prevention of cardiac deaths.

25. RCTs are widely considered the most reliable source of scientific evidence, and in RCT designs the primary importance is given to the nutrient bioavailability as a measure of the nutrient intake compliance. In this respect, the whole discussion on fish versus EPA/DHA intake becomes slightly irrelevant as RCTs increasingly rely on the level of EPA/DHA biomarkers in evaluating intake associations with a particular health outcome.

26. Studies of long-chain PUFA associations commonly take circulating plasma omega-3 levels as a measure of intake compliance [24]. However, it has been argued that long-term intakes are not reflected in plasma levels [25]. Instead, the red blood cell omega-3 PUFAs expressed as the percentage of EPA+DHA in red cell lipids (the omega-3 index) needs to be used in reporting objective compliance of intake at the baseline and post intervention. The omega-3 index has been shown to increase in dose-dependent manner with increases of EPA and DHA intake [26].

27. The omega-3 index is a measure of the proportion of fatty acids in red blood cell membranes that are made up of EPA and DHA. Studies have shown the omega-3 index was a powerful risk factor for chronic diseases. One research demonstrated that the omega-3 index was a stronger risk factor for sudden cardiac death than traditional risk factors like cholesterol, triglycerides and C-reactive protein [27].

28. Most recent attempt to evaluate EPA/DHA intakes required to reach a cardioprotective value of the omega-3 index [28] was undertaken by the authors of the GISSI-Heart Failure (HF) study [29] which has been included in all systematic reviews listed in Table 2. The GISSI study reported benefits of n-3 fatty acid (FA) treatment on cardiovascular (CV) events, but the effects of the intake on the omega-3 index have not been examined in this context. There was a hypothesis that treatment with omega-3 acid ethyl esters would increase the omega-3 index to the proposed cardioprotective value of 8% [30]. Red-blood cell samples (RBCs) were collected from a subset of patients participating in the GISSI-HF study (n = 461 out of 6975 randomized), at baseline and after 3 months of treatment with either an olive oil placebo or EPA/DHA esters (1 g/d). Participants also reported their typical olive oil and fish intakes. RBC oleic acid levels were directly correlated with reported frequency of olive oil consumption, and the omega-3 index was correlated with reported fish intake (p for trends <0.001 for both). After treatment, the omega-3 index increased from  $4.8 \pm 1.7\%$  to  $6.7 \pm 1.9\%$  but was unchanged in the placebo group ( $4.7 \pm 1.7$  to  $4.8 \pm 1.5\%$ ) ( $P < .0001$  for changes between groups). At 3 months, more participants reached the proposed target omega-3 index level of  $\geq 8\%$  in the treated vs placebo group (22.6% vs. 1.3%,  $P < .0001$ ), however, the omega-3 index levels ultimately achieved after four years in this trial are unknown.

29. Most recently, Kleber et al. [31] have studied omega-3 index association with CVD and all-cause mortality in 3259 participants of the Ludwigshafen Risk and Cardiovascular Health Study (LURIC) [32]. Proportions of EPA and DHA were inversely associated with all-cause and cardiovascular mortality in models adjusted for conventional CVD risk factors. The strongest association was observed for EPA with a hazard ratio (HR) of 0.89 (0.83–0.96) per increase of one standard deviation. Furthermore, the evidence was obtained for a non-linear relation between EPA and mortality.

#### 4 SELECTION OF RASBs

30. During the discussions in 2015, the eWG members expressed their agreement that the following WHO/FAO reports on relevant daily intake reference values for EPA/DHA should be taken into consideration as primary sources in establishing NRV-NCD:

- (i) Joint WHO/FAO Expert Consultation on Diet, Nutrition and the Prevention of Chronic Disease (Geneva, Switzerland). Technical Report Series 916 [33].
- (ii) Food and Agriculture Organization (2010) Fats and fatty acids in human nutrition. Report of the Joint FAO/WHO Expert Consultation on Fats and Fatty Acids in Human Nutrition, (Geneva, Switzerland). Technical Report Series 91 [34].
- (iii) 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 [22].

31. In March 2016, the co-chairs requested eWG members to propose scientific and expert bodies that should be considered as RASBs in the context of the NRV-NCD for EPA and DHA. In response, a total of 22 scientific and expert organizations were proposed.

32. For the purposes of establishing an NRV-NCD, the working definition for a Recognized Authoritative Scientific Body (RASB) other than the FAO and/or the WHO was considered as

*organization supported by a competent national and/or regional authority that provides independent, transparent<sup>3</sup>, scientific and authoritative advice on daily intake values through primary evaluation<sup>4</sup> 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.*

<sup>3</sup> 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.

<sup>4</sup> 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.

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

Table 3: RASBs selected by eWG

No	Authority	Publication
1	European Food Safety Authority/the EU	EFSA J 2010;8(3): 1461.
2	The Working Group on Food, Diet and Toxicology/Nordic Council of Ministers	Nordic Nutrition Recommendations 2012 Part 2
3	National Institute of Health and Nutrition/Japan	J. Nutr Sci Vitaminol, 59, S44-S52,2013
4	Australian National Health and Medical Research Council/Australia and New Zealand (NHMRC)	A review of the evidence to address target questions to inform the revision of the Australian Dietary Guidelines (2011)
5	Dietary Guidelines Advisory Committee/the USA	Scientific report of the Dietary Guidelines Committee, (2010)
6	Food and Nutrition Board of the Health and Medicine Division (formerly IOM)/the USA and Canada	Seafood: Selections to Balance Benefits and Risks (2007)
7	Agence nationale de securite sanitaire de l'alimentation, de l'environnement et du travail (ANSES)/France	(2011) Actualization des apports nutritionnels conseilles pour les acides gras.
8	Nutrition Society funded by Germany's Federal Ministry of Food and Agriculture	Evidence-Based Guideline of the German Nutrition Society: Fat Intake and Prevention of Selected Nutrition-Related Diseases (2015)
9	Health Council of the Netherlands/The Netherlands	Guidelines for a healthy diet (2006)
10	Scientific Advisory Committee on Nutrition (SACN)/The UK	SACN Advice on Fish Consumption: Benefits and Risks (2004)

34. In the list of ten, the potential RASBs 1, 2, 5<sup>5</sup>, 7 have produced a quantitative recommendation for the EPA and DHA intake in relation to the target outcome, REDUCTION OF RISK OF CORONARY HEART DISEASE MORTALITY/FATAL CHD EVENTS.

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

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

37. The US IOM 2007 report (6) has also come short of yielding an intake recommendation for EPA/DHA intake. The authors concluded that "*while it is uncertain how much these omega-3s contribute to improving health and reducing risk for certain conditions such as heart disease, there is evidence for benefits both to the general population and to some groups of people. For those with existing heart disease there may be benefits from consuming EPA and DHA in seafood, although more research is needed in this area*". At the same time, no strong scientific evidence was established to suggest a threshold of consumption, such as two servings per week, below which seafood consumption provides no benefit and above which increasing consumption provides additional benefits.

38. We would like to note that a number of RASBs proposed by the eWG and not mentioned in this section did not meet the RASB criteria either because they were not supported by a competent national and/or regional authority or were not recognized through its use in the development of policies in one or more countries (see Appendix II for details).

<sup>5</sup> in the US DGAC recommendation the EPA and DHA intake has been specifically set as a nutritional target to be achieved exclusively through fish consumption.



39. In their responses, the eWG members agreed that 10 RASBs should be shortlisted and that the quality of the evidence they provided need to be discussed at the next CCNFSDU meeting. It was highlighted that despite 3.1.2 provision of the General Principles which states that

*...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...*

the NRV-NCD discussion should not be restricted to those authorities that establish DIRVs.

40. One member country (CMC) has commented that the selection of RASBs should not be limited to those that established DIRVs, but also should consider opinions of those scientific bodies which did not think that the totality of evidence amounted to the establishment of a DIRV as was the case in the work on establishing NRV-R (REP16/CCNFSDU).

41. Another CMC has suggested that reports of the authorities that did not yield DIRVs evaluated evidence for the consumption of fish and/or EPA and DHA and risk of CHD mortality/fatal CHD events, and therefore need to be considered along with the scientific reports supporting the [US] Dietary Guidelines and reports on seafood consumption. The proposal also was raised if the discussion of whether the strength of evidence (the GP section 3.2.2.1) and a DIRV (section 3.2.2.2) should be addressed in two different eWG reports.

42. It was highlighted that the authority 5 could not be accepted as an RASB as its report was not a public policy document. At the same time, another CMC suggested that authority 5 could be accepted as RASB though its earlier 2010 report should be cited as a source of evidence. In this discussion, the co-chairs share the view that the Dietary Guidelines for Americans which recommend an intake of a variety of seafood that provides 250 mg intake of EPA and DHA for general population is a public policy document and thus should be considered in the context of NRV-NCD for EPA and DHA.

43. One observer has recommended the inclusion, as an RASB, of the U.S. Agency for Healthcare Research and Quality (AHRQ), which serves as one of the primary agencies in the United States for conducting scientific assessments like that conducted for health claims (e.g. The AHRQ conducted the scientific evaluation for the 2004 omega-3 qualified health claim). In 2012, the agency published a report entitled "Effects of Eicosapentanoic Acid and Docosahexanoic Acid on Mortality Across Diverse Settings: Systematic Review and Meta-Analysis of Randomized Trials and Prospective Cohorts" [8].

44. The list of all RASBs proposed and shortlisting criteria are shown in the Appendix II.

## **5 CONCLUSION AND RECOMMENDATIONS**

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

46. Members of CCNFSDU 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.

**PROPOSED DRAFT NRV-NCD FOR EPA AND DHA FOR INCLUSION IN THE GUIDELINES ON  
NUTRITION LABELLING (CAC/GL2-1985)**

**(At Step 3)**

3.4.4.2 NRVs-NCD

EPA<sup>11</sup> and DHA<sup>12</sup> 250 mg<sup>13</sup>

<sup>11</sup>Eicosapentaenoic acid

<sup>12</sup>Docosahexaenoic acid

<sup>13</sup>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****A The list of all RASBs proposed by eWG members and shortlisting criteria**

The spreadsheet summarizes proposals by the eWG members to consider potential RASBs that publish their opinions on the intake of EPA and DHA and its associations with various health outcomes. Note that these proposals are considered in support of three primary sources of data for establishing an NRV-NCD for EPA and DHA as outlined in section 4 of this report.

No	Nominated RASB	1) Supported by One or more Government (s) or Competent National or Regional Authorities	2) Provides Independent and Transparent Authoritative Scientific Advice Through Primary Evaluation of the Scientific Evidence Upon Request			3) Is on Whose Advice on DIVES is Recognized Through Use in Policy Development in One or More Countries?	RASB Publication	Recommendation for EPA/DHA Intake	Health Outcome
			Independent	Transparent	Primary Evaluation				
1	European Food Safety Authority (EFSA)	EU member states and the European Commission	EFSA runs policy on Independence and Scientific Decision-Making Processes of the European Food Safety Authority ( <a href="http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/independent_policy.pdf">http://www.efsa.europa.eu/sites/default/files/corporate_publications/files/independent_policy.pdf</a> ). The authority is governed by a Management Board whose members are mandated to act in the public interest.	The scientific basis for the advice is available in the RASB publication	The opinion is based on prospective cohort and dietary intervention studies, systematic reviews as well as meta-analyses	European dietary reference values for nutrient intakes 2010	EFSA J2010;8 (3): 1461.	250 mg for EPA plus DHA in adults considering cardiovascular health.	Mortality from coronary heart disease (CHD) and sudden cardiac death
2	The Working Group on Food, Diet and Toxicology/Nordic Council of Ministers	Norway, Denmark, Iceland, Sweden and Finland	The working group is one of three working groups of the Nordic Council of Ministers for Fisheries and Aquaculture, Agriculture, Food and Forestry in the structure of the Nordic Council of Ministers - independent inter-governmental body for cooperation in the Nordic region.	The scientific basis for the advice is available in the RASB publication	The recommendation is based on systematic reviews	Nordic Nutrition Recommendations 2012	Nordic Nutrition Recommendations 2012 · Part 2	An intake of 200-250 mg/day of EPA + DHA	CVD, CHD mortality
3	National Institute of Health and Nutrition (NIHN)	Japanese Ministry of Health and Welfare	An independent administrative agency acting in a public interest	The scientific basis for the advice is available in the RASB publication	The review is based on cohort and dietary intervention studies	Dietary reference intakes for Japanese 2015	J. Nutr Sci Vitaminol, 59, S44-S52,2013	1000 mg/day of EPA+DHA	Beneficial effects of fish oil intake on coronary artery disease
4	Australian National Health and Medical Research Council (NHMRC)	Australian Ministry of Health	Declarations of interest were made by all Working Committee members during the review process. During meetings where committee members were identified as having a significant real or perceived conflict of interest, the Working Party Chair could request they leave the room or not participate in discussions on matters where they were conflicted.	The scientific basis for the advice is available in the RASB publication	The NHMRC's revision of the Dietary Guidelines for Australians is based on systematic reviews	2013 Australian Dietary Guidelines	NHMRC (2011). A review of the evidence to address targeted questions to inform the revision of the Australian Dietary Guidelines.	not established	Mortality from cardiovascular disease
5	Dietary Guidelines Advisory Committee	U.S. Department of Health and Human Services and the U.S. Department of Agriculture	The 2015 Dietary Guidelines Advisory Committee (DGAC) was established jointly by the Secretaries of the U.S. Department of Health and Human Services (HHS) and the U.S. Department of Agriculture (USDA) for examining the Dietary Guidelines for Americans, 2010	The scientific basis for the advice is available in the RASB publication	The scientific report and recommendations are based on systematic reviews	2015-2020 Dietary Guidelines for Americans	Scientific report of the Dietary Guidelines Committee	250 mg/day of EPA+DHA provided by fish intake	Cardiac deaths among individuals with and without preexisting CVD
6	Food and Nutrition Board of the Institute of Medicine (IOM) [The Institute of Medicine has been renamed Health and Medicine Division]	United States and Canada	IOM has a policy on conflicts of interest for committee members ( <a href="http://www8.nationalacademies.org/cp/information.aspx?key=Conflict_of_Interest">http://www8.nationalacademies.org/cp/information.aspx?key=Conflict_of_Interest</a> )	The scientific basis for the advice is available in the RASB publication	The primary evidence reviewed by the Committee is summarized in an Appendix to the RASB publication	Used to establish daily values in Canada (Part D of Food and Drug Regulations)	Seafood: Selections to Balance Benefits and Risks	not recommended	Cardiovascular deaths and cardiovascular events; Primary prevention of cardiovascular disease

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			Independent	Transparent	Primary Evaluation				
7	Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (ANSES)	French Ministries of Health, Agriculture, the Environment, Labor and Consumer Affairs	Members of expert bodies must complete a public declaration of interests. ANSES addresses conflicts of interests during the selection of expert group members and at each meeting of an expert group. ( <a href="https://www.anses.fr/en/content/what-public-declaration-interests">https://www.anses.fr/en/content/what-public-declaration-interests</a> )	The scientific basis for the advice is available in the RASB publication	The evidence reviewed by the Committee is discussed and cited in the RASB publication	French population reference intakes for fatty acids	ANSES (2011). Actualization des apports nutritionnels conseillés pour les acides gras.	500 mg/day of EPA and DHA (0.25% of energy intake)	Cardiovascular mortality
8	German Nutrition Society	Funded in part by Germany's Federal Ministry of Food and Agriculture ( <a href="https://www.dge.de/wir-ueber-uns/die-dge/">https://www.dge.de/wir-ueber-uns/die-dge/</a> )	The DGE is an official incorporated society and is not influenced by economic or political interests ( <a href="https://www.dge.de/en/">https://www.dge.de/en/</a> )	The scientific basis for the advice is available in the RASB publication	The guidelines are based on meta- analyses of cohort studies	The Reference Values for Nutrient Intake are the basis on which diets are planned to match nutritional requirements for food intake. In addition, they form the basis for food rules and regulations for the food industry and food monitoring.	Evidence-Based Guideline of the German Nutrition Society: Fat Intake and Prevention of Selected Nutrition-Related Diseases (2015)	up to 250 mg/day EPA and DHA.	CHD
9	Health Council of the Netherlands	Netherland's Ministers and Parliament (including Minister of Health, Welfare & Sport)	Experts are asked to submit a declaration of interests. Based on this, the Board of the Health Council decides whether or not someone can participate ( <a href="https://www.gezondheidsraad.nl/en/node/4166/independence">https://www.gezondheidsraad.nl/en/node/4166/independence</a> )	The scientific basis for the advice is available in the RASB publication	to a significant extent based on the conclusions of the various reports on diet- related matters and chronic disease risk that the Health Council has published in recent years.	The Guidelines for a healthy diet are intended to support the food policy of the Dutch government and the monitoring of the impact of such policy. The guidelines also form the basis for nutrition education in the Netherlands.	Guidelines for a healthy diet 2006	450 mg/day of n-3 fatty acids from fish	CVD
10	Scientific Advisory Committee on Nutrition (SACN)	UK's Food Standards Agency (FSA)	Conflict of interests have to be declared by committee members. Guidance on handling conflicts of interest is also provided. ( <a href="https://www.gov.uk/government/publications/scientific-advisory-committees-code-of-practice">https://www.gov.uk/government/publications/scientific-advisory-committees-code-of-practice</a> )	The scientific basis for the advice is available in the RASB publication	The evidence reviewed by the Committee is discussed and cited in the report	The Food Standards Agency (FSA) sought advice from the Scientific Advisory Committee on Nutrition (SACN) and the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) on the benefits and risks of fish consumption, with particular reference to oily fish	SACN Advice on Fish Consumption: Benefits and Risks (2004)	0.45 g/d of long-chain n- 3 PUFA (two portions of fish per week, of which one should be oily)	CVD

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			Independent	Transparent	Primary Evaluation				
11	Agency for Healthcare Research and Quality (AHRQ)	United States	The Agency for Healthcare Research and Quality (AHRQ) serves as the primary agency conducting scientific assessments like that conducted for health claims. The AHRQ conducted the scientific evaluation for the 2004 omega-3 qualified health claim in the United States.	no data	no data	The Agency for Healthcare Research and Quality's (AHRQ) mission is to produce evidence to make health care safer, higher quality, more accessible, equitable, and affordable, and to work within the U.S. Department of Health and Human Services and with other authorities	<a href="http://www.ncbi.nlm.nih.gov/pubmed/health/PMH0041092/">http://www.ncbi.nlm.nih.gov/pubmed/health/PMH0041092/</a>	In 2012, a meta-analysis of RCTs of EPA and DHA supplementation and large prospective cohorts quantifying EPA and DHA intake from fish was published. The results are as follows: In RCTs, the risk for cardiovascular mortality (14 trials, 48,500 patients) was reduced by 11%. From 7 cohorts (123,122 participants), EPA and DHA intake (up to 0.20 grams daily) was associated with a statistically significant 36% decreased risk of cardiac death	Cardiac death
12	Dietitians of Canada	Canada	Dietitians of Canada is the voice of dietitians, supporting ethical, evidence- based best practice in dietetics	no data	no data	Dietitians of Canada	<a href="http://www.voic.ca/Content/Healthy%20Fats%20in%20the%20Diet/Position%20Paper%20on%20Fats.pdf">http://www.voic.ca/Content/Healthy%20Fats%20in%20the%20Diet/Position%20Paper%20on%20Fats.pdf</a>	500 mg/day n-3 long- chain PUFAs	General health
13	Chinese Nutrition Society	China	The Chinese Nutrition Society (CNS) is a non-profit professional organization dedicated to bringing together academics, education and research institutions, and industries to advance our research and application of nutrition science for the promotion of human well-being and disease prevention. As a bridge between nutrition practitioners and government, the Chinese Nutrition Society plays an essential role in the development of nutrition science in China.	no data	no data	Chinese Nutrition Society	no link	250 – 2000 mg /day EPA+DHA	General health
14	Ministry of Health	Malaysia	mission and vision	no data	no data	Ministry of Health	<a href="http://www.acadmed.org.my/index.cfm?&amp;menuid=67">http://www.acadmed.org.my/index.cfm?&amp;menuid=67</a>	0.75-1 g/day EPA+DHA as secondary prevention to prevent sudden death	Dyslipidemia
				no data	no data			1000 mg/day EPA + DHA as supplement for people who don't eat fish	adults at high risk or secondary prevention

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			Independent	Transparent	Primary Evaluation				
15	European Society of Cardiology	Europe	"The European Society of Cardiology (ESC) is an independent, non-governmental organization. Our members and decision makers are health care professionals that give their time and expertise freely, in addition to their daily high-paced clinical and/or research work. The ESC represents over 95 000 cardiology professionals, principally from across Europe and the Mediterranean basin, but also from the rest of the world."	no data	no data	European Society of Cardiology	<a href="http://eurheartj.oxfordjournals.org/content/32/14/1769.long">http://eurheartj.oxfordjournals.org/content/32/14/1769.long</a>	1 g/day n-3 unsaturated fats, which is not easy to derive exclusively from natural food sources, and use of nutraceutical and/or pharmacological supplements may be considered	secondary prevention of cardiovascular disease
16	Academy of Nutrition and Dietetics (formerly American Dietetics Association)	United States	The Academy of Nutrition and Dietetics is the world's largest organization of food and nutrition professionals. The Academy is committed to improving the nation's health and advancing the profession of dietetics through research, education and advocacy.	no data	no data	Academy of Nutrition and Dietetics (formerly American Dietetics Association)	<a href="http://www.andjrn.org/article/S2212-2672(13)01672-9/pdf">http://www.andjrn.org/article/S2212-2672(13)01672-9/pdf</a>	500 mg/day EPA+DHA	general adult population for cardiovascular disease risk reduction
17	American Heart Association (AHA)	United States	Among other activities, the AHA writes scientific statements, practice guidelines and clinical updates on cardiovascular disease and stroke.	no data	no data	American Heart Association	<a href="http://atvb.ahajournals.org/content/23/2/e20.long">http://atvb.ahajournals.org/content/23/2/e20.long</a>	Consume approximately 1 g/day of EPA+DHA preferably from oily fish. EPA+DHA supplements could be considered in consultation with the physician	Patients with coronary heart disease
				no data	no data			2-4 g/day EPA+DHA as capsules under a physician's care	Patients with high triglycerides
18	French Agency for Food, Environmental and Occupational Health & Safety (ANSES)	France	The French Agency for Food, Environmental and Occupational Health & Safety (ANSES) was created on 1 July 2010. It is an administrative public establishment accountable to the French Ministries of Health, Agriculture, the Environment, Labor and Consumer Affairs.	no data	no data	ANSES's duties, established by Ministerial Order No. 2010-18 of 7 January 2010, include risk assessment in the fields of food, the environment and the workplace, for the purpose of assisting the authorities with their policies on health and safety. ANSES	<a href="https://www.anses.fr/fr/system/files/NU2006sa0359.pdf">https://www.anses.fr/fr/system/files/NU2006sa0359.pdf</a>	500 mg/day EPA + DHA	general adult population for cardiovascular disease risk reduction
19	German Nutrition Society (DGE)	Germany	The DGE is an official incorporated society and is not influenced by economic or political interests	no data	no data	German Nutrition Society (DGE)	<a href="http://www.dge.de/fileadmin/public/doc/ws/ll-fett/v2/Gesamt-DGE-Leitlinie-Fett-2015.pdf">http://www.dge.de/fileadmin/public/doc/ws/ll-fett/v2/Gesamt-DGE-Leitlinie-Fett-2015.pdf</a>	250 mg/day EPA+DHA	primary prevention of coronary heart disease
20	Superior Health Council	Belgium	The Superior Health Council is the scientific advisory body of the Federal Public Service Health, Food Chain Safety and Environment. It forms a bridge between the Belgian authorities and the scientific world in all public health related issues.	no data	no data	Superior Health Council	<a href="http://health.belgium.be/internet2Prd/groups/public/@public/@shc/documents/ie2divers/4492395.pdf">http://health.belgium.be/internet2Prd/groups/public/@public/@shc/documents/ie2divers/4492395.pdf</a>	1g EPA+DHA / day	secondary cardioprevention

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			Independent	Transparent	Primary Evaluation				
21	Health Council of the Netherlands	Netherlands	The Health Council of the Netherlands is an independent scientific advisory body for government and parliament	no data	no data	Health Council of the Netherlands	<a href="https://www.gezondheidsraad.nl/en/publications/gezonde-voeding/guidelines-for-a-healthy-diet-2006">https://www.gezondheidsraad.nl/en/publications/gezonde-voeding/guidelines-for-a-healthy-diet-2006</a>	n-3 fatty acids from fish: 450 mg/day	General health
22	British Dietetic Association	United Kingdom	Independent scientific advisory body for government and parliament	no data	no data	British Dietetic Association	<a href="https://www.bda.uk.com/foodfacts/omega3.pdf">https://www.bda.uk.com/foodfacts/omega3.pdf</a>	Two Portions per week of fish, one of which should be oily; equals ~450mg/day EPA+DHA	General health



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### 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 ~~strike through 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.